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Role of Dopaminergic and Glutamatergic Systems of the Striatum in the Mechanisms of d-Amphetamine and Ammonia Neurotoxicity

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ACADEMIC DISSERTATION

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LIST OF ORIGINAL COMMUNICATIONS

This thesis is based on the following original articles:

1. Anderzhanova E.A., Afanas'ev I.I., Kudrin V.S. Rayevsky K.S. The effects of d-amphetamine on the extracellular content of dopamine and hydroxyl radical generation in striatum of freely moving rats. Bull. Exp. Biol. Med. 128, 538-540, 1999 (in Russian).

2. Afanas'ev I.I., Anderzhanova E.A., Kudrin V.S. Rayevsky K.S. Effects of amphetamine and sydnocarb on dopamine release and free radical generation in rat striatum. Pharmacol. Biochem. Behav. 69, 653-658, 2001.

3. Anderzhanova E.A., Rayevsky K.S., Saransaari P., Riitamaa E., Oja S.S. The effects of sydnocarb and d-amphetamine on the extracellular level of neuroactive amino acids in rat caudate-putamen Eur. J. Pharmacol. 428, 87-95, 2001.

4. Hilgier W., Anderzhanova E., Oja S.S., Saransaari P., Albrecht J. Taurine prevents ammonia- and N-methyl-d-aspartate-induced accumulation of cyclic GMP, and attenuates accumulation of hydroxyl radicals in microdialysates of the rat striatum. Eur. J. Pharmacol. 468, 21-25, 2003

5. Anderzhanova E., Oja S.S., Saransaari P., Albrecht J. Changes in the striatal extracellular levels of dopamine and dihydroxyphenylacetic acid evoked by ammonia and N-methyl-D-aspartate: modulation by taurine. Brain Res. 977, 290-293, 2003.

6. Anderzhanova E.A., Rayevsky K.S., Saransaari P., Oja S.S. Effect of sulpiride on the amphetamine-induced changes in extracellular dopamine, DOPAC, and hydroxyl radical generation in the rat striatum. Neurochem. Res. 28, 1265-1272, 2003.

ABBREVIATIONS

AMPA	2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate
ATP	adenosine triphosphate
ADP	adenosine diphosphate
cGMP	cyclic guanosine 3`,5`-monophosphate
CM	calmodulin
COMT	catechol-O-methyl transferase
CSF	cerebrospinal fluid
2,3-DHBA	2,3-dihydroxybenzoic acid
DA	dopamine
DAT	dopamine transporter
DNA	deoxyribonucleic acid
DOPA	3,4-dihydroxyphenylalanine
DOPAC	3,4-dihydroxyphenylacetic acid
EAAC	rabbit glutamate transporter
EAAT	excitatory amino acid transporter
EDTA	ethylenediaminetetra-acetate
GABA	γ-aminobutyric acid
GC	guanylate cyclase
GLAST or GLT	rat glutamate transporter
GluR	glutamate receptor subunit
GMP	guanosine monophosphate
GTP	guanosine triphosphate
HE	hepatic encephalopathy
HPLC	high-performance liquid chromatography
HT	5-hydroxytryptamine (serotonin)
HVA	homovanillic acid
KA	kainate
MAO	monoamine oxidase
MDMA	3,4-methylendioxyamphetamine
mRNA	matrix ribonucleic acid
mGluR	metabotropic glutamate receptor
NAD+	nicotinamide adenine dinucleotide (oxidized form)
NADH	nicotinamide adenine dinucleotide (reduced form)
NADPH	nicotinamide adenine dinucleotide phosphate
NMDA	*N*-methyl-D-aspartic acid
NO	nitric oxide
NOS	nitric oxide synthase
NR	NMDA receptor subunit
OHDA	hydroxydopamine
RNA	ribonucleic acid
ROS	reactive oxygen species
SOD	superoxide dismutase
VMAT-2	vesicular monoamine transporter

ABSTRACT

The neurotoxic effects of psychostimulants at high dosages limit their clinical applicability. Neurotoxic consequences include an increase in the extracellular content of dopamine, stimulation of dopamine oxidation, accumulation of extracellular glutamate, metabolic and oxidative stress, and an increase in body temperature, but the exact mechanism of the neurotoxic damage characterized by degeneration of the terminals of monoaminergic neurons and by depletion of the dopamine and serotonin contents remains to be elucidated.

A comparative study of neurochemical changes in the striatum induced by d-amphetamine and sydnocarb [3-(β-phenylisopropyl)-N-phenylcarbamoylsydnonimine], a Russian psychostimulant with good clinical efficacy, was undertaken in the first stage of research in freely moving Wistar rats using the microdialysis approach. d-Amphetamine (2.5 mg/kg) moderately increased the extracellular dopamine throughout the experiment. The level of hydroxyl radicals was two times higher than in controls but did not change dramatically. d-Amphetamine (5 mg/kg x 4, i.p.) elicited a sharp initial increase in the dopamine level and induced a delayed rise in the production of hydroxyl radicals during subsequent injections. Sydnocarb (23.8 mg/kg x 4, i.p., a dose, equimolar to 5 mg/kg of d-amphetamine) elicited a gradual increase in the extracellular level of dopamine and induced less hydroxyl radical generation than d-amphetamine. Sydnocarb was also able to elicit stereotyped behavior, albeit less markedly than d-amphetamine. Unlike d-amphetamine, sydnocarb significantly lowered the extracellular level of 3,4-dihydroxyphenylacetic acid only after the fourth injection.

Another comparative study of the effects of both psychostimulants on the extracellular levels of neuroactive amino acids was made using halothane-anesthetized Sprague-Dawley rats. Acute d-amphetamine administration (5.0 mg/kg, i.p.) produced a moderate accumulation of extracellular glutamate and aspartate. Sydnocarb (23.8 mg/kg, i.p.) likewise increased extracellular glutamate and also alanine. Subchronic d-amphetamine administration (5.0 mg/kg x 4, i.p.) caused a gradual fivefold increase in the levels of glutamate and taurine and moderate increases in those of aspartate and alanine. Subchronic sydnocarb administration (23.8 mg/kg x 4, i.p.) elicited a marked increase in the level of aspartate and a small increase in that of glutamate. The alanine level increased temporarily after each administration of sydnocarb, while the taurine level increased only after the last injection.

It could be concluded that sydnocarb is less neurotoxic than d-amphetamine, since it elicits lesser changes in the extracellular levels of glutamate and hydroxyl radicals in the rat striatum. The mode of action of sydnocarb also differs from that of d-amphetamine. The increase in the level of extracellular taurine may be regarded as a marker of neurotoxicity.

A wide spectrum of neuroprotective drugs have been applied to counteract amphetamine neurotoxicity. The dopamine receptor antagonists prevent long-term dopamine depletion in rodents. We showed with freely moving Sprague-Dawley rats that sulpiride, a dopamine D_2 receptor antagonist, at a dose of 75 mg/kg x 2, when co-administered with d-amphetamine (7.5 mg/kg x 4), potentiated the increase in extracellular dopamine and slightly enhanced stereotypy in the first stage of experiments. However, sulpiride was able to prevent the delayed loss of dopamine and 3,4-dihydroxyphenylacetic acid and depressed the

gradual accumulation of hydroxyl radicals induced in the rat striatum by d-amphetamine administration. Sulpiride counteracts the production of hydroxyl radicals and attenuates the neurotoxic effect of d-amphetamine probably by inhibiting postsynaptic receptors. The gradual increase in extracellular hydroxyl radicals may predict the dopamine and 3,4-dihydroxyphenylacetic acid depletion in the rat striatum consequent upon d-amphetamine administration.

Ammonia is a neurotoxin which causes an imbalance between inhibitory and excitatory neurotransmission in the brain, underlying symptoms of hepatic encephalopathy. There is evidence that dopamine receptors, dopamine-metabolizing enzymes, dopamine metabolites and the glutamatergic control of dopaminergic neurotransmission are affected in subacute or chronic hyperammonemia. The actions of amphetamine and ammonium chloride on dopamine release are very similar. Ammonium chloride causes a collapse in the transvesicular pH gradient responsible for monoamine leakage into the cytosol. Ammonium chloride (60 mM) administered directly to the rat striatum by microdialysis in vivo evoked a prompt release of dopamine and 3,4-dihydroxyphenylacetic acid by a mechanism not efficiently counteracted by the potential neuromodulator taurine (85 mM). Acute ammonia neurotoxicity caused by i.p administration of ammonium salts is mediated by overactivation of N-methyl-D-aspartate receptors, with an ensuing generation of free radicals and an extracellular accumulation of cyclic guanosine 3`,5`-monophosphate arising from stimulation of nitric oxide synthesis. Direct infusion of ammonium chloride into the striatum of rats via microdialysis probes increased the generation of hydroxyl radicals and the content of cyclic guanosine 3´,5´-monophosphate in the microdialysates 2.5- and 3-fold, respectively. Co-infusion of taurine substantially reduced the ammonia-induced accumulation of hydroxyl radicals and abolished the accumulation of cyclic guanosine 3´,5´-monophosphate. This constitutes the first evidence of the anti-excitotoxic activity of taurine in vivo. It also confirms our suggestion that the gradual accumulation of taurine in the striatum induced by d-amphetamine may reflect not only the neurotoxic potential of a drug, but also the activation of endogenous neuroprotection.

- Our findings point to a number of critical neurochemical changes in the development of neurotoxicity in the striatum of rats under amphetamine and ammonia exposure. Only when they all act together toxic effects are elicited and switching off any of them may stave off danger.
- The release of taurine is a marker of toxicity and taurine itself may serve as a neuroprotector.
- Sydnocarb shows less toxic potential in comparison with amphetamine.

INTRODUCTION

Systemic administration of psychostimulants results in impairment of the function of dopaminergic neurons in the nervous system. This complex phenomenon is known as amphetamine neurotoxicity and includes degeneration of the dendrites of dopaminergic neurons, a decline in the number of high-affinity uptake sites for dopamine and inhibition of tyrosine and tryptophan hydroxylases in the rat striatum and hippocampus, short-term and long-term dopamine depletion in the striatum, cerebral cortex and amygdala, and a subsequent decrease in dopaminergic functions in the brain [Fibiger and McGeer 1971, Hotchkiss and Gibb 1980, Ricaurte et al. 1980, 1982, Wagner et al. 1980, Nakayama et al. 1992]. According to the widely accepted hypothesis, a transient increase in the extracellular dopamine level after amphetamine and methamphetamine injections has a crucial role in the mechanisms of neurotoxic damage. The term "dopaminergic" toxicity is used as a synonym for "amphetamine" toxicity. The toxic properties of psychostimulants consist in the neurochemical changes they evoke. These include an increase in the extracellular content of dopamine in brain structures innervated by dopaminergic neurons, stimulation of dopamine oxidation, enhanced generation of reactive oxygen species, accumulation of extracellular glutamate, and an increase in body temperature.

The interactions of the dopaminergic and glutamatergic systems at intrastriatal and functional (basal ganglia circuitry) levels call attention to the role of the excitatory amino acid systems in the neuronal damage caused by psychostimulants. As suggested by Sonsalla [1995], dopaminergic and glutamatergic neurons are reciprocally excited in the striatum upon methamphetamine exposure and this interplay exacerbates oxidative stress and results in destruction of dopaminergic synaptic terminals. Glutamate release and hyperthermia contribute to metabolic stress and both may be key mediators in the toxic effects of amphetamines. The association of monoaminergic neuronal damage with an increased extracellular level of glutamate affords suggestive evidence for the involvement of glutamate in the neurotoxicity of systemically administered amphetamines. Both local and systemic administrations of amphetamines acutely enhance dopamine release, but only systemic administration results in neurotoxicity and increases the extracellular concentration of glutamate [Nash and Yamamoto 1992, Stephans and Yamamoto 1994, Abekawa et al. 1994, Wolf and Xue 1998, Burrows et al. 2000a]. The mechanism by which amphetamines increases extracellular glutamate is poorly understood. It has been suggested that activation of both dopamine D_1 and D_2 receptors enhance the release of intracellular glutamate in the striatum of freely moving rats.

The antagonists of dopamine D_2 receptors have been studied as neuroprotective agents. When administered alone they moderately increase the basal dopamine efflux and induce a slow gradual increase in the extracellular levels of dopamine metabolites [Boyar and Altar 1987, Miroshnichenko et al. 1988]. Blockade of presynaptic autoreceptors disrupts the regulatory negative feedback which prevents the inhibition of neurotransmitter release by endogenous dopamine. Hence, D_2 receptor antagonists stimulate the amphetamine-induced dopamine overflow and potentiate stereotypic behavior [Sharp et al. 1986]. However, dopamine receptor antagonists prevent the methamphetamine-induced injury to striatal terminals. Blockade of postsynaptic dopamine D_2 receptors may effectively counteract some of the physiological effects of psychostimulants [Filloux et al. 1987] and inhibit glutamate efflux in the striatum and cerebral cortex [Morari

et al. 1998]. This decrease in extracellular glutamate may then prevent the excessive generation of reactive oxygen species [Frost and Cadet 2000, Tapia et al. 1999].

There obtains a principal similarity in the mechanisms of dopamine release induced by pathological concentrations of ammonia and d-amphetamine [Erecińska et al. 1987]. Ammonium chloride may collapse the transvesicular pH gradient and be responsible for monoamine leakage into the cytosol [Sulzer and Rayport 1990, Sulzer et al. 1995]. The vesicular pH gradient is required for monoamine accumulation [Johnson et al. 1981, Peter et al. 1994, Henry et al. 1998]. Both weak bases and amphetamine could abolish the intracellular pH gradient, causing a huge increase in cytosolic dopamine and giving rise to dopamine overflow [Schuldiner et al. 1995]. The same mechanism may explain the dopamine-releasing action of 3,4-methylendioxymethamphetamine ("ecstasy"), and the release of serotonin by fenfluramine [Rudnick and Wall 1992]. The increase in extracellular dopamine leads to an increase in the production of its oxidized forms which damage cell proteins and nucleic acids and provoke generation of reactive oxygen species.

In current research the emphasis is on the generation of hydroxyl radicals [Obata and Chiueh 1992] and on changes in the other neurochemical parameters induced by d-amphetamine, sydnocarb and ammonia in the rat striatum in vivo and on the manner in which they are modulated by taurine and the dopamine D_2 receptor antagonist sulpiride.

REVIEW OF THE LITERATURE

Dopaminergic neurotransmission

Dopamine was long degraded as merely the precursor of norepinephrine, but a biological significance of its own in the brain is now fully acknowledged. A failure in dopaminergic neurotransmission results in movement disorders, e.g., in Parkinson's disease. Dopamine also participates in the mechanisms of award behavior, drug abuse and thermoregulation [Kuhar et al. 1999].

Dopaminergic cells in the brain stem project widely to the telencephalic structures. A major group of dopaminergic cell bodies lies in the zona compacta (A9) of the substantia nigra and projects to the striatum. Another group of dopaminergic cell bodies lies in the ventral medial tegmentum (A10) and projects to the limbic system structures, including olfactory tubercule, septum, amygdala, nucleus accumbens and prefrontal cortex. Some cell bodies in the zona compacta send projections to the limbic structures, while some dopaminergic cell bodies in the ventral medial tegmentum project to the structures of the striatum. All these projections follow a topographical principle, innervate strictly determined patches within the respective areas and practically never evince cross innervation [Lindvall and Björklund 1974, Björklund and Lindvall 1984, Fuxe et al. 1985, Nieuwenhuys 1985, Gerfen 1992].

Like other catecholamine neurotransmitters, dopamine is synthesized from the amino acid precursor tyrosine, which is taken up across the blood brain barrier [Colombo et al. 1996]. The first step in this synthesis is the hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase (EC 1.14.16.2), which is also the rate-limiting enzyme in the synthetic cascade. Blashko [1957] already predicted this pathway, though tyrosine hydroxylase was discovered only later [Nagatsu et al. 1964]. The synthesis rate of dopamine depends on end-product inhibition, neuronal firing rates and autoreceptor regulation. These factors regulate the phosphorylation of tyrosine hydroxylase, which is the major regulatory mechanism in its activity [Feldman et al. 1997]. In the cytoplasma of cells, DOPA decarboxylase (EC 4.1.1.28) converts DOPA to dopamine. In the cellular cytosol, dopamine is broken down in two consecutive reactions. In rodents, the first transformation is effected by monoamine oxidase (MAO) (EC 1.4.3.4), which converts dopamine to the corresponding aldehyde. In turn, it serves as a substrate for aldehyde dehydrogenase (EC 1.2.3.1) to yield 3,4-dihydroxyphenylacetic acid (DOPAC). DOPAC diffuses out of the cells and is conjugated with glucuronides or transformed by catechol O-methyltransferase (COMT) (EC 2.1.1.6) into 4-hydroxy-3-methoxyphenylacetic acid, commonly known as homovanillic acid (HVA) [Westerink 1985, Männistö et al. 1992, Richards et al. 1996]. A part of MAO is located outside the neurons, i.e., in glial cells, while COMT is found only outside neurons [Fowler et al. 1984, Waldmeier 1987, Männistö et al. 1992].

Inside nerve endings, dopamine is stored in two pools: vesicular and cytoplasmic. Newly synthesized dopamine is actively taken up by synaptic vesicles and released from them by exocytosis. The transport of dopamine across vesicular membranes and its subsequent retention inside the vesicles depend on two components: vesicular transporters and the proton pump [Philippu and Matthaei 1988]. The vesicular monoamine transporter (VMAT-2) [Liu et al. 1992] transfers amines into vesicles in exchange for protons.

VMAT-2 is a member of the toxin-extruding antiporter gene family, which also includes some bacterial antibiotic resistance genes [Schuldiner et al. 1995]. This proton removal is balanced by a ATPase/Mg^{2+}-dependent mechanism which pumps protons back into the vesicle and thus maintains a highly acidic environment and an electrochemical gradient across the vesicular membrane [Erickson et al. 1992, Parsons 2000].

Dopamine is stored inside the vesicles at very high concentrations, of the order of 0.5 M. It exists in complexes with ATP and acidic proteins known as chromogranins. The pH level in a vesicle is 5.2-5.7 [Johnson et al. 1981, Njus et al. 1981]. The chemical features of the dopamine molecule result in a rather low (in comparison with other amines) buffer capacity. This renders dopamine-containing vesicles highly susceptible to changes in pH. Weak basic compounds, including amines, may perturb neurotransmitter storage by means of alkalinization of the vesicle contents. In turn, some specific compounds, e.g., reserpine or tetrabenazine, block the transport of dopamine. However, since the dopamine-mediated behavioral effects of amphetamine are not blocked by reserpine pretreatment, Braestrup [1977] suggested the existence of a second pool, and it has therefore been concluded that dopamine stores also exist in the cytoplasmic pool [Schoemaker and Nickolson 1983].

The discovery that norepinephrine-containing neurons take up norepinephrine from the extracellular space against a concentration gradient led to the conception of a carrier-mediated active transport system as a mechanism of the termination of the action of neuromediators in the synaptic cleft [Iversen 1974]. This carrier-mediated active uptake process was postulated to be similar to the transport of sugars and amino acids across cell membranes. The physiological action of dopamine is terminated primarily by a rapid re-uptake by the plasma membrane dopamine transporter (DAT), a member of the Na^+/Cl^--coupled neurotransmitter transporter family which includes the plasma membrane transporter for serotonin and norepinephrine [Blakely et al. 1991]. In resting state the dopamine concentration outside a cell is higher than that inside. When the complex of dopamine, transporter and sodium ion orients to the inside of the cell dopamine is released from the terminal. When recycled to the outside of the membrane, the transporter can bind dopamine available there when the dopamine concentration is high. In this manner the transporter could both release and take up catecholamines in the nerve endings.

Dopamine can be released by two mechanisms: exocytotic release, which is impulse-dependent, and transporter-mediated release, which is not. The former depends largely on the transmembrane gradient of K^+ and ATP hydrolysis and is initiated by Ca^{2+}. Any inhibition of dopamine re-uptake increases the extracellular concentration in the synaptic cleft and the life-span of dopamine, which leads to prolonged stimulation of dopamine receptors. The DAT-mediated release is dependent on Na^+ and Cl^- and independent of Ca^{2+} [Giros and Caron 1993]. Cocaine apparently inhibits the uptake and release of dopamine (and/or norepinephrine). In the presence of amphetamine the direction of transport is reversed and dopamine moves out of the cell.

