ELSEVIER

European Journal of Pharmacology 428 (2001) 87–95

ejp

www.elsevier.com/locate/ejphar

Effects of sydnocarb and D-amphetamine on the extracellular levels of amino acids in the rat caudate-putamen

Elmira Anderzhanova [a,b,*], Kirill S. Rayevsky [b], Pirjo Saransaari [a], Esa Riitamaa [a], Simo S. Oja [a,c]

[a] *Brain Research Center, University of Tampere, Medical School, Tampere, Finland*
[b] *Laboratory of Neurochemical Pharmacology, Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow, Russia*
[c] *Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland*

Received 12 July 2001; accepted 7 August 2001

Abstract

The neurotoxic effects of psychostimulants at high dosages limit their clinical applicability but the mechanism of neurotoxicity is still unsettled. We now studied by microdialysis how acute and subchronic (four times at 2-h intervals) administrations of D-amphetamine and sydnocarb [3-(β-phenylisopropyl)-*N*-phenylcarbamoylsydnonimine], an original novel Russian psychostimulant, affected the extracellular levels of amino acids in the caudate-putamen of halothane-anesthetized male 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., a dose equimolar to 5.0 mg/kg D-amphetamine) also increased extracellular glutamate and alanine. Subchronic D-amphetamine administration (5.0 mg/kg × 4, i.p.) caused gradual fivefold increases in the glutamate and taurine levels and moderate increases in the aspartate and alanine levels. Subchronic sydnocarb administration (23.8 mg/kg × 4, i.p.) elicited a marked increase in the aspartate level and a small increase in the level of glutamate. The alanine level increased temporarily after each administration of sydnocarb, while the taurine level increased only after the last injection. We conclude that the mode of action of sydnocarb differs from that of D-amphetamine. Sydnocarb also seems to be less neurotoxic than D-amphetamine, since it elicits lesser changes in the extracellular level of glutamate.

Keywords: D-amphetamine; Sydnocarb