There are two main types of dopamine receptors, namely D_1 and D_2, both of them having subtypes, i.e., D_2, D_3 and D_4 belonging to the D_2 family and D_1 and D_5 to the D_1 family [Jackson and Westlund-Danielsson 1994]. Both receptor families are G-protein-coupled, but D_1 receptors activate and D_2 receptors

inhibit the adenylyl cyclase pathway [Andersen et al. 1990, Clarck and White 1997]. In the striatum, dopaminergic receptors are located on GABAergic neurons. The D_2 receptors participate in the autoregulation of dopamine release and are also located presynaptically on dopaminergic terminals [Jaber et al. 1996]. Recent data from dopamine receptor mapping based on pharmacological and immunohistochemical methods suggest that different types of dopamine receptors are co-localized on different types of GABAergic neurons in the striatum [Mansour et al. 1990, Hersh et al. 1995, Surmeier et al. 1996].

Glutamatergic neurotransmission

Glutamate, the main excitatory neurotransmitter in the mammalian brain, has important roles in many physiological and pathological events [Ozawa et al. 1998]. It is the most abundant amino acid in the adult nervous system and has also other roles besides neurotransmission (it is incorporated into peptides and involved in fatty acid synthesis, and serves as a precursor for various Krebs cycle intermediates). Glutamate is a non-essential amino acid produced from 2-oxoglutarate, glutamine, ornithine or proline. The diversity of routes for glutamate synthesis is reflected in the variability of intracellular pools. The neurotransmitter glutamate is formed mostly from glutamine by glutaminase (EC 3.5.1.2) [Dingledine and McBain 1999]. The vesicular transport system is essential for its intraneuronal storage. Synaptic vesicles actively accumulate glutamate by an Mg^{2+}/ATP-dependent process. Substances which destroy the electrochemical gradient inhibit this uptake. The concentration of glutamate within synaptic vesicles is particularly high, in excess of 20 mM [Fykse and Fonnum 1996, Wolosker et al. 1996). Glutamate stored inside the synaptic vesicles is available for release when the presynaptic membranes are depolarized. It is released in a Ca^{2+}-dependent manner both in vitro and in vivo.

In order to terminate the neurotransmitter action and to avoid the excessive increase in extracellular glutamate and consequent hyperactivation of glutamatergic receptors accompanied by neuronal damage, glutamate must be taken up from the synaptic cleft to the cytosol of glial and neuronal cells and stored in synaptic vesicles in nerve endings. The released glutamate is rapidly eliminated from the extracellular space by a high-affinity transport system which is present in both nerve endings and surrounding glial cells [Danbolt 2001]. These Na^+-dependent carriers are located at the cell membranes of astrocytic and neuronal cells [Robinson and Dowt 1997, Anderson and Swanson 2000]. Five distinct high-affinity, Na^+-dependent glutamate transporters have been cloned from rodent and human tissues: GLAST (EAAT1), GLT-1 (EAAT2), EAAC1 (EAAT3), EAAT4 and EAAT5 [Danbolt 2001]. These proteins have distinct structures, functions and distributions. Immunohistochemical studies have shown that GLAST and GLT-1 are both present primarily in astrocytes, while EAAC1 and EAAT4 are primarily neuronal. The Na^+-dependent glutamate uptake system in astrocytes is the most significant for the maintenance of glutamate levels below neurotoxic concentrations, as clearly demonstrated by knock-out studies of astrocytic glutamate transporters [Rothstein et al. 1996]. The coordinated actions of vesicular and cell membrane transport systems effectively keep the glutamate concentrations in the synaptic cleft at low micromolar levels. In addition, the re-uptake processes

are also essential for the recycling of the amino acid pool which replenishes the supply of neurotransmitters in the glutamatergic terminals [Seal and Amara 1999].

Glutamate activates several classes of receptors, which have been divided into "ionotropic" and "metabotropic" [Ozawa et al. 1998]. Glutamate released from the nerve endings may act at presynaptic or postsynaptic ionotropic glutamate receptors, which gate cation channels and mediate fast and prolonged excitatory effects. The ionotropic receptors have been divided into N-methyl-D-aspartate (NMDA) (with a number of regulatory sites), 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate receptors, according to their preferred agonists [Bettler and Mulle 1995, McBain and Mayer 1994]. Since neither agonists nor antagonists clearly distinguish between AMPA and kainate receptors, they are often collectively referred to non-NMDA receptors. Further studies by molecular biologic methods have demonstrated that ionotropic glutamate receptors are composed of sub-units encoded by different gene families. Two families of sub-units, $NMDAR_1$ and $NMDAR_{2(A-D)}$, have been identified for the NMDA receptor [McBain and Mayer 1994]. As to the AMPA receptor, four subunits, $GluR_1$–$GluR_4$, have been cloned, while five subunits, $GluR_5$, $GluR_6$, $GluR_7$, KA_1 and KA_2, have been identified for the kainate receptor [Bettler and Mulle 1995]. The conductance properties of ions in the ionotropic receptors depend on their subunit composition. The AMPA and kainate receptors are rapidly activated and desensitized in response to glutamate. They pass Na^+ and Ca^{2+} ions. The presence of the $GluR_2$ subunit determines the Ca^{2+} permeability of recombinant AMPA receptors, whereas the homomeric $GluR_6$ kainate receptors are fairly permeable to Ca^{2+}. The NMDA receptors are activated and desensitized slowly and their Ca^{2+} permeability is regulated by a voltage-dependent Mg^{2+} block [Ozawa et al. 1998]. Activation of metabotropic receptors, which are linked to G proteins, produces changes in cyclic nucleotides or phosphoinositol metabolism. The metabotropic receptor family comprises eight subtypes ($mGluR_1$–$mGluR_8$), subdivided into three groups [Schoepp and Conn 2002].

The NMDA receptors are functionally different from the others. Specifically, the NMDA receptor seems to be crucial in plasticity processes associated with normal brain functions [Izguierdo and Medina 1997]. Among the various factors involved in the modulation of glutamate release, the activation of presynaptic NMDA receptors may be stimulatory [Breukel et al. 1998]. Rosenmund and associates [1995] reported that intracellular Ca^{2+} inactivates NMDA receptors in cultured hippocampal neurons and a Ca^{2+} influx through NMDA receptors provides a negative feedback on NMDA receptor activity. The NMDA receptor is sensitive to oxygen free radicals, which may exert a regulatory influence through the redox modulatory site [Aizenman et al. 1990]. The AMPA and NMDA receptors are co-localized at synapses in different parts of the central nervous system [Bekkers and Stevens 1989]. Inactivation of NMDA receptors can also be induced by AMPA receptor activation. A Ca^{2+} influx through a subpopulation of AMPA receptors in cultured neurons from the rat spinal dorsal horn and hippocampal cells can induce desensitization of the adjacent NMDA receptors [Medina et al. 1994]. These observations are consistent with those from in vivo experiments in which the activation of NMDA or AMPA receptors in the rat neocortex has been seen to prevent the actions of topically applied NMDA [Addae et al. 2000], although in an intact in-vivo neuronal network the involvement of inhibitory interneurons cannot be ruled out.

Corpus striatum and the basal ganglia circuitry

The basal ganglia are located in the basal telencephalon and consist of five interconnected nuclei: caudate nucleus, putamen, globus pallidus, substantia nigra and subthalamic nucleus. The basal ganglia circuitry is a functional part of the extrapyramidal motor system and processes signals flowing from the cortex, allowing the correct execution of voluntary movements [Carlsson 1993, Blandini et al. 2000]. The descending pathways from cortical and hippocampal pyramidal cells are glutamatergic. These tracts include corticostriatal, entorhinal-hippocampal, cortical and hippocampal projections to various hypothalamic, thalamic and brain stem nuclei. The striatum receives glutamatergic tracts from the cerebral cortex, neo- and mesocortical areas, and thalamus [Smith and Bolam 1990]. Glutamatergic transmission in these corticostriatal and thalamostriatal pathways seems to play a crucial role in cognitive functions, motor coordination and plasticity [Calabresi et al. 2000] and in neurodegenerative disorders of the basal ganglia, i.e., Parkinson's and Huntington's diseases [Alexi et al. 2000]. In the striatum, glutamatergic terminals make contact with medium spiny (GABAergic) neurons. The glutamatergic input in the striatum has a multilevel organization which underlies the morphological separation of neuronal pathways. The dorsolateral and ventromedial parts are innervated independently by the neocortical and mesocortical neurons. The different compartments in the striatum receive projections from pyramidal neurons in different layers in the cerebral cortex [Fonnum et al. 1981, 1984, Dounoghue and Herkenham 1986, McGeorge and Faull 1989].

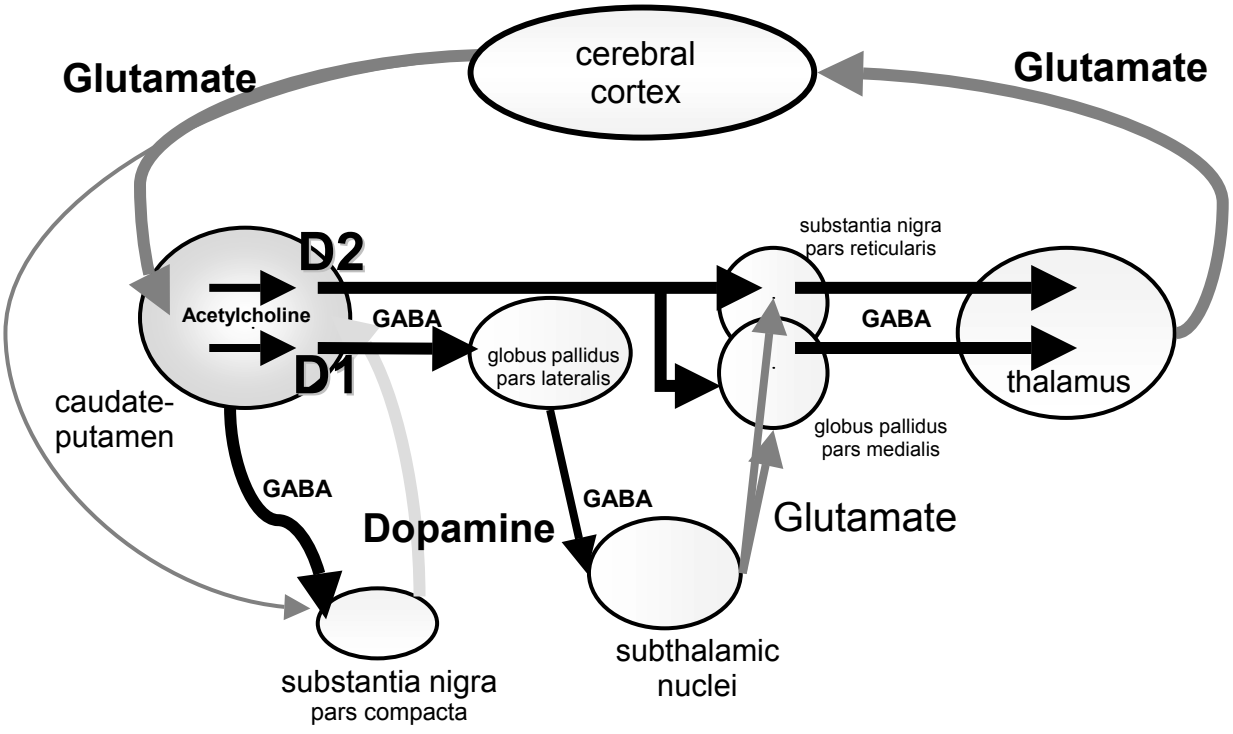

Fig. 1. The basal ganglia circuitry. D1 and D2 mark the locations of dopamine receptors of different classes on the indirect and direct pathways, respectively. From Lange et al. (1997).

The striatum is the main input structure in the basal ganglia circuitry (Fig. 1). It receives excitatory glutamatergic and inhibitory dopaminergic projections. The interaction of these two and some other (particularly acetylcholine) neurotransmitters in the striatum plays a crucial role in the regulation of locomotor activity. In primates, the caudate nucleus and putamen are partly separated by corticofugal and corticopetal fibers of the internal capsule. Several bridges of cells connect the two nuclei, which are similar in terms of anatomical and functional characteristics. The two structures together are therefore generally referred to the corpus striatum or striatum. In rodents, the striatum presents an anatomically homogeneous structure. The nucleus accumbens, which is the other major component in the striatum, is located rostroventrally to the nucleus.

The spiny projection neurons constitute the major neuronal population in the striatum, accounting for almost 95% of total cells [Kemp and Powell 1971]. They use γ-aminobutyric acid (GABA) as a neurotransmitter [Kita and Kitai 1988]. Within these projection neurons, GABA can be co-localized, alternatively, with enkephalin or substance P/dynorphin [Beckstead 1985]. The remaining 5% of striatal cells consists of aspiny interneurons containing, alternatively, acetylcholine, somatostatin, NADPH-diaphorase or GABA associated with parvalbumin or calretin [Kawaguchi et al. 1995]. Recently, the presence of dopaminergic neurons intrinsic to the striatum has also been suggested [Betarbet et al. 1997].

The main targets of striatal projections are the medial and lateral segments of the globus pallidus and the substantia nigra pars reticulata [Parent and Hazrati 1995a]. It has been suggested that neurons containing enkephalin project to the lateral globus pallidus, while the neurons containing substance P/dynorphin project to the medial globus pallidus and substantia nigra pars reticulata. This functional segregation of the striatal output is the apparent basis for the direct and indirect pathway models of the functional organization of the basal ganglia.

The major neural input to the striatum is excitatory in nature. Glutamatergic projections from cortical areas converge onto striatal neurons [McGeorge and Faull 1989]. Other important excitatory inputs to the striatum arise from the midline and intralaminar nuclei of the thalamus [Berendse and Groenewegen 1990] and from the limbic structures, particularly from the amygdala [Kelley 1982]. Another important input to the striatum originates from dopaminergic neurons located in the pars compacta of the substantia nigra and in the ventral tegmental area [Nieuwenhuys 1985]. The striatum also receives serotoninergic afferent projections from the dorsal nucleus of the raphe and caudal linear nucleus [Halliday et al. 1995] and a sparse norepinephrinergic innervation from the locus coeruleus [Aston-Jones et al. 1995]. By reason of its nature as an input nucleus, the striatum possesses a variety of neurotransmitter receptors with a considerably higher density than in the other basal ganglia nuclei.

Glutamate plays an important role in the regulation of striatal activity. The nucleus shows the highest density of glutamate receptors within the structures of the basal ganglia circuitry [Albin et al. 1992]. This reflects the abundance of glutamatergic projections which extend to the striatum, particularly from the cerebral cortex [McGeorge and Faull 1989]. Various components of both ionotropic and metabotropic classes of glutamate receptors are present in the striatum. Earlier studies have shown that NMDA receptors have a

higher density than AMPA receptors in the striatum, while the opposite seems to be the case in the other basal ganglia nuclei [Albin et al. 1992, Tallaksen-Greene et al. 1992]. Subsequent studies, using in situ hybridization and immunocytochemical techniques for the investigation of single subunits composing the NMDA and AMPA receptors, have provided further insights and partially modified the picture. Bernard and Bolam [1998], for example, have shown that 80% of the spiny projection neurons in the striatum express both NMDA NR1 and AMPA $GluR_{2/3}$ subunits. It has also been shown that projection neurons differ from interneurons in terms of the specific NR subunit mRNAs expressed [Landwehrmeyer et al. 1995]. The AMPA receptor subunits also evince a differential expression in projection neurons and interneurons; in particular, the GluR1 subunit does not appear to be expressed in the projection neurons [Tallaksen-Greene and Albin 1994]. Furthermore, Kosinski and associates [1998] have recently shown a preferential expression of NR1, NR2B and NR2C subunits of the NMDA receptor in the human striatum when compared to the globus pallidus. The striatum also possesses a high density of binding sites for metabotropic glutamate receptors [Albin and Greenamyre 1992, Fotuhi et al. 1993]. Various mRNAs encoding different members of the three groups of metabotropic receptors are expressed by striatal neurons.

Striatal neurons express both D_1 and D_2 dopamine receptors, which mediate the modulatory effects of dopamine released from nigrostriatal terminals. It has been suggested that D_1 and D_2 receptors are functionally segregated to different subsets of striatal neurons. According to this view, D_1 receptors are expressed by neurons projecting to the substantia nigra pars reticulata and medial globus pallidus, while D_2 receptors are expressed by neurons projecting to the lateral globus pallidus [Gerfen 1992, Gerfen et al. 1995]. A population of projection neurons expresses both D_1 and D_2 receptors [Surmeier et al. 1996].

Though the role played by dopamine at striatal level has been extensively studied, many aspects are still poorly understood. In Parkinson's disease, the degeneration of dopaminergic neurons of the substantia nigra pars compacta triggers a cascade of functional changes affecting the entire basal ganglia network. The most relevant alterations affect the output nuclei of the circuit, the medial globus pallidus and substantia nigra pars reticulata, which become hyperactive. Such hyperactivity is sustained by the enhanced glutamatergic input the output nuclei receive from the subthalamic nucleus. Electrophysiological studies suggest that dopaminergic transmission modulates the striatal responses to incoming inputs, particularly those mediated by glutamate [Calabresi et al. 1997, Cepeda and Levine 1998]. The release of glutamate in the striatum seems to be modulated, in part, by nigrostriatal dopaminergic projections. Chronic blockade of dopamine D_2 receptors increases the levels of both basal extracellular and K^+-releasable glutamate in the striatum [Yamamoto and Cooperman 1994]. There is also electrophysiological evidence that dopamine depletion increases spontaneous glutamate release in the striatum [Calabresi et al. 1993]. In keeping with this view, behavioral studies conducted on freely moving animals show that intrastriatal administration of dopamine attenuates the neuronal excitation elicited by cortical activation in rats [Kiyatkin and Rebec 1996]. Recently, Kiyatkin and Rebec [1999] have shown that systemic administration of the D_1 antagonist SCH-23390, but not that of the D_2 antagonist eticlopride, elevates basal activity and attenuates neuronal responses to dopamine in the striatum of freely moving rats. The D_1 blockade also enhances the glutamate-mediated activation of striatal neurons.

Another neuromodulator which influences the functional responses of dopamine receptors in the striatum is adenosine. Adenosine acts on specific receptors (A_1, A_{2A}, A_{2B} and A_3) which appear to be co-localized with dopamine receptors. In particular, A_1 receptors are co-localized with D_1 receptors [Ferre et al. 1996] and A_{2A} receptors with D_2 receptors [Schiffman et al. 1991]. In both cases, adenosine antagonizes the effects on striatal neurons mediated by dopamine. For example, activation of striatal A_1 receptors prevents the release of GABA in the entopeduncular nucleus (the rodent homologue of the medial globus pallidus in primates) elicited by stimulation of striatal D_1 receptors. Analogously, stimulation of A_{2A} receptors inhibits the release of GABA from the globus pallidus (the rodent homologue of the lateral globus pallidus in primates) secondarily to activation of striatal D_2 receptors [Ferre et al. 1993, 1996a].

$GABA_A$ receptors are present in the striatum and have been described in detail in rats [Wisden et al. 1992]. Striatal GABAergic synapses are derived primarily from the local collaterals of the axons of GABAergic projection neurons and from the axons of GABAergic interneurons [Kultas-Ilinsky et al. 1998]. Striatal neurons also express receptors for serotonin, particularly 5-HT_{2A}, 5-HT_{2C} and 5-HT_6 subtypes [Wright et al. 1995]. Serotoninergic receptors seem to be preferentially located on projection neurons containing enkephalin, substance P and dynorphin [Ward and Dorsa 1996].

The functional architecture of basal ganglia has attracted the interest of numerous researchers in the last decade. This has led to the formulation of a model of basal ganglia functions which has became particularly popular [Alexander and Crutcher 1990, Graybiel 1990, Gerfen 1992, Albin et al. 1995]. According to this model, the striatum – the main input nucleus of the circuit – transmits the flow of information received from the cerebral cortex to the basal ganglia output nuclei, substantia nigra pars reticulata and medial globus pallidus, via direct and indirect pathways. The two pathways originate from different subsets of striatal neurons and remain functionally segregated. In the direct pathway, striatal GABAergic neurons, containing dynorphin as a co-transmitter and expressing dopamine D_1 receptors, project monosynaptically to the substantia nigra pars reticulata and medial globus pallidus. In the indirect pathway, the striatal output reaches the target nuclei via a more complicated route. In fact, a different subset of GABAergic neurons – containing enkephalin and expressing D_2 receptors – projects to the lateral globus pallidus, which sends GABAergic projections to the subthalamic nucleus. The subthalamic nucleus, in turn, sends its glutamatergic efferents to the output nuclei and to the lateral globus pallidus. From the output nuclei, inhibitory GABAergic projections reach the ventral lateral and ventral anterior nuclei of the motor thalamus. The thalamic nuclei then send glutamatergic projections to the motor cortex, thus closing the loop.

According to this scheme, the functional consequence of such organization is that activation of the direct and indirect pathways leads to opposite changes in the net output of the basal ganglia circuitry. In fact, activation of the striatal GABAergic neurons which give rise to the direct pathway causes inhibition of GABAergic neurons in the output nuclei. This leads to disinhibition of thalamic nuclei which are under the inhibitory control of the output nuclei projections. Conversely, activation of the striatal neurons projecting to the lateral globus pallidus in the indirect pathway causes inhibition of the lateral globus pallidus and subsequent disinhibition of the subthalamic nucleus. The activation of the subthalamic nucleus – which is

glutamatergic – increases the activity of the output nuclei. Consequently, their inhibitory control over the motor thalamus is enhanced [Alexander and Crutcher 1990].

This model has recently been criticized and is being revised and integrated with data provided by the latest studies [Albin et al. 1995, Chesselet and Delfs 1996, Parent and Cicchetti 1998]. One of the major criticisms pertains to the hypothesized segregation of striatal output pathways. Striatal spiny neurons give rise to extensive local axon collaterals. As a consequence, the two populations of neurons giving rise to the direct and indirect pathways are, in fact, synaptically interconnected [Yung et al. 1996]. Striatofugal axons are also highly collateralized. It has been shown, for example, that a single striatofugal axon can arborize in both pallidal segments and in the substantia nigra [Parent and Hazrati 1995a]. Recently, Reiner and colleagues [1999] have confirmed that striatal neurons projecting to the medial globus pallidus contain both substance P and dynorphin, but not enkephalin, and that the striatal neurons projecting to the lateral globus pallidus contain only enkephalin. However, within the neuronal population giving rise to the direct pathway, the authors describe cells containing substance P but not dynorphin. Moreover, some of these neurons contained enkephalin, alone or co-localized with substance P. Recent data from dopamine receptor mapping based on pharmacological and immunohistochemical methods suggest that different types of dopamine receptors are co-localized on GABAergic neurons in the striatum [Meador-Woodruff et al. 1991, Hersh et al. 1995, Surmeier et al. 1996]. Such conceptions would thus seem to contradict the assumption that the striatal output reaches the output nuclei through two completely separated channels.

Another two elements have recently emerged which must be taken into account in a re-modeling of the current scheme of basal ganglia organization. First, various studies have noted the existence of direct projections connecting the lateral globus pallidus to the medial globus pallidus and to the substantia nigra pars reticulata [Parent and Hazrati 1995b, Smith et al. 1998]. Thus, in contrast to the outlines of the previous model, the lateral globus pallidus may interfere directly with the basal ganglia output without the interposition of the subthalamic nucleus. Second, the subthalamic nucleus receives direct excitatory projections from the primary motor cortex [Smith et al. 1998]. These recent data on basal ganglia connectivity have therefore been incorporated in the current model of basal ganglia functional organization. The result is a more articulate organization of the circuit from which a central and to a certain extent independent role of the subthalamic nucleus seems to emerge.

Excitotoxicity of glutamate

Glutamate is the predominant fast excitatory transmitter in the central nervous system. Besides its central role in excitatory neurotransmission, it also acts as a neurotoxin. First described by Olney [1971], *excitotoxicity* has since been characterized as representing an excessive synaptic release of glutamate which overactivates postsynaptic glutamate receptors. Excitotoxicity is one of the most extensively studied processes of neuronal cell death. It plays an important role in many diseases of the central nervous system, including ischemia, trauma and neurodegenerative disorders [Lipton and Rosenberg 1994, Ozawa et al. 1998]. Although the molecular basis of glutamate toxicity is not exactly known, there is general agreement that it is to a

considerable extent Ca^{2+} dependent. Almost every class of glutamate receptors has been implicated in excitotoxic cell death, but it is now unanimously accepted that the NMDA receptors play a major role, mainly owing to their high Ca^{2+} permeability. Nonetheless, other glutamate receptors such as AMPA and kainate receptors have also been thought to contribute to excitotoxic neuronal cell death (Fig. 2).

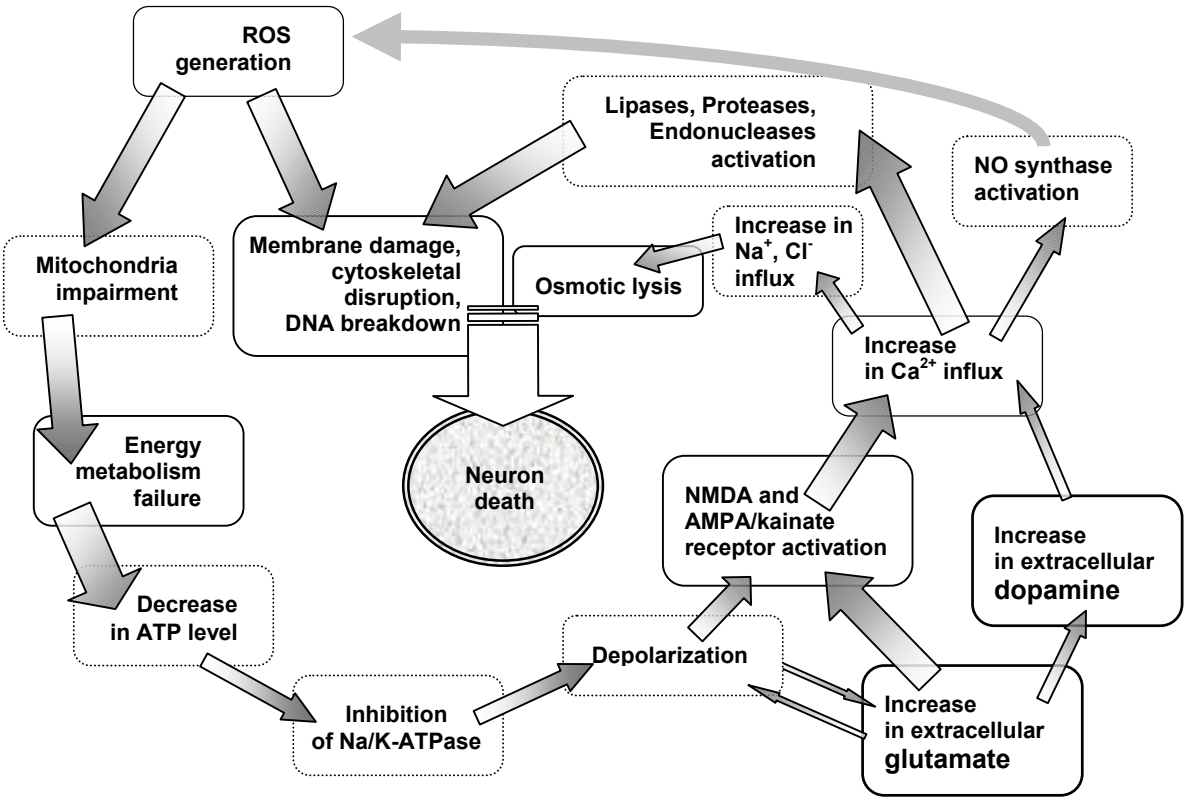

Fig. 2. The mechanisms of neuronal toxicity.

A massive influx of extracellular Ca^{2+} is secondary to activation of the NMDA receptor [Meldrum and Garthwaite 1990]. The increase in cytoplasmic Ca^{2+} activates a number of Ca^{2+}-dependent enzymes involved in the catabolism of proteins, phospholipids and nucleic acids, as well as in the synthesis of nitric oxide. This leads to necrotic cell death through different pathways, including membrane breakdown, cytoskeletal alterations and nitric-oxide-derived free radicals [Coyle and Puttfarcken 1993]. Glutamate can also trigger apoptosis [Kure et al. 1991], a gradual process of cell elimination resulting from the activation of cell death programs, characterized by membrane blabbing, compacting of organelles and chromatin condensation. An alternative mode of toxicity is based on the ability of glutamate to induce the formation of reactive oxygen species (ROS) in neuronal cells by a mechanism which does not involve the activation of glutamate receptors. In this case, glutamate inhibits the uptake of cystine, which is required for the intracellular synthesis of glutathione. The diminished availability of cystine causes a reduction in glutathione levels, increased formation of ROS and, ultimately, cell death [Murphy et al. 1989]. Interestingly, cell death

induced by glutamate via this mechanism evinces the morphological characteristics of both apoptosis and necrosis [Tan et al. 1998].

Excitotoxicity can be the direct result of excessive stimulation of the NMDA receptor, due to the increased levels or decreased removal of glutamate from the synaptic cleft. Direct excitotoxicity was initially proposed as a causative factor in the pathogenesis of neurodegenerative disorders. However, it soon became evident that a direct action of glutamate is likely to play a role in acute neurological disorders such as hypoxic/ischemic brain damage, but not in chronic disorders such as Parkinson's disease. Substantial increases in extracellular glutamate in fact occur in hypoxic/ischemic damage [Rothman and Olney 1986], but not in Parkinson's disease.

Glutamate can also be indirectly toxic. Under normal conditions, extracellular Mg^{2+} blocks the ion channel associated with the NMDA receptor [Mayer et al. 1984]. This blockade, which prevents the influx of Ca^{2+} in the presence of physiological concentrations of glutamate, is voltage-dependent. Thus, if a neuron is depolarized, the Mg^{2+} block is relieved and the binding of glutamate leads to a large Ca^{2+} influx. The maintenance of membrane polarity is a process requiring continuous energy supplementation. Consequently, an impaired mitochondrial function causes depolarization [Erecińska and Dagani 1990]. If a cell is depolarized by such a bioenergetic deficit, even non-toxic levels of glutamate ultimately become lethal [Novelli et al. 1988]. This observation has led to the formulation of the "indirect excitotoxic hypothesis" [Albin and Greenamyre 1992, Beal et al. 1993b]. Accordingly, any process which impairs the ability of a neuron to maintain the normal membrane potential enhances its vulnerability to the toxic effects of glutamate. Substantial experimental evidence has already accumulated to support this hypothesis, showing that inhibition of mitochondrial respiration – both in vitro and in vivo – causes excitotoxic lesions. The excitotoxic origin of these lesions is confirmed by the fact that NMDA antagonists prevent them [Greene and Greenamyre 1996].

The NMDA-receptor-dependent Ca^{2+} influx stimulates neuronal nitric oxide synthase (NOS, EC 1.14.13.39) and increases the production of nitric oxide (NO), which stimulates guanylyl cyclase to form cGMP (Fig. 3a) [Garthwaite and Boulton 1995]. NO stimulates glutamate release and inhibits glutamate reuptake, which effects elicit more NMDA receptor stimulation and more NO formation [Strijbos et al. 1996]. On the other hand, NO can nitrosylate the receptor and thus act as a feedback inhibitor of the NMDA receptor function [Choi et al. 2000].

NO is a paramagnetic, diatomic radical. It and its congeners are both neurotoxic and neuroprotective [Lipton 1999] NO has been shown to regulate an ever-growing list of biological processes. While NO normally functions as a physiological modulator of the cerebral blood flow and as a neuronal mediator, it is in excess neurotoxic. By virtue of being a free gas, the highly reactive NO can diffuse to millions of cells within its short biological half-life. Under pathological conditions associated with excitotoxicity, NO is recognized as a major mediator of neuronal death [Snyder 1993]. However, the neuroprotective or neurotoxic roles of NO depend on its redox state, local microenvironment and pH.

In many instances NO mediates its biological effects by activating guanylyl cyclase and increasing cyclic GMP synthesis from GTP. However, the list of effects of NO which are independent of cyclic GMP is also growing at a rapid rate. For example, NO can interact with transition metals such as iron, thiol groups,

other free radicals, oxygen, superoxide anion, unsaturated fatty acids etc. Some of these reactions result in the oxidation of NO to nitrite and nitrate, which transformations terminate its effect, while other reactions can lead to an altered protein structure, function and/or catalytic capacity. These diverse effects of NO, either cGMP-dependent or –independent, can alter and regulate important physiological and biochemical events in cell regulation and function [Murad 1999]. Altered NO formation and functionality have been shown to play a major role in neuronal death in acute and chronic neuropathological conditions, including cerebral ischemia, traumatic brain injury, Alzheimer's disease, Parkinson's disease and Wernicke–Korsakoff's syndrome [Przedborski et al 1996, Pieper et al. 1999, Yew et al. 1999). Increased NO production has also been shown to be associated with certain other disorders involving less significant neuronal damage, for example hepatic encephalopathy (HE) and hyperammonemic syndromes [Rao et al. 1997, Hermenegildo et al. 1998, Muñoz 2000].

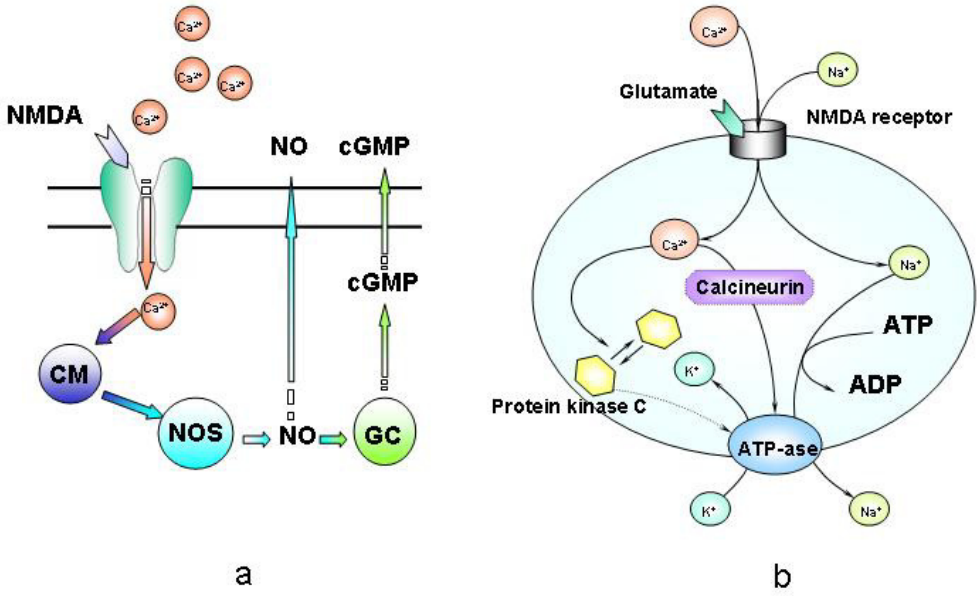

Fig. 3. The effects of NMDA receptor activation on NO and cGMP production (a) and on energy metabolism (b). From Monfort et al. (2002).

Ammonia neurotoxicity: the role of overactivation of NMDA receptor

Ammonia is a ubiquitous degradation product of proteins and other nitrogen-containing compounds. However, at high levels it is toxic, inducing functional disturbances of the central nervous system which can lead to coma and death. Ammonia toxicity was first described more than a century ago in the laboratory of Pavlov [Hahn et al. 1893]. More recently, it has been shown that acute intoxication with large doses of ammonia produces marked alterations in brain energy metabolism, including increased lactate, pyruvate and mitochondrial [NAD^+]/[NADH] and decreased cytosolic [NAD^+]/[NADH]. At a later stage, the

ATP content decreases [Schenker et al. 1967, Hindfelt and Siesjö 1971, Hawkins et al. 1973, Hindfelt et al. 1977, Kosenko et al. 1993, 1994].

Acute hyperammonemic episodes are associated with congenital disorders of the urea cycle, Reye syndrome and acute fulminate hepatic failure. Chronic alcoholism, viral hepatitis and overdoses of hepatotoxic drugs likewise cause liver dysfunction, which may lead to a neuropsychiatric disorder called hepatic encephalopathy. Although the exact molecular mechanisms responsible for the disturbances in brain functions and symptoms associated with HE are not clearly understood, an imbalance between excitatory and inhibitory neurotransmitters is thought to play a major role. Ammonia may alter neuronal functions by direct and indirect mechanisms [Butterworth 1993]. Ammonia disturbs both postsynaptic inhibition and excitatory neurotransmission in the brain and spinal cord by blocking chloride efflux from postsynaptic neurons, by reversible depression of synaptic transmission [Raabe 1989, 1990, Fan et al. 1990] and by membrane depolarization [Raabe 1990]. Neurotransmission can also be affected by impairment of the systems transporting amino acids across the blood-brain barrier. Hyperammonemia also alters the substrate levels for synthesis of the biogenic amines norepinephrine, dopamine and serotonin [Hawkins and Mans 1994]. Changes in water and electrolyte transport occur likewise during hyperammonemia [Cordoba and Blei 1996].

Acute ammonia toxicity has been proposed to be mediated by excessive activation of one class of ionotropic glutamate receptors, the NMDA receptors. Extracellular glutamate increases in the brain in acute ammonia intoxication [Marcaida et al. 1992, Hermenegildo et al. 1996]. However, the increase in glutamate occurs later than activation of NMDA receptors and is prevented by the NMDA receptor antagonist dizocilpine [Hermenegildo et al. 2000]. This would indicate that the ammonia-induced increase in extracellular glutamate is a consequence, not a cause of NMDA receptor activation. On the other hand, membrane depolarization ameliorates NMDA receptor activation. The ion channel in the NMDA receptor complex is modulated by Mg^{2+} in a voltage-dependent manner [Mayer et al. 1984]. Upon depolarization, the Mg^{2+} block is relieved and the NMDA receptor can then be activated by the physiologically relevant extracellular concentration of glutamate. Activation of the NMDA receptors has several consequences. The entry of Na^{+} is fomented into postsynaptic neurons. In order to maintain Na^{+} homeostasis, Na^{+} entering through the NMDA channel must be extruded from the neuron. The concomitant increase in intracellular Ca^{2+} activates calcineurin, which dephosphorylates and activates Na^{+}, K^{+}-ATPase. This allows a subsequent extrusion of the excess of Na^{+}, consuming cellular stores of ATP (Fig. 3b). The ammonia-induced increase in Na^{+}, K^{+}-ATPase activity is also completely prevented by pretreatment with NMDA receptor antagonists [Kosenko et al. 1994, Monfort et al. 2002]. A large part of the Ca^{2+} entering the cells is sequestered into mitochondria. Acute ammonia intoxication reduces the activity of succinate dehydrogenase (EC 1.3.99.1) and 2-oxoglutarate dehydrogenase (EC 1.2.4.2) in mitochondria [Kosenko et al. 1997a]. The mitochondrial Ca^{2+} buffering capacity and Ca^{2+} uptake rates are reduced and spontaneous Ca^{2+} release increased.

Altered mitochondrial Ca^{2+} homeostasis results in impairment in the enzyme activities of the respiratory chain, which may lead to a decreased synthesis of ATP and an increased formation of free radicals [Kosenko et al. 2000]. Intraperitoneal injections of large doses of ammonia increase (more than twofold) the formation of superoxide radicals in brain mitochondria. Moreover, the activities of glutathione peroxidase

(EC 1.11.1.9), superoxide dismutase (EC 1.15.1.1) and catalase (EC 1.11.1.6) decrease in the brain of rats injected with ammonia [Kosenko et al. 1997b]. The glutathione content is also reduced by 50% and lipid peroxidation increased [Kosenko et al. 1999]. Blockage of NMDA receptors with dizocilpine prevents the ammonia-induced effects in the activities of antioxidant enzymes, glutathione content, lipid peroxidation and superoxide formation, indicating that all these effects of ammonia on mitochondrial parameters result from the preceding activation of NMDA receptors.

One of the consequences of ATP depletion is the reversal of glutamate transporter functions [Sanchez-Prieto and Gonzalez 1988, Mald and Burgesser 1993]. Instead of taking up glutamate, the transporters release it from the cytosol into the extracellular space, increasing extracellular glutamate. Activation of NMDA receptors activates neuronal NOS and increases the formation of NO. NO reduces the activity of glutamine synthetase, which catalyzes the reaction between ammonia and glutamate forming glutamine [Olde Damnik et al. 2002, Suárez et al. 2002], thus reducing the elimination rate of ammonia in the brain. Subsequent generation of free radicals in both NO-dependent and NO-independent manners may then underlie acute ammonia neurotoxicity.

Of the various neurotransmitter systems, the GABAergic and dopaminergic systems have attracted interest in that hyperammonemias are associated with moderate to severe motor disturbances. Ammonia at pathophysiologically relevant concentrations enhances GABAergic neurotransmission by several mechanisms. These include increases in the levels of GABA in the synaptic cleft due to enhanced release [Wysmyk and Oja 1992] and in the concentrations of endogenous benzodiazepine receptor agonists [Basile 2002]. Excessively enhanced GABAergic neurotransmission impairs motor functions and lowers the level of consciousness, two cardinal clinical features in HE. Changes in dopaminergic neurotransmission also evoke motor dysfunction in a number of neurological diseases. There is some evidence available of changes in the properties of dopamine receptors, activities of dopamine-metabolizing enzymes and concentrations of dopamine metabolites in the brain in subacute or chronic HE [Basile et al. 1991, Jalan and Hayes 1997].

Dopamine release is under strong control of glutamate input in the striatum. Overstimulation of the presynaptic NMDA and non-NMDA receptors may evoke tonic dopamine release [Moghaddam et al. 1990, Jin 1997]. The induced release can occur both with and without the involvement of generation of NO and/or free radicals [Chéramy et al. 1998]. Additional factors to be taken into consideration, depending on the activation of glutamate receptors, include the increase in Ca^{2+} and Na^{+} influx into dopaminergic neurons, disturbance in Ca^{2+} homeostasis in mitochondria and impairment of energy metabolism. It has been suggested that the Ca^{2+}-dependent component in the vesicular release of dopamine is important at high doses of ammonia [Erecińska et al. 1987, Borkowska et al. 2000]. The characteristics of dopamine release upon exposure to pathologically relevant ammonia concentrations are similar to the features of dopamine release elicited by amphetamine administration. Erecińska and her associates [1987] have also shown that one component in dopamine release from synaptosomes is due to the rapid alkalinization of neurotransmitter storage granules and the collapse of the transgranular pH gradient. A linear relationship between the ammonia-induced decrease in transvesicular pH gradient and the stimulation of dopamine release rate indicates that the transfer of dopamine to the cytoplasma and its subsequent leakage into the external

environment are triggered by an alkalinization of the neurotransmitter storage compartment. Excessive dopamine release must be taken into account as an additional factor in the mechanisms of ammonia neurotoxicity. An excess of dopamine has also been found to be toxic to cells both in vivo and in vitro (Figs 2 and 4) [Cadet and Brannock 1998, Stokes et al. 1999].

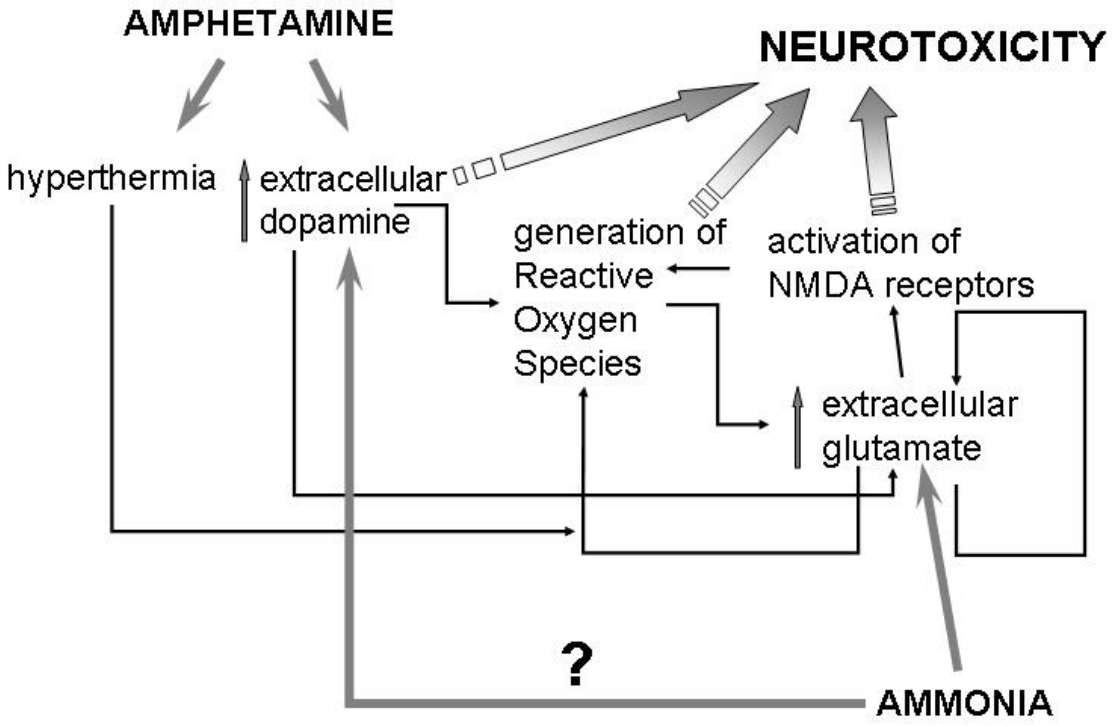

Fig. 4. The common mechanisms of amphetamine- and ammonia-induced toxicity.

Reactive oxygen species and the toxic potential of dopamine

Reactive oxygen species are continuously formed in the body as byproducts of numerous biochemical reactions. Due to the presence of an unpaired electron, ROS are extremely unstable but tend to be stabilized particularly by oxidizing cellular elements, membrane lipids and nucleic acids. Such oxidative reactions account for the potential toxicity of ROS [Ebadi et al. 1996].

The role of dopamine in the brain is not restricted to its actions as a neurotransmitter. The analysis of possible mechanisms of neuronal damage attributable to amphetamine and methamphetamine evolves from "dopaminergic neurotoxicity". Dopamine elicits its toxic effects in several ways (Fig. 5). First, it possesses a strong potential for free radical generation and exhibits genotoxicity and cytotoxicity in vitro and in vivo. Second, the activation of dopamine D_1 receptors results in a prolonged opening of Ca^{2+} which potentiates the effects of NMDA receptor activation. The cell swelling consequent upon the overstimulation of NMDA

receptors is amplified by D_1 receptor co-activation and suppression of D_2 receptors [Dodt et al. 1993]. There obtains an equilibrium in the excitation of dopaminergic D_1 and D_2 receptors at the physiological levels of extracellular dopamine. However, at physiologically irrelevant high concentrations of dopamine, e.g. due to amphetamine administration, this balance is perturbed. Dopamine may also potentiate NMDA receptor activation, since it behaves as a reverse inhibitor of mitochondrial respiration.

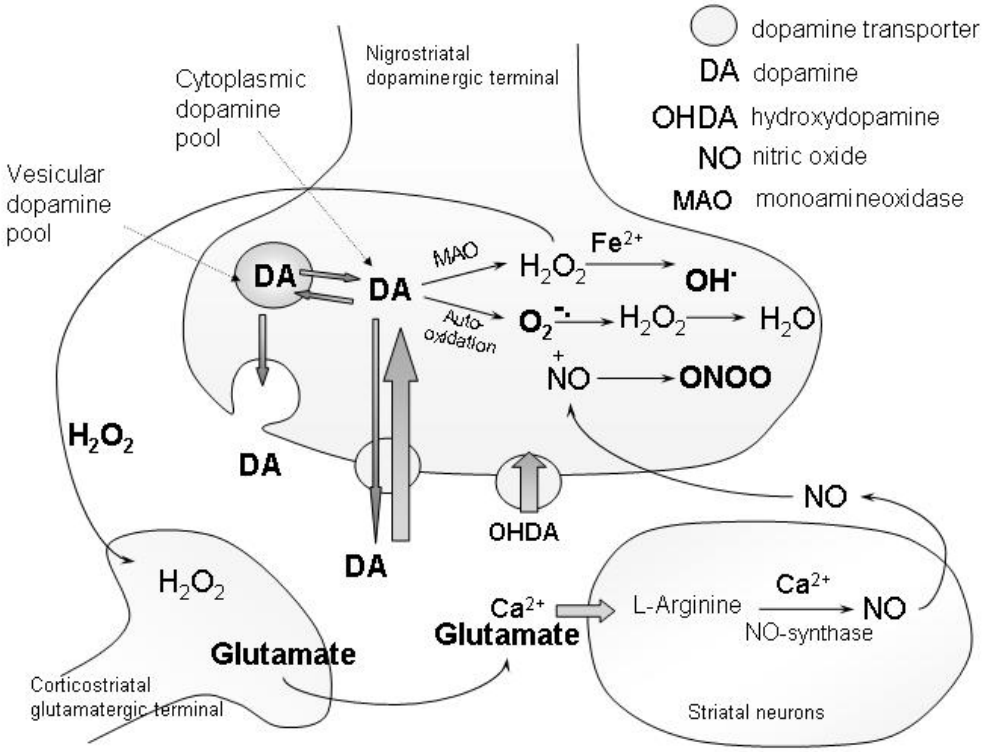

Fig. 5. Dopamine transporter as a trigger of oxidative stress. From Cadet and Brannock (1998).

Free radicals and the brain dopamine systems. Recent progress in cellular and molecular neurobiology has identified the essential role of free radicals in brain functions. It has become manifest that free radicals are intimately involved in the cascade of events leading to cell death after exposure to glutamate agonists. However, the pathways in this reactive cascade are as yet incompletely understood. The recent cloning of a number of cell death-related genes promises to provide a strong boost towards further elucidation of the role of oxidative stress in neurodegenerative disorders. Free radicals are a molecular species which contain unpaired electrons. They are highly reactive and damage nucleic acids, lipids and proteins. Damaging oxyradical species can originate from both endogenous and exogenous sources. The latter include xenobiotics, radiation and chemical toxins, while the endogenous sources are mitochondrial respiration, cytochrome P-450 reactions, phagocytic oxidative bursts and peroxisomal leakage.

Aerobic organisms take up oxygen, which is used by the mithochondria in a process which produces water. However, the process also results in the formation of superoxide radicals ($O_2.^-$), hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH^-) according to the following scenario:

$O_2 + e \Rightarrow O_2.^-$

$O_2.^- + e \Rightarrow H_2O_2$

$H_2O_2 + e \Rightarrow {}^{\cdot}OH + OH^-$

${}^{\cdot}OH + OH^- + e \Rightarrow H_2O + O_2$

The actions of enzymes such as amino acid oxidase (EC 1.4.3.2), cytochrome oxidase (EC 1.9.3.1), monoamine oxidase, xantine oxidase (EC 1.1.3.22), and aldehyde oxidase (EC 1.2.3.1) also generate superoxide. Auto-oxidation of catecholamines, leukoflavins, tetrahydropterins, hydroquinones and ferrodoxins also produce $O_2.^-$ [Fridovich 1983, 1986]. Superoxide is also formed during reperfusion subsequent to ischemia. It has recently been shown that stimulation of glutamate receptors and nitric oxide synthase causes production of superoxide radicals. The superoxide radicals are converted to H_2O_2 by superoxide dismutase (SOD). H_2O_2 is also formed in the reactions catalyzed by amino acid oxidase and monoamine oxidase. It can also be produced during auto-oxidation of ascorbate and catecholamines [Chance et al. 1979, Stokes, 1999]. H_2O_2 is not a free radical, since it does not contain unpaired electrons. However, it can interact with transition metals to form highly reactive hydroxyl radicals, which are thought to be the main cause of H_2O_2-induced toxicity [Mellow-Filho and Meneghini 1984]: thus

$H_2O_2 + Fe^{2+} \Rightarrow {}^{\cdot}OH + OH^- + Fe^{3+}$.

The hydroxyl radicals are highly reactive and can damage sugars, amino acids, phospholipids and nucleic acids. They can start the process of membrane lipid peroxidation with subsequent membrane damage. Membrane dysfunction increases its permeability to ions and water. Accumulation of these substances causes cell swelling, activation of proteases and initiation of the cell death cascade. NO produced by NOS is a ubiquitous generator of free radicals [Moncada et al. 1991, Nathan 1992]. NO can form peroxynitrite ($ONOO^-$) by interacting with superoxide radicals. In turn, $ONOO^-$ is a neurotoxin by means of its interaction with thiol groups and owing to its decomposition to OH^- radicals [Radi et al. 1991]. NO has been implicated in the toxic effects of glutamate in several in vitro models [Dawson et al. 1993, Lafon-Cazal et al. 1993]:

$O_2.^- + NO \Rightarrow ONOO^-$

$ONOO^- + H+ \Rightarrow ONOOH$

$ONOOH \Rightarrow NO_2 = OH^-$

Iron plays an important role in initiating and catalyzing reactions in the presence of oxygen [Halliwell and Gutteridge 1985]. At physiological pH, iron is bound to transferrin and lactoferrin. Under oxidative stress or other acute insults iron is released, causing exacerbation and propagation of the toxic injury. Other transition metals such as manganese and copper may also participate, causing a pro-oxidant state in the brain.

In the central nervous system, catecholamines constitute an important source of free radical production. For example, the step catalyzed by monoamine oxidase during the metabolic breakdown of

dopamine, serotonin and norepinephrine produces H_2O_2 [Cohen 1987]. In addition, catecholamines can be auto-oxidized to form quinones in the following order of decreasing susceptibility: 6-hydroxydopamine ⇒ dopamine ⇒ norepinephrine ⇒ epinephrine [Graham 1978]. The rate of cyclization to less reactive leukochromes exhibits the reverse order. It is thought that, in addition to generating H_2O_2 or superoxide radicals, quinone byproducts might damage proteins via nucleophilic attacks on their side chains. The auto-oxidation of catecholamines is inhibited by ascorbic acid, dithiothreitol, glutathione, SOD and tetrahydrobiopterin. A number of monoaminergic toxins, including amphetamine analogs, have been shown to exert their toxic effects via production of oxygen-based radicals.

Neuropharmacology of amphetamine and sydnocarb

Psychomotor stimulants such as amphetamine were once in general clinical use in the treatment of psychiatric disorders and physical and mental fatigue. Further interest in these compounds was engendered by the discovery that amphetamine interacts with the catecholamine system in the brain and produces wide-ranging effects on behavior [Seiden and Sabol 1993]. It is generally accepted that the dopaminergic system is the main target of amphetamine actions. Amphetamine and its congeners act as indirect dopaminomimetics. Stimulation of both types of dopamine receptors by the excessive release of dopamine results in a significant increase in the level of locomotor activity [Sealfon 2000].

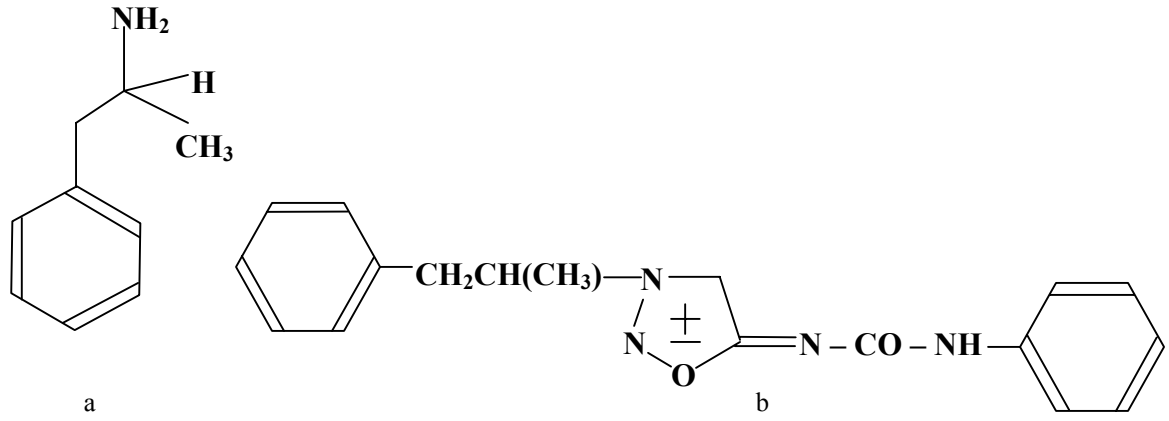

Fig. 6. Structural formulae of d-amphetamine (a) and sydnocarb (b).

Amphetamine was first synthesized in 1887 (Fig. 6a). Its respiratory and stimulatory effects were described in 1933. In 1935 its stimulatory actions were found to be useful in the treatment of narcolepsy. Amphetamine has been used for treatment of obesity, attention deficits, hyperactivity disorders and occasionally of Parkinson's disease. Amphetamine causes euphoria in humans, which frequently leads to its habitual use or abuse. With repeated amphetamine intake, tolerance to its effects on mood develops and the dose escalates. Large doses of amphetamine can induce a psychotic state resembling paranoid schizophrenia. The effects of amphetamine in humans have close parallels in animals. At low doses, amphetamine increases

stereotypic locomotor activity and at high doses species-specific stereotypies. Amphetamine interferes with the intake of both food and water, which would suggest its participation in the mechanisms of reward behavior. This diversity of amphetamine actions on behavior has led to its widespread clinical and experimental use, though it is no longer frequently administered in medical practice to counteract sedation induced by depressants. Profound neurotoxic effects and the tolerance and dependence developing with repeated administrations are the primary reasons for its reduced clinical use. Nevertheless, amphetamines continue to be widely abused. For example, the illicit use of methamphetamine increased more than twofold during the 1990s [Johnston et al. 1997].

The release, uptake and enzymatic inactivation of neurotransmitters are three fundamental processes to be taken into account when analyzing the mechanisms of action of amphetamine at neuronal level. Under normal physiological conditions the amount of dopamine in the synapse is determined by exocytotic release followed by uptake and metabolic degradation. In the presence of amphetamine, the synaptic concentration of dopamine is determined by the transporter-mediated release and inhibition of dopamine uptake. Both the release-enhancing and uptake-inhibiting actions of amphetamine are mediated by the dopamine transporter (Heikkilä et al. 1975, Raiteri et al. 1979). In addition, amphetamine releases dopamine from vesicular storages. Amphetamine may thus affect both transporting systems: DAT in the synaptic plasma membrane and VMAT-2 in the synaptic vesicles [Miller et al. 1999]. However, DAT appears to play the critical role in the amphetamine-induced dopamine release. Amphetamine also inhibits MAO activity [Mantle et al. 1976], being considered to be a non-competitive MAO inhibitor [Zeller et al. 1959]. Release and uptake can be discriminated using the microdialysis approach. If the neuronal firing is depressed, the amount of extracellular dopamine is determined by the blockade of uptake. For example, in the presence of tetrodotoxin (a fast Na^+ channel blocker) the amphetamine-induced release of dopamine has been 66% of the amphetamine-induced release without tetrodotoxin [Westerink et al. 1987].

Fisher and Cho [1979] and Liang and Rutledge [1982] proposed the so-called exchange diffusion model. They assume that amphetamine attaches to DAT outside the cell and the transporter protein “moves” toward the intracellular space where it exchanges amphetamine for dopamine. Once inside the synaptic terminal, amphetamine interacts with VMAT-2 and as a weak base evokes alkalinization of vesicular media. However, other factors such as lipophility, binding to intravesicular constituents and interaction with DAT may also be responsible for alkalinization [Fisher and Cho 1979, Liang and Rutledge 1982, Sulzer and Rayport 1990]. The differential dose theory unites the above exchange diffusion and vesicular alkalinization mechanisms. At low doses (less than 5 mg/kg) amphetamine releases dopamine from the cytoplasmic stores, while at higher doses dopamine is released from both cytoplasmic and vesicular pools [Liang and Rutledge 1982, Zetterstrom et al. 1986]. The increase in extracellular dopamine is accompanied on the behavioral level by neurotoxic consequences: stereotypic locomotor activity and psychosis (in humans). Considerable efforts have been made to understand the mechanisms underlying amphetamine-induced stereotypies. At low doses, amphetamine causes an increase in all types of stereotypic behavior. With increasing doses of the drug, behavioral sequences of briefer duration are elicited and behavioral sequences of longer duration (such as locomotion) are truncated. At high doses amphetamine initiates many types of behavior, but only those of

short duration such as licking and gnawing are completed [Lyon and Robbins 1975, Rebec and Bashore 1984].

The neurotoxicity of amphetamine is the result of catecholamine depletion. A one-day acute toxic dose of amphetamine already depletes dopamine and serotonin from synaptic terminals. Repeated systemic administration of amphetamine or methamphetamine has led to monoamine depletion in the rat and monkey striatum, frontal cortex and amygdala [Ricaurte et al. 1980, 1982], to a decline in the number of high-affinity uptake of sites for dopamine and to inhibition of tyrosine and tryptophan hydroxylases in the rat striatum and hippocampus [Fibiger and McGeer 1971, Hotchkiss and Gibb 1980, Ricaurte et al. 1980, Wagner et al. 1980]. One of the signs of amphetamine neurotoxicity is stereotypic behavior in rodents. A good correlation has been reported between the toxic effects of psychostimulant drugs and this kind of behavior [Wallace et al. 1999].

Methamphetamine can likewise cause neurotoxic damage to the monoaminergic system in rats, mice and non-human primates. Several functional markers in dopamine and serotonin terminals are severely affected by both drugs. These include the neostriatal dopamine levels, striatal hydroxylase activity and dopamine uptake sites [Hotchkiss and Gibb 1980, Ricaurte et al. 1980, 1982, Nakayama et al. 1992]. Although the cellular and molecular events involved in amphetamine-induced neurotoxicity remain to be elucidated, a number of investigators have hinted at a role of oxide-based free radicals in the action of these drugs. For example, administration of antioxidants such as ascorbic acid or vitamin E has attenuated methamphetamine-induced neurotoxicity, whereas inhibition of superoxide dismutase by diethyldithiocarbamate increases the neurotoxicity of methamphetamine [Wagner et al. 1985, Devito and Wagner 1989, Shankaran et al. 2001]. One current theory is that an excessive release of dopamine triggers an accumulation of reactive dopamine metabolites and overproduction of hydroxyl radicals. Dopamine can be toxic in vitro and in vivo [Graham et al. 1978, Hastings et al. 1996, McLaughlin et al. 1998]. Dopamine toxicity in vivo is associated with its non-enzymatic and enzymatic degradation. Pharmacological interventions which lower the striatal dopamine content have proved protective against methamphetamine-induced toxicity [Gibb and Kogan 1979, Schmidt et al. 1985, Johnson et al. 1987]. It has also been suggested that the magnitude of dopamine release after methamphetamine exposure is predictive of the long-term toxicity [O`Dell et al. 1991].

However, an excessive accumulation of extracellular dopamine may be not accompanied by neuronal damage. Microdialysis experiments have shown that the toxicity of methamphetamine is reduced at low environmental temperature (5°C), even though dopamine release is not changed [LaVoie and Hastings 1999]. In addition, it has been established in experiments with VMAT2 knock-out mice that methamphetamine-induced neurotoxicity depends on the level of cytosolic dopamine [Fumagalli et al. 1999, Miller et al. 1999]. These findings call in question the view that the release of endogenous dopamine plays a primary role in amphetamine neurotoxicity.

Systemic administration of psychostimulants increases the core body temperature and this effect would also seem to be an important factor [Askew 1962, Bowyer et al. 1992, Ali et al. 1994, Colado et al. 1998]. Glutamate release and hyperthermia contribute to metabolic and oxidative stress and both may be key mediators in the toxic effects of amphetamines [Cadet and Brannock 1998, Burrows et al. 2000a]. It has been

suggested that the intracellular oxidation of dopamine facilitated by hyperthermia increases the susceptibility of dopaminergic neurons to oxidative stress [LaVoie and Hastings 1999]. NMDA receptor antagonists counteract the elevation in temperature and attenuate methamphetamine-induced toxicity in mice [Sonsalla et al. 1991, Weihmuller et al. 1992, Bowyer et al. 1994, Albers and Sonsalla 1995, Farfel and Seiden 1995]. However, the degree of suppression of methamphetamine-induced hyperthermia does not correlate with the extent of protection afforded by pharmacological treatment [Albers and Sonsalla 1995]. Methamphetamine-induced neurotoxicity can occur in the absence of any substantial changes in body temperature [Miller and O`Callaghan 1994, Albers and Sonsalla 1995].

Energy consumption in the brain is increased after systemic methamphetamine administration, as evidenced by an immediate and sustained increase in extracellular lactate in the striatum. ATP is depleted in the brain regions susceptible to amphetamines [Chan et al. 1994, Stephans et al. 1998]. The activation of NMDA receptors by glutamate activates NOS [Lizasoain et al. 1996]. The subsequent enhanced generation of NO is followed by the formation of ROS and mitochondrial dysfunction due to a direct inhibition of complex IV in the electron transport chain, cytochrome c oxidase [Cleeter et al. 1994, Lizasoain et al. 1996]. On the other hand, under experimentally induced metabolic stress (e.g. glucose deprivation), NMDA receptors are activated more readily and even normally non-toxic concentrations of glutamate can produce NMDA-receptor-mediated toxicity [Zeevalk and Nicklas 1992, Zeevalk et al. 1995]. Hyperthermia can foment enzymatic and non-enzymatic degradation of dopamine and excitatory amino acid-dependent formation of ROS. Indeed, when the incubation temperature is lowered in in vitro toxicity models (e.g. cortical cultures of the chick retina), damage produced by excitotoxins or oxygen-glucose deprivation is reduced [Zeevalk and Nicklas 1993, Bruno et al. 1994]. In addition, hyperthermia increases the toxic effects of locally perfused glutamate [Ferger et al. 1998].

Amphetamine enters the synaptic terminals/neurons via the membrane transporter of dopamine or serotonin and displaces both vesicular and intracellular dopamine and serotonin. These displaced amines are oxidized (by MAO and auto-oxidation) to ROS [Seiden and Ricaurte 1987, Cubells et al. 1994], with further production of ROS via H_2O_2 and NO [Bowyer et al. 1995], this resulting in necrotic cell death. However, other mechanisms have since been recognized, including glutamate- [Lipton and Rosenberg 1994, Yamamoto and Zhu 1998] and peroxynitrite-mediated [Bolanos et al. 1997] neurotoxicity. The glutamate receptor blockers attenuate the toxic effects of methamphetamine in vivo [Sonsalla et al. 1991, Sonsalla, 1995]. Both reactive oxygen and nitrogen species may be involved. Dizocilpine prevents the NO generation induced by amphetamine in the rat striatum (Kraus et al. 2002). Amphetamine may also exert its adrenomimetic effects and produce constriction of blood vessels and ischemia. All this, in turn, increases the vulnerability of neurons to any damaging agent [Del Arco et al. 1999]. It has also been shown that amphetamine, due to its lipophility, can diffuse through cell membranes, including intracellular organelles, e.g. mitochondria, where it dissipates the electrochemical gradient. It is thus possible that amphetamine kills neurons not only by the direct production of free radicals but also by triggering a mitochondrial-dependent induction of apoptotic cascades [Lemasters et al. 1999]. It would therefore appear that amphetamine can kill neurons by multiple mechanisms over an extended time scale.

The phenomenon of amphetamine neurotoxicity involves here degeneration of synaptic terminals. After a systemic administration of amphetamine or methamphetamine, depletion of dopamine (and/or serotonin), loss of DAT and decrease in tyrosine (or tryptophan) hydroxylase activity occur in the brain structures which correspond to the projections of midbrain monoaminergic neurons (striatum, nucleus accumbens). Cell loss in the brains of rodents and non-human primates is possible, but it is not regarded as a critical marker. Pharmacological intervention or other manipulations (lowering of ambient temperature, cooling some animal body parts, isolation, and restriction of movements) which prevent the loss in striatal dopamine and/or other parameters of neurotoxicity are neuroprotective.

Sydnocarb, 3-(β-phenylisopropyl)-*N*-phenylcarbamoylsydnonimine, molecular weight 322 kDa, synonyms: mesocarb and mesocarbum (Fig. 6b), was synthesized in the Russian Center for Drug Chemistry (Moscow) [Mashkovsky et al. 1971]. Sydnocarb has a phenylisopropyl group and thus shares some chemical features with amphetamine. However, unlike amphetamine, sydnocarb has no free amino group; the corresponding nitrogen atom in sydnocarb is a part of heterocyclic group sydnonimine.

Sydnocarb was introduced for clinical practice as a drug effective in the treatment of all forms of neurasthenia, apathy, adynamia and some forms of depression. This psychostimulant is now used in clinical practice in Russia as primary and adjunct therapy for psychiatric disorders, including schizophrenia, depression, narcolepsy, attention deficit hyperactivity disorders in children, and asthenic syndromes of different etiology [Altshuler et al. 1973, Krasov 1988]. Animal studies and clinical trials have shown that sydnocarb may be effective in reducing the myorelaxant and hypnotic effects of benzodiazepines while not affecting their tranquilizing action. Sydnocarb also ameliorates the asthenic effects of neuroleptics and does not reduce they clinical effectiveness [Voronina and Tozhanova 1981, Valueva and Tozhanova 1982].

The efficacy of sydnocarb in the treatment of alcohol abusers has also been shown. The drug corrects asthenic and depressive symptoms related to chronic alcohol consumption and counteracts the abstinence syndrome [Rudenko and Altshuler 1979]. The stimulating profile of sydnocarb in humans combined with reports of its safety and mild euphoria have called attention to the potential use of sydnocarb in treatment of stimulant drug abuse. Several important features of sydnocarb which distinguish the drug from d-amphetamine have been demonstrated in clinical trials, for example the gradual development of the mild stimulatory effect, long-lasting action and lack of peripheral sympathomimetic effects (tachycardia, increase in peripheral blood pressure), moderate euphoria and motor excitation. There is no pronounced weakness and soporic effect after a period of stimulation [Zapletálek et al. 1974, Baturin 1977, Rudenko and Altshuler 1979, Ganiev et al. 1987]. Sydnocarb has also been characterized as a stimulant with low addiction risk. Neither behavioural nor physical dependence on sydnocarb has been noted (Mashkovsky et al. 1971, Rudenko and Altshuler 1978).

The exact mechanisms by which sydnocarb elicits psychostimulant effects remain however uncertain. Like other indirect dopaminergic antagonists, sydnocarb evinces a pharmacological profile reminiscent of other stimulants. Data from animal studies indicate a possible involvement of the brain dopaminergic system [Altshuler et al. 1976b, Erdo et al. 1981, Gainetdinov et al. 1997]. Sydnocarb elicits locomotor hyperactivity and stereotyped behavior in rats and mice in a reserpine-sensitive manner [Rudenko

and Altshuler 1979], inhibits the reuptake of dopamine and norepinephrine by rat brain synaptosomes [Erdo et al. 1981], and increases the extracellular concentration of dopamine in the striatum of freely moving rats [Gainetdinov et al. 1997].

Although the available information is limited, sydnocarb appears to differ from d-amphetamine with respect to its mechanism of action. Early neurochemical findings raised the possibility that sydnocarb acts by blocking the uptake of dopamine into the presynaptic neurons. The affinity of sydnocarb for the dopamine uptake system is higher than that of amphetamine [Erdo et al. 1981]. Unlike amphetamine, sydnocarb releases dopamine in a tetrodotoxin-sensitive and Ca^{2+}-dependent manner. It does not lower the extracellular levels of the dopamine metabolites DOPAC and homovanillic acid. It has been suggested that a likely mechanism of sydnocarb action is blockade of dopamine uptake after its physiologically controlled release via a calcium-dependent vesicular process [Gainetdinov et al. 1997].

No significant toxic episodes have been noted with sydnocarb. Compared to the stimulatory effects of amphetamines, the activating effects of sydnocarb develop more gradually, last longer and are to a lesser degree accompanied by stereotypy. In a recent neurochemical study, sydnocarb was shown to display psychomotor stimulatory effects in mice which are shared by methamphetamine, while demonstrating a lower potency and toxicity. When the behavioral and toxic effects are compared, sydnocarb is less neurotoxic than methamphetamine. It produces a slow and gradual increase in the parameters indicative of dopaminergic dysfunction when administered at a dose of 30 mg/kg. The interaction of sydnocarb with cocaine merits special attention. The convulsive effect of cocaine (55 mg/kg) was significantly enhanced by the co-administration of nontoxic doses of methamphetamine (10 mg/kg) but not of sydnocarb (100 mg/kg) [Witkin et al. 1999].

Sydnocarb and amphetamine possess fairly similar pharmacokinetic features. They are well absorbed in the intestine when administered *per os* and achieve maximal plasma concentration within 2-4 hours. The drugs do not undergo significant biotransformation and 30-50 per cent of the dose is excreted unchanged. In the case of intravenous, intramuscular and intraperitoneal administrations the bio-accessibility is close to 100 %. The maximum plasma concentration is reached 30-60 min after the infusion. The drugs penetrate readily through the hematoencephalic barrier and the peak brain concentrations coincide with the maximum in the plasma concentrations. Both drugs are relatively long retained in the body, but there is a difference in the half-life time ($t_{1/2}$), i.e. 12-14 hours for amphetamine and 18-20 hours for sydnocarb. in the light of the general similarity of pharmacokinetics, the differences in their pharmacological effects seem to depend on differences in their neurochemical actions.

Taurine

Taurine (2-aminoethanesulfonic acid) is a component of bile salts and a ubiquitous constituent of all animal cells. In the past, the biological role of taurine as an end product of methionine metabolism and its conjugation with bile acids in the liver was considered relatively trivial. However, the physiological actions of

taurine have received considerably more attention since the reports of Curtis and Watkins in 1960 and 1961. The next investigations placed high emphasis on the significance of taurine in brain functions [Oja and Piha 1966]. Groups under Hayes [1975] and Pion [1987] have shown that cats fed a taurine-deficient diet develop central retinal degeneration and cardiomyopathy. Now, taurine has been proposed to be involved in a wide range of important physiological functions [Oja and Saransaari 1996]. It is one of the most abundant free amino acids in the brain in most mammalian species, only glutamate being generally present at higher concentrations in adults.

Taurine serves as a trophic factor in the development of the central nervous system, at least in some species [Sturman and Gaull 1975, Sturman et al. 1985b, 1986, Palackal et al. 1991]. Moreover, during ontogenic development the concentration of taurine in the rodent central nervous system even exceeds that of glutamate [Oja and Kontro 1983]. Animals are able to synthesize taurine from the sulfur-containing amino acids, methionine and cysteine, but they lack the enzymatic machinery for its breakdown [Huxtable 1986]. However, this simple sulfonic acid has been shown to be an essential nutrient for cats, and probably also for primates, at least during development [Sturman 1993]. When cats are subjected to taurine deficiency during development, the mitotic activity of granule cells in the external granule cell layer in the cerebellum persists longer and cell migration to the inner layer is delayed [Sturman et al. 1985a]. It is now widely accepted that taurine plays an important role in maintaining the integrity of the retina and the viability of photoreceptor cells, since the concentration in the retina decreases in cats in the absence of dietary taurine, followed by morphological degradation of the retina and tapetum lucidum. Defects have also been observed in the electroretinogram and visual evoked potentials in cats and monkeys, leading to degeneration of the photoreceptors and eventual blindness [Hayes et al. 1975, Sturman et al. 1986]. Such observations have given the impetus to taurine supplementation to infant formulas derived from taurine-poor cow milk.

In marine animals taurine acts as an osmoregulator [Simpson et al. 1959], and this function may also be of significance in the central nervous system of terrestrial species [Walz and Allen 1987, Solis et al. 1988a, Wade et al. 1988]. Taurine induces hyperpolarization and inhibits firing of central neurons and has been thought to act as a modulator of synaptic activity in the brain [Oja et al. 1977, Kuriyama 1980, Oja and Kontro 1983, Saransaari and Oja 1992]. The maintenance of the integrity of membranes [Pasantes-Morales and Cruz 1985, Moran et al. 1988], regulation of Ca^{2+} binding and transport [Lazarewicz et al. 1985, Lombardini 1985] and transmembrane Cl^- flux [Taber et al. 1986] are also probable important functional features of taurine in the brain.

The taurine molecule at physiologically relevant pH is characterized by a high polarity which apparently limits its penetration through biological membranes. The uptake of taurine does not vary much from one brain area to another and shows no clear correlation to the regional distribution of endogenous taurine. The release of taurine from neural tissue could be mediated by several possible mechanisms, including simple physical diffusion, penetration through membrane ion channels, carrier-mediated transport and exocytosis of vesicular taurine from nerve endings. A salient feature of taurine release from all preparations of the nervous system in vitro and in the brain in vivo is a slow time course [Saransaari and Oja 1992]. For instance, only one fourth of total taurine is spontaneously released from mouse cerebral cortical

slices into taurine-free medium during a 50-min superfusion [Kontro and Oja 1987b]. The release is fomented by extracellular taurine via homoexchange and by a number of structural analogs owing to heteroexchange. Taurine itself, hypotaurine, β-alanine, homotaurine, 2-guanidinoethanesulfonate, nipecotate, 2,4-diaminobutyrate and GABA are all able to elicit taurine release [Korpi et al. 1983, Kontro and Oja 1987b). Heteroexchange is also abolished in the absence of Na^+ [Saransaari and Oja 1999b]. These findings indicate the involvement of plasma membrane transport sites in the release process.

Depolarizing agents such as high extracellular K^+ [Korpi et al. 1981, Kontro and Oja 1987a], veratridine [Saransaari and Oja 1999a] and electrical pulses [Collins and Topiwala 1974, Bradford et al. 1976] evoke taurine release from brain slices, synaptosomal preparations and cultured neurons. Such depolarization-evoked release is apparently consistent with the exocytotic liberation of taurine from neural preparations, but results on the Ca^{2+} dependency of this stimulated release have been strikingly inconsistent [Saransaari and Oja 1992]. The release of taurine is controlled by endogenous glutamate [Segovia et al. 1997]. The agonists of glutamate receptors have also been shown to evoke taurine release from cerebral cortical and hippocampal slices [Saransaari and Oja 1991, Shibanoki et al. 1993, Saransaari and Oja 1997b, Bianchi et al. 2000]. On the other hand, it is well documented that taurine fluxes across brain cell membranes are driven by changes in external osmolality [Oja and Saransaari 1996]. Taurine release from cerebral cortical slices [Oja and Saransaari 1992a, b], cultured neurons [Schousboe et al. 1990], cultured astrocytes [Pasantes-Morales and Schousboe 1988, Kimelberg et al. 1990] and isolated synaptosomes [Sanchez Olea and Pasantes-Morales 1990] is enhanced in vitro by hypoosmolalic incubation media. Hypoosmotic solutions in brain microdialysis have likewise markedly increased the levels of extracellular taurine in vivo [Solis et al. 1988b]. The release elicited by hypoosmolality is probably mediated by diffusion through volume-sensitive anion channels [Pasantes-Morales et al. 1990, Jackson and Strange 1993] and does not involve carrier-mediated transport [Sanchez-Olea et al. 1991, Schousboe et al. 1991].

Taurine exerts a beneficial effect under a variety of cell-damaging conditions, but the mechanism of this protection it still unknown [Saransaari and Oja 2000]. The release of endogenous taurine is increased in models of ischemic injury, during hypoglycemia and hypoxia and upon exposure to free radicals and oxidative stress [Saransaari and Oja 2000]. The high tolerance of the eye lens to damage is also associated with a high level of taurine in this tissue [Devamanoharan et al. 1998]. Taurine protects neurons against excitotoxicity evoked by glutamate and its congeners [French et al. 1986, Tang et al. 1986, Trenkner 1990, Boldyrev et al. 1999]. However, at relatively low concentrations taurine may even potentiate excitotoxicity in cell cultures. The interaction of taurine with the GABAergic neurotransmitter system [Kontro and Oja 1987a, del Olmo et al. 2000, O`Byrne and Tipton 2000] may play a critical role in these anomalic effects on the toxic actions of glutamate. A high level of taurine is strongly neuroprotective [Tang et al. 1996]. Taurine prevents harmful metabolic cascades induced by ischemia or hypoxia [Schurr et al. 1987] and attenuates Ca^{2+} influx in ischemia [Lehmann et al. 1984, 1985, Matsuda et al. 1996]. It is also possible that taurine may be taken up inside the cell and act as an osmolyte and in this manner regulate cell volume and prevent cell swelling.

Many studies have shown that taurine possesses an antioxidant role. It attenuates oxidative damage to DNA in vitro [Messina and Dawson 2000] and protects against menadion-induced oxidative stress in cell

cultures [Devamanoharan et al. 1998]. Taurine has also been proposed to have radical-scavenging properties under certain conditions. However, the taurine analogs cysteamine and hypotaurine are far more likely to act as antioxidants in vivo than taurine, provided that they are present at sufficient concentrations at the sites of oxidant generation [Aruoma et al. 1988, Shi et al. 1997]. It is possible that taurine itself suppresses some reactions which produce free radicals or potentiates endogenous antioxidant defense and lipid membrane stabilizing activity [Mankovskaya et al. 2000, Obrosova et al. 2001, Balakrishnan et al. 2002].

Under normal conditions taurine is generally tightly retained by the cells [Kontro and Oja, 1987a] and exerts its trophic and protective actions within them. The release of taurine the cell environment under critical physiological or pathological changes to indicates that the cell attempts to protect itself. For example, taurine can serve as a free radical scavenger. However, at the same time the intracellar pool of taurine diminishes and hence weakens internal defense. Because the released taurine can enhance its further outflow, a substantial loss in the intraneuronal pool may ensue.

Taken together, all these data suggest that taurine release may reflect a critical and precarious situation in the cell. Estimation of the extracellular taurine content could therefore be a useful tool to monitor toxicity.

AIMS OF THE STUDY

The present aims were the following:

To evaluate the effects of d-amphetamine and sydnocarb at a repetitive dosage (acute toxic dose) on the level of stereotypic behavior and the long-term effects on tissue dopamine and DOPAC contents.

To compare the changes in neurochemical parameters in the rat striatum in vivo (extracellular levels of dopamine, DOPAC, glutamate, aspartate, taurine and hydroxyl radicals) induced by acute toxic doses of amphetamine and sydnocarb using the microdialysis approach with high-performance liquid chromatography.

To evaluate the neuroprotective effect of the D_2 dopamine receptor antagonist sulpiride in a model of amphetamine neurotoxicity and to estimate the changes evoked by sulpiride on the extracellular levels of dopamine, DOPAC and hydroxyl radicals in amphetamine-treated rats.

To estimate the possible relationships between the extracellular levels of dopamine, cyclic GMP and hydroxyl radical generation induced by ammonium chloride infusion into the rat striatum and to analyze the possible modulatory effect of taurine on these neurochemical parameters

MATERIALS AND METHODS

1. Animals

Adult male Sprague-Dawley rats, 200-250 g (Orion, Espoo, Finland) and Wistar rats, 250-300 g (Institute of Pharmacology, RAMS, Moscow, Russia) were given food and water ad libitum and maintained in a temperature-controlled room (22±1°C) with constant relative humidity (50%) under a 12-h light/dark cycle. The procedures were conducted in accordance with the guidelines set by the European Community Directive for the ethical use of experimental animals (86/609/EEC). All efforts were made to minimize both the suffering and the number of animals used.

2. Animal preparations (brain microdialysis)

2.1 Microdialysis with anesthetized rats

The rats were anesthetized with 4% halothane in air within 2 min and then maintained under anesthesia with 1% halothane in air delivered at 1.2 l/min. They were placed in a stereotaxic frame with blunt ear bars and a small incision (3-5 mm) was made in the skin over the skull. Holes were drilled for skull screws and microdialysis probes implanted in the left and right caudate-putamen (coordinates from bregma, AP= +0.5, ML= ±0.3, DV= -6.5 according to the atlas of Paxinos and Watson [1986]). Microdialysis probes of concentric design (0.5 mm o.d., a 2-mm dialysing membrane) were used (CMA 12, CMA/Microdialysis AB, Sweden). All probes were perfused at 2 µl/min with artificial cerebrospinal fluid (CSF) (composition in mM: Na^+ 150; K^+ 3.0; Ca^{2+} 1.4, Mg^{2+} 0.8; PO_4^{3-} 31.0; Cl^- 155; pH 7.4), for 1-2 h before commencement of sample collection, and the same constant flow rate was maintained with a microdialysis pump (CMA/Microdialysis AB, Sweden) throughout the experiment. Dialysate fractions were collected every 20 min. The location of the microdialysis probes in the brain was verified with cryostate microtome sections post mortem.

2.2. Microdialysis with freely moving rats

Male rats were anesthetized with chloral hydrate (400 mg/kg, i.p.). Custom–made dialysis probes [0.5 mm o.d, 3 mm dialysing membrane, recovery for dopamine, DOPAC and 2,3-dihydroxybenzoic acid (2,3-DHBA) 8-9 %] or commercial probes CMA 12 (CMA/Microdialysis AB, Sweden) were implanted in the right striatum (coordinates: AP, +0.5; L, +3.0; DV, -7.0; relative to bregma, according to Paxinos and Watson [1986]. At 24 hours after surgery, the dialysis probes were connected to a microinfusion system, perfused at 2 µl/min with artificial CSF and then equilibrated for 1 h. Dialysate fractions were subsequently collected every 20 (30) min. The location of the microdialysis probes in the brain was verified as above.

3. Evaluation of stereotypic behavior

In a separate set of experiments, immediately prior to and at certain intervals after each drug administration, the rats were assessed for their stereotypic behavior. Each animal was individually observed

for a 10-s period every 20 min. Stereotypic behavior was divided into stereotypic sniffing (rhythmic movement of the snout and head along the cage wall or floor, accompanied by rapid movements of the vibrissae), licking (protrusion of the tongue against the cage wall or floor) and gnawing [Koph and Kuschinsky, 1993]. Further qualification of the behavior was made using the conventional 0-6 point stereotypy rating scale: (0) no stereotypies, (1) occasional sniffing, (2) continuous sniffing, (3) discontinuous licking, (4) continuous licking, (5) sporadic gnawing, and (6) continuous gnawing [Havemann et al. 1986].

4. High-performance liquid chromatography

4.1. Chromatography of amino acids

The amino acids were assayed in dialysates kept frozen at –70°C and thawed immediately prior to the analysis. The concentrations of glutamate, aspartate, alanine and taurine were measured by high-performance liquid chromatography with fluorescence detection (Shimadzu Scientific Instruments, Kyoto, Japan) after pre-column derivatization with *o*-phthalaldehyde (Sigma, St. Louis, MO, USA) [Kendrick et al. 1996]. Derivatization was performed with an autoinjector SIL-10AD (Shimadzu Scientific Instruments, Kyoto, Japan). The samples in the autoinjector were maintained at 4°C by a Peltier thermoelectric sample cooler. The samples and the reagent were allowed to react for 2 min, whereafter a portion of the mixture was injected onto a C18-HC column (ODS, 5 µm packing, 4.6 mm i.d. x 25 cm, Waters, UK) equipped with a guard column (4x20 mm). The mobile phase was 0.075 M phosphate buffer (pH 6.5); methanol and acetonitrile were used as organic eluents with gradient profiles of 14-25% and 0-10 %, respectively. The amino acid derivatives were assayed using an RF-10A fluorescence detector with excitation and emission wavelengths set at 340 and 450 nm, respectively. The data were analyzed by PC using VPclass5 software and quantified by comparing the peak areas to these of standards.

4.2. Chromatography of monoamines

The monoamines were separated by high-performance liquid chromatography and detected in a system designed for monoamine assays [Sharp et al. 1986]. The mobile phase was 0.1 M citrate-phosphate buffer (pH 3.0), 1.1 mM octanesulfonic acid, 0.1 mM ethylenediaminetetra-acetate (EDTA) and 9-13% acetonitrile. The analytic reverse-phase columns used were (1) PR-C18 column, 3 µm packing, 3 mm i.d. x 15 cm (ESA Inc., Chelsford, MA, USA) and (2) Ultrasphere ODS, 5 µm, 4.6 - 150 mm (Bioanalytical System, West Lafayette, USA). The flow rate with the columns was 700 µl/min. Detection was electrochemical; when using Coulochem II (ESA Inc.), electrodes 1 and 2 were set at –175 mV and +200 mV, respectively, and when using BAS LC-4B, the glassy carbon working electrode was set at +0.8 V. The data were analyzed using BMDP software (BMDP Software Inc, Los Angeles, USA).

4.3. Determination of tissue contents of dopamine and DOPAC

The rats were sacrificed 7 days after drug treatments. The brain was excised and the dissected striata homogenized and centrifuged (15000 x 10 min, 0°C). The supernatant was passed through a microfilter (0.2 μm). HPLC was used for determination of monoamines.

4.4. Determination of hydroxyl radical generation

The generation of hydroxyl radicals was determined by quantifying the rate of formation of 2,3-DHBA (a reaction product of salicylic acid and hydroxyl radicals) in the microdialysis perfusates [Obata and Chiueh 1992, Yamamoto and Zhu 1998]. Sodium salicylate (5 mM) was dissolved in CSF at pH 7.4 immediately before perfusion. The 2,3-DHBA was separated by high-performance liquid chromatography and detected in a system designed for monoamine assays [Sharp et al. 1986].

5. Determination of cyclic GMP

For cGMP assays, microdialysate fractions were collected in tubes containing 4 mM EDTA. cGMP was assayed with the BIOTRAK cGMP enzyme immunoassay kit [Hermenegildo et al. 2000].

6. Pharmacological treatments

A single administration or repeated acute toxic doses (four subsequent injections two hours apart) were used as a model of neurotoxicity with the psychostimulants. d-Amphetamine (Sigma, St. Louis, MO, USA) was dissolved in 0.85% NaCl and sydnocarb (Russian Center for Drug Chemistry, Moscow, Russia) in 0.85% NaCl-propyleneglycol mixture (50/50, v/v) [Witkin et al. 1999]. Both drugs were administered to the rats by intraperitoneal injections. d-Amphetamine was given at a dose of 5 or 7.5 mg/kg. Sydnocarb was used at the dose equimolar to 5 mg/kg of d-amphetamine (23.8 mg/kg). Sulpiride (Sigma, St. Louis, MO, USA) was dissolved in 0.85 % NaCl and administered i.p. at a dose of 75 mg/kg twice with a 3-h interval [Albers and Sonsalla 1995].

Direct infusion of ammonium chloride through the microdialysis probes was used as a model of acute ammonia-induced toxicity. Sixty mM ammonium chloride and/or 85 mM taurine were infused for 40 min. The extracellular concentrations of ammonia and taurine during infusions were 5 mM and 10 mM, respectively, when corrected for the probe efficiency [Zielińska et al. 2002].

7. Statistics

In microdialysis experiments, the average basal levels of the catecholamines, cGMP, 2,3-DHBA and amino acids for each rat in at least three consecutive samples before drug or vehicle administrations were defined to be 100%. The relative magnitudes of the evoked effects of different treatments were estimated by expressing them as percentage changes from this baseline. Statistical analyses were made with Excel2000 software (Microsoft, USA). Comparisons of different groups were made using two-way analysis of variance

(ANOVA), group x time, with the repeated measures as one variable. The data are presented as mean values ± SEM. In all cases the limit of significance was set at $P < 0.05$.

In behavioral studies, each point in the time-course graphs represents the group mean ± SEM. The data obtained in all these experiments were statistically analyzed using Student's unpaired *t* test (the group consisted of 8-10 animals) and Mann-Whitney test (the group consisted of 5-6 animals). The use of parametric criteria was considered possible in view of (1) the strong homogeneity in the sampling which allowed the assumption of normal distribution of variances in each drug-treated group and (2) the relatively low dispersion of variances.

RESULTS

1. Changes in stereotypic locomotor activity

1.1. Changes in the stereotypic locomotor activity evoked by d-amphetamine and sydnocarb in Wistar rats

d-Amphetamine (5 mg/kg x 4, i.p.) produced a specific pattern of stereotypic behavior discernible soon after the first injection and reaching almost 6 intensity points 2 h from the beginning of the experiment. This pattern persisted at the same level for about 5 h and decreased rapidly thereafter. At the end of the experiment, the rats became exhausted and were practically unable to move.

Sydnocarb (23.8 mg/kg x 4, i.p.) was also able to elicit stereotypic behavior, albeit less than d-amphetamine The maximal intensity of abnormal movements achieved 4.0 ± 0.7 points 3 h after the beginning of the experiment, and this level was maintained until the end of the experiment. The rats were not exhausted and some signs of stereotypic behavior were obvious even 5–6 h after the end of the experiment.

1.2. Effect of sulpiride on d-amphetamine-induced stereotypic locomotor activity in Sprague-Dawley rats

Administration of neuroprotective sulpiride (75 mg/kg x 2) increased d-amphetamine (7.5 mg/kg x 4) -induced stereotypy during 2 h after the first d-amphetamine injection. There was subsequently no significant difference in the level of stereotypy between the groups treated with d-amphetamine alone and with d-amphetamine together with sulpiride.

2. Tissue monoamine contents in the rat striatum

2.1. Long-term effects of the acute toxic dose of sydnocarb on dopamine and DOPAC in the striatum of Wistar rats

When measured 1 week after treatment with sydnocarb, the dopamine content in the rat striatum was not significantly altered. Likewise no changes in DOPAC content were observed.

2.2. Effects of sulpiride on d-amphetamine-induced changes in Sprague-Dawley rats

d-Amphetamine (7.5 mg/kg x 4, i.p.) induced a twofold decrease in the striatal tissue level of dopamine and DOPAC 7 days after psychostimulant administration. In contrast to this result, d-amphetamine at a smaller dose of 5.0 mg/kg x 4 did not significantly after the tissue content of dopamine and DOPAC. A dose of 7.5 mg/kg was therefore chosen to model d-amphetamine neurotoxicity. The depletion of dopamine and DOPAC evoked by d-amphetamine was completely prevented by sulpiride co-treatment (75 mg/kg x 2), which proves the neuroprotective activity of this D_2 dopamine receptor antagonist at the dosage used.

3. Effects of acute toxic doses of amphetamine and sydnocarb on the extracellular levels of dopamine, DOPAC and 2,3-DHBA in the striatum in freely moving Wistar rats

3.1. The basal concentrations of dopamine, DOPAC, and 2,3-DHBA in the dialysates from the rat dorsal striatum were 5.56 ± 0.28, 750 ± 114 and 489 ± 174 nM, respectively (n=24). The values are not corrected for the recovery in the dialysate samples.

3.2 The dose-dependent effects of d-amphetamine

A single injection of d-amphetamine (5 mg/kg, i.p.) resulted in a transient 9-10-fold increase in the extracellular level of dopamine. This returned to the basal within 2 h after the injection (unpublished data). d-Amphetamine (2.5 mg/kg x 4, i.p.) evoked a gradual accumulation of dopamine in the extracellular space. The final concentration measured in microdialysates was 4 times greater than in the controls. d-Amphetamine (5 mg/kg x 4, i.p.) caused an immediate dramatic increase in the dopamine concentration in striatal perfusates up to 950 ± 450%. This effect was most pronounced 20 min after drug administration and was thereafter quickly reduced towards the baseline. The subsequent d-amphetamine injections were followed by much smaller but still significant increases in the extracellular concentration of dopamine (about 300 ± 80%), which gradually declined, becoming non-significant 80–100 min after the injection.

The DOPAC concentration decreased within about 1 h after the first dose of d-amphetamine. The level of this metabolite was lowered when compared to control until the end of experiment (about 40 ± 20%).

A single injection of d-amphetamine (5 mg/kg, i.p.) elicited a temporary twofold increase in extracellular 2,3-DHBA (unpublished data). Four injections of d-amphetamine at a dose of 2.5 mg/kg resulted in a subtle increase in extracellular 2,3-DHBA during the whole experiment. The higher dose of d-amphetamine (5 mg/kg) evoked a marked increase in the 2,3-DHBA level. The most pronounced effect was observed 80–140 min after the second injection (up to 700 ± 200%). This enhancement persisted for 2 h (within the period of 180–320 min after the first injection of d-amphetamine), gradually declining thereafter.

3.3. Effects of the acute toxic doses of sydnocarb

Sydnocarb at a dose of 23.8 mg/kg (equimolar to 5 mg/kg of d-amphetamine) elicited a moderate increase in the extracellular level of dopamine, up to 200 ± 30% after the first dose. Unlike the effect of d-amphetamine, this enhancement persisted for at least 4 h with a subsequent further increase. The maximal dopamine level reached was 400 ± 70% of the basal at the end of the experiment.

Unlike d-amphetamine, sydnocarb slightly increased the extracellular level of DOPAC after the first and second injections (up to 200 ± 50%), followed by a gradual decrease which became significantly lower than the control level (50 ± 15%) at 6 h after the beginning of the experiment.

The extracellular concentration of 2,3-DHBA in the rats treated with sydnocarb increased to a much lesser degree (up to 200 ± 25%) as compared to that produced by d-amphetamine at the equimolar dose. The most pronounced effect of sydnocarb took place within the period of 120 to 180 min after the beginning of the experiment, followed by a decline.

4. Effect of sulpiride on the changes in the extracellular levels of dopamine, DOPAC and 2,3-DHBA in the rat striatum evoked by an acute toxic dose of d-amphetamine in freely moving Sprague-Dawley rats

4.1. The basal concentrations of dopamine, DOPAC, and 2,3-DHBA in the dialysates from the rat dorsal striatum in these experiments were 1.26 ± 0.18, 450 ± 29 and 104 ± 12 nM, respectively (n=18). The values are not corrected for the recovery in the dialysate samples.

4.2 The effect of drug co-treatment on the extracellular levels of dopamine and DOPAC

d-Amphetamine (7.5 mg/kg x 4, i.p.) elicited increases in the extracellular dopamine level after each injection. The magnitude of the increase was 15-17-fold and did not notably vary from injection to injection. After the sharp increase following each psychostimulant dose, the level of dopamine decreased and achieved 500-700 % of the basal level. Co-treatment with sulpiride stimulated the increase in extracellular dopamine after the first amphetamine injection and maintained extracellular dopamine at significantly higher lever than in the d-amphetamine-treated group.

d-Amphetamine administration produced a fast decrease in extracellular DOPAC, which achieved 25-30% of the basal level at 90 min after the first injection and subsequently remained at this level. Sulpiride (75 mg/kg x 2, i.p.) weakened this effect of d-amphetamine, partially preventing the decrease in the extracellular content of DOPAC to 45-50%.

4.3. Effects of drugs on the extracellular level of 2,3-DHBA

A toxic dosage of d-amphetamine induced an accumulation of 2,3-DHBA in the extracellular space. Tris was characterized by a gradual increase to 300-350 % of the basal level between the 3rd and 4th injections of the psychostimulant. In the striatum of rats treated with d-amphetamine together with sulpiride, the level of 2,3-DHBA increased sharply after the first injection of d-amphetamine and declined to the basal level before the second psychostimulant administration. The level of 2,3-DHBA was slightly elevated after the second d-amphetamine administration (130-170% of the control), but the increase remained significantly smaller in comparison with the amphetamine-treated group.

5. Effects of a single administration and acute toxic doses of d-amphetamine and sydnocarb on the extracellular levels of glutamate, aspartate, alanine and taurine in the striatum in halothane-anesthetized Sprague-Dawley rats

5.1 The basal extracellular levels of amino acids, measured in 69 rats, were in the caudate-putamen 0.38 ± 0.14 μM for glutamate, 0.24 ± 0.09 μM for aspartate, 0.22 ± 0.03 μM for alanine and 1.21 ± 0.22 μM for taurine. The values are not corrected for the recovery in the dialysate samples.

5.2. Effects of a single administration and acute toxic doses of d-amphetamine

A single dose of d-amphetamine (5.0 mg/kg x 1, i.p.) significantly elevated (ANOVA, $P< 0.05$, when compared to the saline-treated group) the extracellular levels of glutamate in the caudate-putamen at 40 and 120 min after the injection. No immediate increase in glutamate occurred after saline administration due

to the possible stress of injections. d-Amphetamine increased the extracellular levels of aspartate in the same samples. The effect remained significant (compared with the saline-treated group) until the end of experiments. A gradual accumulation of extracellular alanine occurred at the end of experiments from 160 min onward. The extracellular level of taurine was not affected by d-amphetamine administration.

Subchronic d-amphetamine administration (5.0 mg/kg x 4, i.p.) caused a marked gradual increase in the extracellular levels of glutamate and taurine up to 400-550% and 480-580% of controls, respectively, and a moderate increase in the aspartate and alanine levels up to 170-200% and 140-210%, respectively. In the case of glutamate, aspartate and alanine the effect was already discernible after the first injection of d-amphetamine, whereas in taurine only after the third administration. After an increase within 3 h, an abrupt decline was observed in the alanine concentration, but the level was quickly restored after the third d-amphetamine Injection.

5.3. Effects of a single administration and acute toxic doses of sydnocarb

A single sydnocarb injection (23.8 mg/kg x 1, i.p.) increased the extracellular glutamate level temporarily and did not after the levels of aspartate and taurine. A short-lasting but significant increase in the extracellular alanine level was observed during the second hour after the injection (the maximum increase was 160 ± 42% of control at 100 min). The injection of vehicle (propylenglycol/0.85 % NaCl) resulted in a twofold increase in the glutamate level, which was significantly different from the mean basal value.

Subchronic sydnocarb administration (23.8 mg/kg x 4, i.p.) elicited marked increases in the aspartate level after the second and fourth injections (up to 250-350% in both cases). The level of glutamate was practically unaffected when compared to the control group. The alanine level increased temporarily after each administration of sydnocarb. The taurine level was not altered within the first six hours and significantly increased only after the last (fourth) injection. The final extracellular level of taurine attained after sydnocarb treatment was 3 times less than that after d-amphetamine administration.

6. Effects of intrastriatal ammonia infusion on the extracellular levels of dopamine, DOPAC, 2,3-DHBA and cGMP in the striatum of halothane-anesthetized Sprague-Dawley rats

6.1. The basal levels of dopamine, DOPAC and 2,3-DHBA in the perfusates were in these experiments 1.6 ± 0.3, 375 ± 76 and 102 ± 7 nM, respectively (n=27). The values are not corrected for the recovery in the dialysate samples.

6.2 Effects of taurine and ammonia on the dopamine efflux and the extracellular of accumulation DOPAC

The intrastriatal infusion of taurine (85 mM) within 40 min produced no significant changes in the extracellular level of dopamine. The extracellular level of DOPAC had a tendency to decline gradually after the taurine injection.

The intrastriatal infusion of ammonium chloride (60 mM) evoked within 40 min a 250- to 300-fold increase in the extracellular level of dopamine, which persisted throughout the whole period of

administration. When the infusion of ammonium chloride was stopped, the extracellular level of dopamine rapidly decreased and reached the control level within 40 min. The co-infusion of ammonium chloride and taurine did not affect the magnitude of enhanced dopamine release but the level promptly declined after the sharp initial elevation.

The extracellular level of DOPAC started to increase at the beginning of the ammonia infusion and achieved its maximal level 40 min later (217 ± 29 %). The cessation of ammonia administration lowered the extracellular DOPAC level to the control value. The simultaneous administration of ammonia and taurine clearly attenuated DOPAC accumulation (138 ± 16 %), but the elevation was still significant in comparison to the control level.

Ammonia alone caused a 2.5-fold increase in the extracellular hydroxyl radical content (2,3-DHBA level) in microdialysates. Taurine co-administration reduced the increase to about 1.7-fold of the control.

6.3. Effect of ammonia on the cGMP content in the striatum of halothane-anesthetized Sprague-Dawley rats

In the absence of ammonia, the cGMP content in microdialysates remained at an approximately constant low level throughout the whole period of taurine infusion. Ammonia alone increased the cGMP content in microdialysates threefold. Taurine co-administration completely prevented this ammonia-induced increase in the cGMP content.

DISCUSSION

Taken together, the results of the present study allow the conclusion that changes in the extracellular level of dopamine have a triggering role in the mechanisms of toxicity. However, this triggering effect of increased extracellular dopamine can be counteracted by pharmacological treatments. An increase in glutamate as well as a gradual accumulation of hydroxyl radicals in the striatum reflect the degree of damage and could be regarded as markers of neurotoxicity. Taurine accumulates in the extracellular space due the hyperactivation of glutamatergic neurotransmission and may act as an endogenous neuroprotector. Neuronal damage could be effectively prevented by drugs which influence cellular functions and metabolism (e.g. sulpiride) or by endogenous substances which act as antioxidants (e.g. taurine).

Methodological considerations

The neurotoxic consequences of amphetamine administration have been associated with hyperthermia and metabolic and oxidative stress. The role of the interplay of different neurotransmitters in the development of neurotoxicity is intriguing, since they function in close interaction, producing different effects, for example, in behavior. The mode of drug administration is a particularly important factor when evaluating the toxic actions of amphetamine and its congeners. Systemic amphetamine administration is a more adequate approach in animal models of neurotoxicity in that this mode does not exclude hypothermic effects, sympathomimetic vascular actions and interactions of different neurotransmitters in the basal ganglia circuitry. In our opinion, it was necessary to emphasize in the studies not only the direct excitotoxic effects of amphetamine but also the role of the increased extracellular contents of dopamine and glutamate elicited by the systemic administration of drugs in the changes in neurotoxicity parameters (stereotypy and hydroxyl radical level).

Subchronic systemic administration of psychostimulants is widely accepted as an appropriate means of establishing amphetamine neurotoxicity. Repetitive administration of this psychostimulant maintains the drug level in the brain high and at the same time prevents the death of experimental animals due to sympathomimetic side effects. The selection of the dosage in our experiments was determined by the ability to reduce the dopamine and DOPAC tissue contents in the striatum. One part of the studies was performed on freely moving animals. In Wistar rats a dose of 5 mg/kg x 4 was then sufficient to achieve a 50% decrease in monoamine tissue levels, whereas in Sprague-Dawley rats a higher dose (7.5 mg/kg x 4) was necessary to achieve the same effect. The established dose of amphetamine was used as the reference dose and the dose of sydnocarb was calculated to be equimolar to this.

The data of Miller and O`Callaghan [1994] suggest a substantial difference between rats and mice. Mice may not necessarily become hyperthermic during methamphetamine administration to show any significant depletion of striatal dopamine. An increase in body temperature in rats as well as in humans usually occurs. This observation renders rats a more appropriate animal model for amphetamine neurotoxicity.

In rodents, the striatum presents an anatomically homogeneous structure. However, histochemical and neurochemical studies demonstrate marked and complex heterogeneity of the striatum. The in vivo changes in extracellular dopamine and DOPAC in its subregions are thus heterogeneous and dependent on the pharmacological agent used (Yamamoto and Pehek 1990). Dopamine release following amphetamine administration shows a rostrocaudal gradient which corresponds to the density of dopaminergic innervation and may also indicate dissociation between the dopamine-releasing properties and dopamine-uptake blockade of amphetamine. However, the striatal dopamine release is regulated by the dopamine receptors, which are also distributed differently. The neurochemical compartmentalization of the striatum determines the exact localization of the microdialysis probe in the striatum.

Giovanni and colleagues [1999 showed that after neurotoxic doses of amphetamine, salicylate administration resulted in an increased formation of 2,3-DHBA, which indicates hydroxyl radical production. This correlation allows us to regard the increase in 2,3-DHBA production as a neurochemical marker of neurotoxic action.

It should be noted that technically the assay for taurine (fluorometric detection after HPLC separation) is easier than that for other amino acids (the measurements yield markedly stable data) and therefore this amino acid can be readily used as a marker of neurotoxicity.

Effects of d-amphetamine, sydnocarb and sulpiride on stereotypic behavior

d-Amphetamine and its congeners at relatively moderate doses (2.5-5.0 mg/kg, i.p.) produce substantial psychomotor stimulation by elevating the extracellular level of dopamine (Wolf and Xue, 1998). The increase in extracellular dopamine is accompanied on the behavioral level by all types of stereotypic behavior and psychosis (in humans). Hypermotility induced by amphetamine is also stereotyped in nature [Moore and Kenyon 1994]. A good correlation between the toxic effects of psychostimulant drugs and stereotyped behavior has been reported in rodents [Rebec and Bashore 1984, Wallace et al. 1999]. The increase in dopamine release elicits behavioral sequences of brief duration while at the same time behavioral sequences of long duration (e.g. locomotion) are truncated. At a high extracellular concentration, dopamine initiates many types of behavior, but only those of short duration, for example licking and gnawing, are completed [Lyon and Robbins 1975, Rebec and Bashore 1984]. In our experiments, both d-amphetamine and sydnocarb produced stereotyped behavior in rats, but the severity was different with the two drugs. d-Amphetamine treatment elicited most intense stereotyped behavior, rated with a score of 6 according to the conventional 0–6 point stereotypy scale. Sydnocarb elicited less pronounced manifestations of stereotyped behavior. Sulpiride pretreatment potentiates the stereotypy which accompanied stimulation of dopamine release after the first d-amphetamine injection. The blockade of autoreceptors and possible inhibition of dopamine transporter by sulpiride induce the maximal increase and prolong the clearance time of the neurotransmitter [Jaworski et al. 2001]. After the 2^{nd}, 3^{rd} and 4^{th} amphetamine injections the level of stereotypy was not affected by sulpiride.

Effects of d-amphetamine and sydnocarb on dopaminergic neurotransmission and generation of hydroxyl radicals in the rat striatum

The mechanisms of sydnocarb actions have been only fragmentarily studied hitherto. The psychostimulant effects of sydnocarb at doses of 4.4-23.8 mg/kg are accompanied by a facilitation of dopaminergic neurotransmission, but its efficacy in elevating extracellular dopamine is less than that of d-amphetamine [Gainetdinov et al. 1997] or methamphetamine [Witkin et al. 1999]. In contrast to the action of d-amphetamine, sydnocarb may also evoke dopamine release, which is independent of extracellular Ca^{2+} [Gainetdinov et al. 1997]. d-Amphetamine (2.5 mg/kg) resulted in a moderate increase in extracellular dopamine throughout the experiment. The level of hydroxyl radicals was twofold higher than in controls but did not change dramatically. d-Amphetamine (5 mg/kg) induced a sharp increase in the extracellular dopamine level in the rat striatum. Subsequent d-amphetamine injections elicited a less drastic increase in extracellular dopamine, but evoked rapid increases in the extracellular concentration of hydroxyl radicals. These achieved their maximum 80 min after the second injection of the drug. Our findings tally with the observed delayed increase in hydroxyl radical formation in desipramine-treated rats after a single injection of this psychostimulant [Huang et al. 1997]. In contrast to d-amphetamine, sydnocarb (23.8 mg/kg) elicited a gradual accumulation of extracellular dopamine. The increase in the level of hydroxyl radical generation in sydnocarb-treated rats was much less pronounced than that caused by d-amphetamine. The extracellular level of DOPAC rapidly declined during d-amphetamine exposure, which reflects the ability of the drug to inhibit MAO [O'Dell et al. 1991]. Sydnocarb failed to modify the decline of the extracellular level of DOPAC during two first injections. However, in the later phase of the experiment (last 4 h) sydnocarb reduced the extracellular DOPAC level, which resembles the action of d-amphetamine. Sydnocarb itself has been reported not to inhibit MAO, but a possible inhibitory effect of its metabolites accumulated during the experiments may not be excluded [Altshuler et al. 1976a]. The first d-amphetamine injection evoked a subtle increase in the hydroxyl radical level. In contrast to d-amphetamine, sydnocarb failed to deplete striatal dopamine and DOPAC content.

Effects of d-amphetamine and sydnocarb on the extracellular levels of neuroactive amino acids in the rat striatum

The glutamatergic afferents to the striatum have been held to modulate psychostimulant-induced locomotor activation [Ohmori et al. 1996, Rockhold 1998]. As suggested by Sonsalla [1995], dopaminergic and glutamatergic neurons are reciprocally excited in the caudate-putamen upon methamphetamine exposure and this interplay exacerbates oxidative stress and results in destruction of dopaminergic synaptic terminals. The association of monoaminergic neuronal damage with an increased extracellular level of glutamate affords suggestive evidence for the involvement of glutamate in the neurotoxicity of systemically administered amphetamines [Nash and Yamamoto 1992, Abekawa et al. 1994, Stephans and Yamamoto 1994, Wolf and Xue 1998, Burrows et al. 2000b]. In addition to the excessive release of glutamate, other factors such as

amphetamine-induced hyperthermia and increased dopamine oxidation may also be involved in the toxicity [Ali et al. 1994, LaVoie and Hastings 1999].

In our present studies, the increases in extracellular glutamate and aspartate after a single dose of systemically administrated d-amphetamine were relatively moderate. The mechanism by which amphetamines increase extracellular glutamate is poorly understood. They may evoke the release of amino acids either by affecting the release (or uptake) processes or by modulating brain dopaminergic neurotransmission. α-Adrenoreceptors also seem to be involved in the increase in glutamate and aspartate after an intrastriatal infusion of d-amphetamine [Del Arco et al. 1999]. Dopaminergic nerve endings may activate glutamatergic tracts. It has been suggested that activation of both dopamine D_1 and D_2 receptors enhances the release of intracellular glutamate in the striatum of freely moving rats [Cepeda and Levine 1998, Exposito et al. 1999, Vizi 2000]. There are several possible additional mechanisms underlying the gradual increase in extracellular glutamate after the repeated administration of d-amphetamine as in our experiments. An excessive release of dopamine triggers an accumulation of reactive dopamine metabolites and hyperproduction of hydroxyl radicals. It has been suggested that glutamate uptake is inhibited by oxygen radicals [Trotti et al. 1998, Wolf et al. 2000], nitric oxide [Ye and Sontheimer 1996] and arachidonic acid [Volterra et al. 1994] upon d-amphetamine administration. The slowly occurring effects of these agents could underlie the delayed increase in extracellular glutamate seen in the present experiments.

The increase in extracellular glutamate was now largely paralleled by a similar increase in extracellular taurine, a general modulator of neural excitability and regulator of cell volumes [Oja and Saransaari 1996]. It has been demonstrated that taurine release both in vivo in the brain and in vitro in brain tissue preparations is markedly enhanced by glutamate and its agonists [Oja and Saransaari 2000]. The released taurine is believed to originate from both neurons and glial cells [Saransaari and Oja 1992] and to act neuroprotectively and osmoregulatorily [Saransaari and Oja, 2000], counteracting the harmful metabolic cascades initiated by an excess of extracellular glutamate. The level of extracellular taurine would also appear to be a good indicator of the extent of neural damage under various cell-damaging conditions [Saransaari and Oja 1997a, 1998]. We now showed a substantional increase in extracellular alanine during amphetamine exposure. Alanine could serve as a mediator in nitrogen transport between glutamatergic neurons and adjacent glial cells and dispose of ammonia generated by glutaminase in the former [Waagepetersen et al. 2000]. This mechanism could explain the changes in extracellular alanine noted here.

The pharmacokinetics of amphetamine and sydnocarb are fairly similar in humans and rats, which affords a theoretical possibility for extrapolation of experimental results. Both drugs in the present modes of administration exhibited similar pharmacokinetic features. The maximum plasma concentration is reached within 30-60 min after infusion. The sharp increase in the extracellular level of dopamine coincides with the peak in the plasma concentration of amphetamine after an intraperitoneal injection. The high permeability of amphetamine through the hematoencephalic barrier corresponds to this peak and maximally increases the psychostimulant level in the brain. After a single drug administration the extracellular dopamine level returns to the basal level within an hour, whereas repetitive injections induce recurring increases. Although the effects of functional pharmacological cumulation have been observed in humans, the present schedule of drug

administration (acute toxic doses) does not offer a possibility to speculate on this phenomenon. On the other hand, the gradual increase in the glutamate level elicited by repetitive amphetamine administrations, which is secondary in its mechanism, may point to some kind of functional cumulation, though not precisely in the pharmacological sense, which results in toxicity. It should also be noted here that some investigators have thought that sydnocarb may have active metabolites which underlie the gradual and prolonged action of this drug (personal view of Dr. M. Baumann). The decrease in the extracellular level of DOPAC occurred only after the 3rd injection of sydnocarb, which may point to inhibition of MAO. On the other hand, the direct effects of amphetamine elicit an immediate reduction in DOPAC after exposure to this drug.

Effect of sulpiride on the neurochemical changes evoked by d-amphetamine

In the present study, administration of sulpiride at a dose of 75 mg/kg x 2 resulted in a twofold increase in the dopamine level in comparison with the group treated with d-amphetamine alone. The absolute values of extracellular dopamine measured in the striatum after drug treatments were different in the two experimental groups. However, the relative magnitude of the increase in dopamine level (in comparison with the maximal value in each series) upon the 2nd, 3rd and 4th injections did not change in the rats treated with amphetamine alone and had a tendency to decrease in those co-treated with sulpiride. The significant difference in the relative magnitude of the increase in dopamine level occurring after the 4th injection of d-amphetamine may reflect a difference in the transmembrane dopamine flow. Despite the stimulation of dopamine release, the sulpiride injections prevented dopamine and DOPAC depletion 7 days after d-amphetamine administration. This is consistent with the partial neuroprotective effects of the dopamine receptor antagonists haloperidol and eticloprid against amphetamine-induced neurotoxicity [O`Dell et al. 1993, 1994, Stephans and Yamamoto 1994, Albers and Sonsalla 1995].

As has recently been suggested, the accumulation of dopamine in the cytosolic pool due to the lack of VMAT2 results in an increase in amphetamine neurotoxicity [Fleckenstein et al. 2000]. d-Amphetamine diverts the direction of the membrane dopamine transporter function to intensive dopamine pumping from the vesicular storage out of the cell and into the cytosolic pool. This pool is the site of dopamine oxidation. Replenishing this dopamine pool results in an increase in the content of oxidized products, which damage proteins and provoke generation of other highly reactive species. The dopamine D_2 receptor is able to interact with the dopamine transporter [Crass and Gerhard 1994, Schmitz et al. 2002] and inhibition of presynaptic dopamine receptors inhibits the transporter [Meiergerd et al. 1993, Parsons et al. 1993, Rahman et al. 2001]. This may suppress the intensive flow of dopamine through the cytoplasma and reduce the probability of the formation of oxidized products. It also prevents the entrance of oxidized dopamine from the extracellular space.

The inability of locally applied methamphetamine to increase extracellular glutamate may explain the absence of a long-term effect on the dopamine content and may corroborate the importance of glutamate in mediating terminal damage caused by systemic methamphetamine exposure [Sonsalla et al. 1991, Abekawa et al. 1994, Stephans and Yamamoto 1994]. Selective lesions of striatal output neurons also block

amphetamine neurotoxicity [O`Dell et al. 1994], indicating that activation of the extrapyramidal motor loop may be a critical step in mediating the excitotoxic effects of amphetamine. This is consistent with the observation that methamphetamine-induced glutamate release is dependent on dopamine receptor activation, since D_2 receptor antagonism with haloperidol attenuates the increase in extracellular glutamate ensuing upon systemic methamphetamine administration. This assumption also underlines the importance of dopamine receptors in methamphetamine-induced neurotoxicity [O`Dell et al. 1994; Albers and Sonsalla 1995]. Some animal studies point to interactions between the antipsychotic agents and the activity and regulation of NMDA receptor at functional [Verma and Kulkarni 1992, Banerjee et al. 1995] and structural (haloperidol) levels [Ilyin et al. 1996, Lynch and Gallagher 1996, Coughenour and Cordon 1997]. Blockade of D_2 receptors attenuates the toxicity induced by NMDA receptor agonists to the same extent as does depletion of dopamine by 6-hydroxydopamine [Garside et al. 1996].

Sulpiride prevents amphetamine-induced hyperthermia [Albers and Sonsalla 1995]. Lowering of the ambient temperature prevents the accumulation of cysteinyl derivatives of dopamine. The extracellular concentration of cysteinyl-dopamine could constitute a useful tool in estimating the level of dopamine oxidation and may serve as a predictor of the toxic effects of methamphetamine [LaVoie and Hastings 1999]. Hyperthermia can contribute to the toxic properties of amphetamine by increasing the vulnerability of dopaminergic neurons through a decrease in mitochondrial functions and subsequent depletion of energy stores [Nowak 1988, Huether et al. 1997, Malberg and Seiden 1998]. Hyperthermia can foment not only the enzymatic and non-enzymatic degradation of dopamine, but also the excitatory amino acid-dependent formation of reactive oxygen species [Zeevalk and Nicklas 1993, Bruno et al. 1994]. The D_2 receptor antagonists have been shown to possess protective activity in a model of malonate-induced toxicity. Inhibition of mitochondrial functions is also observed in the d-amphetamine model of neurotoxicity. The effects of systemic 3,4-methylendioxymethamphetamine (MDMA) appear to parallel the biochemical consequences of malonate infusion [Beal et al. 1993a, Burrows et al. 2000a, Nixdorf et al. 2001]. The energy consumption of the brain is increased after systemic methamphetamine administration, as evidenced by an immediate and sustained increase in extracellular lactate in the striatum. ATP is depleted in all brain regions susceptible to amphetamines [Chan et al. 1994, Stephans et al. 1998]. The depletion of vesicular stores of dopamine by reserpine or exhaustion of the cytoplasmic pool by α-methyl-*p*-tyrosine does not completely prevent the methamphetamine-induced long-term depletion of dopamine [Yuan et al. 2001], but the increase in the 2,3-DHBA level during malonate perfusion was not counteracted by the same treatment [Xia et al. 2001]. In the striatum, the neurotransmitter NO is found in the subset of aspiny neurons which also contain the neuropeptides somatostatin and neuropeptide Y [Dawson et al. 1991]. Garside and colleagues [1992] found that stimulation of these neurons by dopamine through D_2 receptors results in an increase in somatostatin release from striatal cultures and also increases NO release. D_2 agonists will thus stimulate these neurons in the striatum, leading to an increase in NO production. The reduction in NO production by NOS inhibitors and by genetic disruption of the neuronal NOS gene has attenuated malonate- and methamphetamine-induced damage to the striatum [Itzhak and Ali 1996, Schulz et al. 1996, Itzhak et al. 1998]. The generation of NO by neuronal NOS is mediated by Ca^{2+}. Stimulation of D_2 receptors potentiates the Ca^{2+}-dependent release of

arachidonic acid [Felder et al. 1991, Kanterman et al. 1991, Piomelli et al. 1991]. The metabolites of arachidonic acid formed by the epoxygenase pathway are potent inhibitors of K^+/Na^+-ATPase [McGiff 1991]. The D_2 receptor also inhibits K^+/Na^+-ATPase [Bertorello et al. 1990, Motohashi et al. 1992]. The antagonists of dopamine D_1 and D_2 receptors can attenuate methamphetamine-induced toxicity [Hotchkiss and Gibb 1980, Sonsalla et al. 1986, O`Dell et al, 1993].

The foregoing would serve to explain the difference in 2,3-DHBA production observed in our experiments. Upon an acute toxic dose of amphetamine a slight primary increase was detected after the first injection and a gradual increase in extracellular 2,3-DHBA occurred thereafter. The first injection of amphetamine following sulpiride pretreatment resulted in a twofold increase in the 2,3-DHBA level. The magnitude of dopamine release at the same time point likewise differed twofold, which could also constitute proof that dopamine is the source of the initial 2,3-DHBA accumulation. Surprisingly, irrespective of the higher absolute amount of extracellular dopamine in the striatum of rats treated with sulpiride and amphetamine, only a subtle increase in the level of hydroxyl radical generation was observed.

Effects of intrastriatal ammonia chloride infusion on the extracellular levels of dopamine, DOPAC, 2,3-DHBA and cyclic GMP

Ammonia concentrations of the order of 5 mM in the brain are reached under severe hyperammonemic conditions [Swain et al. 1992]. The present extracellular levels of dopamine and DOPAC induced by ammonia apparently show how dopaminergic transmission is disturbed in acute hyperammonemic encephalopathy. So far, changes in dopamine receptors and dopamine-metabolizing enzymes have been described in animal models in which exposure to increased ammonia has lasted a few days or longer, thus reflecting chronic hyperammonemia. To our knowledge, the present report describes for the first time a robust extracellular accumulation of dopamine in the brain as an instant reaction to acute ammonia exposure.

There is evidence that acute ammonia neurotoxicity is mediated by overactivation of ionotropic glutamate receptors of the NMDA class [Marcaida et al. 1992, Hermenegildo et al. 2000]. Also presynaptic non-NMDA receptors affect dopamine release in the striatum [Moghaddam et al. 1990, Jin 1997]. It is thus plausible that a significant proportion of ammonia-induced dopamine release is induced by these two classes of receptors, with and without the involvement of NO [Chéramy et al. 1998]. However, there is reason to assume that a part of the ammonia-induced dopamine release bypasses activation of ionotropic glutamate receptors, being nonsynaptic and Ca^{2+}-independent. First, the ammonia-induced release from synaptosomes shows characteristics similar to the amphetamine-induced efflux triggered by the reversal of dopamine uptake [Arnold et al, 1977] or Na^+ gradient [Connor and Kuczenski 1986]. Second, dopamine release becomes Ca^{2+}-dependent only at high doses of ammonia and a part of the release from synaptosomes is due to a rapid alkalinization of the storage granules resulting in the collapse of the transgranular pH gradient [Erecińska et al. 1987]. Third, [^{3}H]dopamine efflux from brain slices and synaptosomes evoked by hyperammonemia in a hepatotoxic model is likewise partly Ca^{2+}-independent [Borkowska et al. 2000].

Taurine attenuates the extracellular accumulation of dopamine by at least two mechanisms. First, it depresses stimulated glutamate release from neurons [Holopainen and Kontro 1988, Saransaari and Oja 1994]; glutamate receptors are thus activated less and consequently less dopamine is released. Second, it also tends to diminish spontaneous dopamine release in the striatum [Kontro and Oja 1988]. On the other hand, locally applied high doses of taurine have been shown to elicit a moderate release of dopamine from a neuronal pool in the striatum [Ruotsalainen and Ahtee 1996]. However, in the present study taurine markedly diminished the later phase of dopamine accumulation, which result tallies with the assumption of a slightly delayed attenuating effect of taurine via NMDA receptors. Taurine apparently does not enhance the clearance of dopamine from the extracellular space, since it does not affect striatal dopamine uptake [Kontro 1987]. Although high doses of taurine have increased the extracellular levels of DOPAC in the striatum [Ruotsalainen et al. 1996, 1998], stimulation of dopamine metabolism is likewise less likely, because the DOPAC level now tended to decline when taurine was infused alone. A part of the massive amount of dopamine released from the cells by ammonia and escaped reuptake may be broken down by extracellular monoamine oxidase B [Waldmeier 1987]. The activity of monoamine oxidase B increases in acute hyperammonemia [Rao et al. 1994]. This sequence of events would explain the increase in DOPAC. The attenuation of DOPAC increase by taurine apparently stems from its direct and indirect effects on dopamine release. In addition to the above effects on receptors and enzymes, taurine is assumed to stabilize membranes [Timbrell et al. 1995] and may in this unspecific manner counteract the effects of ammonia.

As is well known, the release of dopamine from axon terminals is impulse- and Ca^{2+}-dependent. There are two intraneuronal pools of dopamine. These pools are in the equilibrium and have different ways to discharge and replenish. Thus, the dopamine release by nerve stimulation originates in a newly synthesized vesicular pool. For example, however, amphetamine-like drugs elicit the ion-exchange mechanism which activates dopamine re-uptake and depletes the cytoplasmic dopamine pool. The mechanism by which ammonia may induce dopamine and DOPAC accumulation is not clear. Study of the dopamine release from the synaptosomes upon ammonia exposure shows characteristics resembling the efflux of catecholamines induced by amphetamine (reversal of dopamine uptake) [Arnold et al. 1977] or reversal of the Na^+ gradient [Connor and Kuczenski 1986].

There is evidence that overactivation of NMDA receptors and subsequent generation of free radicals in NO-dependent and NO-independent manners prompt acute ammonia neurotoxicity [Kosenko et al. 1995]. The release of a neuroactive amino acid, taurine, upon ammonia treatment as in the present study is indeed mediated by activation of both the NMDA and AMPA/kainate receptors. The magnitude of dopamine release plus the inability to reduce it with a high dose of an antioxidant (taurine) suggests that possible damage to synaptic terminals (increase in membrane permeability or fluidity or impairment of uptake due to the radical attacks) has a non-leading role in the ammonia-induced release of dopamine. Thus other possibilities must be invoked to explain this release. The presynaptic NMDA and AMPA/kainate receptors affect the tonic and stimulated dopamine releases in the striatum [Moghaddam et al. 1990, Jin 1997]. Overstimulation of these receptors increases dopamine release. The additional factors dependent upon glutamate receptor activation which must be taken into consideration are the increase in Ca^{2+} and Na^+ influx

into dopaminergic neurons, the increase in the intracellular pH level, disturbance in the mitochondrial homeostasis of Ca^{2+} and impairment of energy metabolism. The Ca^{2+}-dependent component in vesicular dopamine release seems to be important at high ammonia doses [Erecińska et al. 1987]. All these factors together may contribute to the extracellular accumulation of dopamine upon intrastriatal ammonia infusion. Such a massive increase in the extracellular level of dopamine as seen in our study may point to extremely severe conditions which evoke dopamine release under toxic ammonia exposure. Erecińska and her co-workers [1987] have shown that dopamine release from the synaptosomes is due to a rapid alkalinization of the neurotransmitter stores and a collapse of the transgranular pH gradient. This rapid alkalinization may be a main reason for the massive dopamine release.

The accumulation of DOPAC in the extracellular space during and after ammonia infusion in our experiments reflects the activation of MAO. This finding is in accordance with the well-known phenomenon wherein acute hyperammonemia leads to an increase in the MAO-B activity [Raghavendra Rao et al. 1994]. This increase and the concomitant increase in serotonin oxidation have been shown in the hyperammonenic state [Batshaw et al. 1986]. Since the decrease in dopamine accumulation during taurine co-infusion coincided with the decline in the extracellular DOPAC level, it may point to extracellular sites of dopamine oxidation [Fowler et al. 1984]. We observed two downstream effects of intrastriatal administration of ammonia via the microdialysis probe: the accumulation of free radicals and cGMP. They are fully consistent with the previous observations in rats treated i.p. with toxic doses of ammonium salts [Kosenko et al., 1995; 1998, 1999; Hermenegildo et al. 2000; Monfort et al. 2001].

Ammonia administered at a 60-mM concentration via microdialysis probes overactivates both NMDA and kainate classes of ionotropic glutamate receptors in the rat striatum (Zielińska et al. 2002). Studies on primary cultures of cerebellar neurons have clearly demonstrated that while the excessive accumulation of cGMP results from overactivation of the NMDA receptor/NO pathway [Montoliu at al., 1999], the excitotoxic generation of free radicals is also attributable to glutamate interactions with kainate receptors [Boldyrev et al. 1999]. Co-administration of taurine now fully prevented the generation of cGMP but only partially reduced the formation of hydroxyl radicals. It would thus appear that taurine is more effective in counteracting overactivation of the NMDA receptor/NO pathway than in preventing the generation of free radicals following overactivation of kainate receptors. It might be noted that in cultured cerebellar neurons, taurine has prevented kainate-induced cell death without reducing the free radical levels [Boldyrev et al. 1999]. The antiexcitotoxic action of taurine in brain slices appears to be related to the activation of $GABA_A$ receptors [O'Byrne and Tipton 2000]. The issue is further obscured by the complex interrelation between the mechanisms underlying the ammonia-induced generation of NO and/or free radicals via NMDA and kainate receptors. For instance, the ability of the NOS inhibitor nitroarginine to attenuate ammonia toxicity in acutely hyperammonemic mice has been relatively much stronger than that of the NMDA channel blocker dizocilpine, indicating the coexistence of NMDA-dependent and -independent mechanisms of NOS activation [Kosenko et al. 1995]. Since taurine poorly crosses the blood-brain barrier under both control and hyperammonemic conditions [Hilgier et al. 1996], its therapeutic use is problematic. However, taurine

derivatives which more readily penetrate the barrier are worth testing for this purpose [Oja et al. 1983, Van Gelder and Bowers 2001].

The overall design and outcome of this investigation are illustratively depicted in Figures 7 and 8.

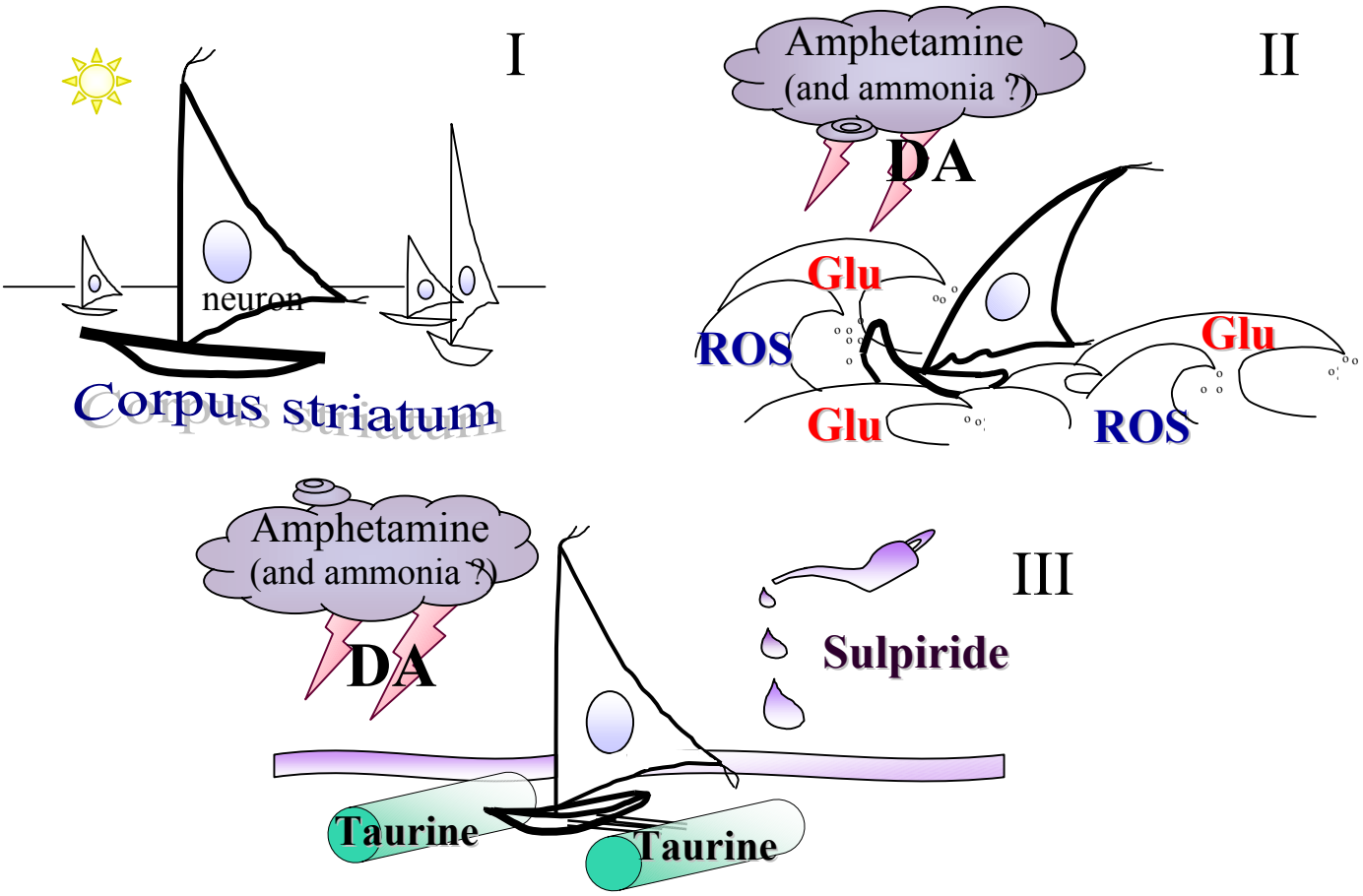

Fig. 7. Amphetamine and ammonia toxicity: how to avoid abandoning ship.
I - physiological transmission, II – toxic intervention, III – neuroprotective treatment.
(DA – dopamine, Glu – glutamate, ROS – reactive oxygen species).

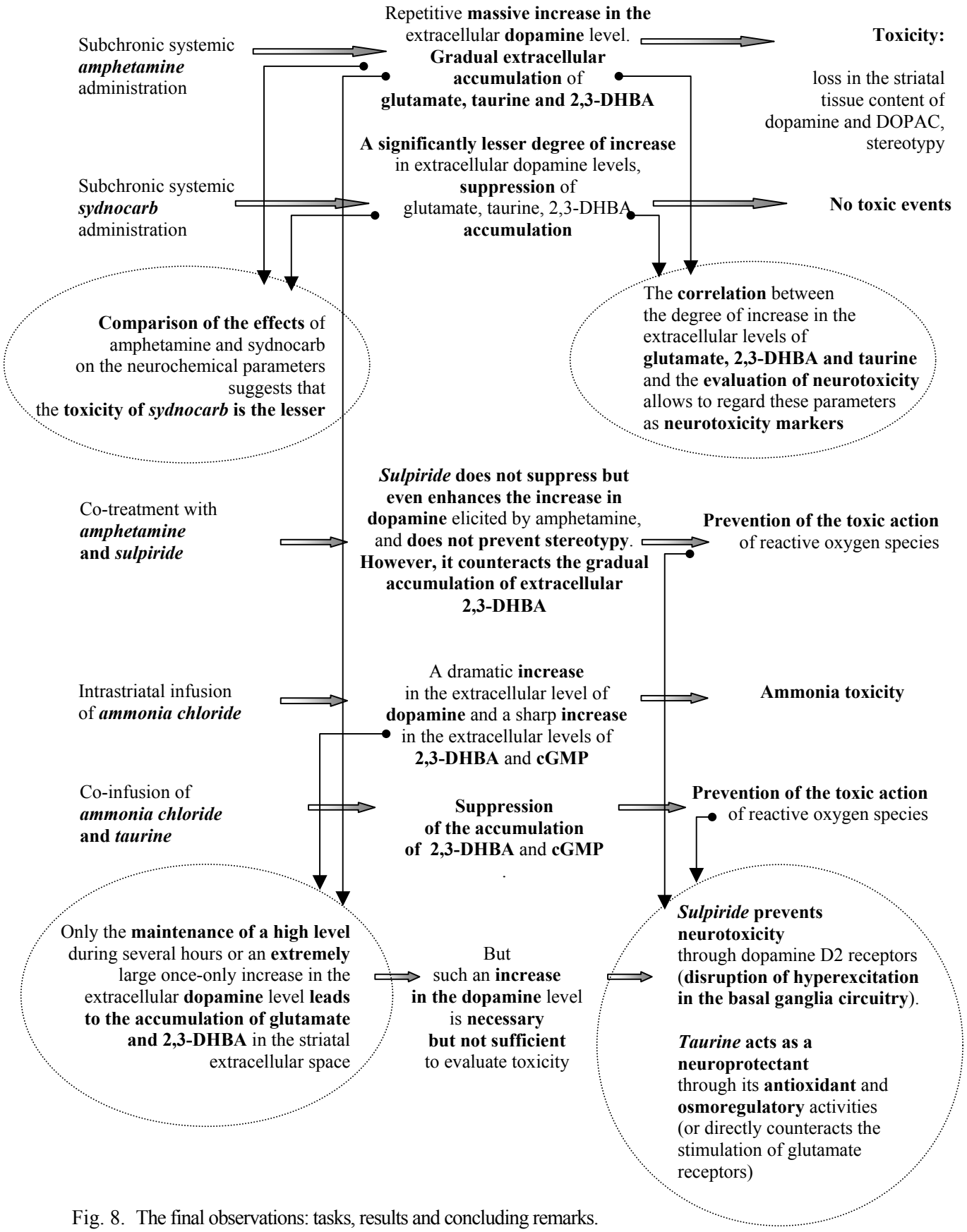

Fig. 8. The final observations: tasks, results and concluding remarks.

CONCLUSIONS

1. Systemic repetitive administration of d-amphetamine (acute toxic dose) leads to stimulation of stereotypic behavior and long-term depletion of dopamine and DOPAC in the rat striatum, which proves its neurotoxic action. Sydnocarb elicits less pronounced changes in the level of stereotypic behavior and does not induce dopamine and DOPAC depletion.

2. Systemic repetitive administration of d-amphetamine (5 and 7.5 mg/kg) leads to a permanent increase in the extracellular dopamine level, which results in a gradual increase in the extracellular 2,3-DHBA level. A single injection of d-amphetamine at the same doses or injections of smaller doses and repetitive sydnocarb administration do not result in such an increase in extracellular 2,3-DHBA. The delayed generation of hydroxyl radicals predicts the neurotoxic effects of psychostimulants.

An acute toxic dose of d-amphetamine evokes a gradual increase in the extracellular level of glutamate and taurine. A massive increase in extracellular taurine reflects hyperactivation of glutamatergic neurotransmission elicited by d-amphetamine. Extracellular taurine could be a useful biochemical marker of neurotoxicity.

Sydnocarb produces a persistent increase in the extracellular level of DOPAC and a significant increase in the extracellular level of aspartate. The mode of action of sydnocarb may thus differ from that of d-amphetamine. Sydnocarb is less neurotoxic than d-amphetamine, since it elicits less marked changes in the extracellular level of glutamate and does not provoke a robust stimulation of hydroxyl radical production.

3. Systemic administration of sulpiride, a dopamine D_2 receptor antagonist, potentiates the neurochemical effect of d-amphetamine and maintains the dopamine content at a higher level. Sulpiride potentiates the initial slight increase in hydroxyl radical generation due to the preceding increase in extracellular dopamine. However, sulpiride depresses the delayed gradual increase in the extracellular content of hydroxyl radicals and prevents the long-term depletion of dopamine and DOPAC in the rat striatum.

4. Intrastriatal infusion of ammonium chloride into the striatum of rats drastically increases the extracellular content of dopamine. This massive efflux of dopamine provokes an increase in the level of hydroxyl radicals in the extracellular space. Intrastriatal taurine infusion partially attenuates the increase in extracellular dopamine and significantly suppresses hydroxyl radical production. The effect of taurine may stem from its ability to interact with glutamate receptors and/or its possible antioxidant potency.

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ORIGINAL COMMUNICATIONS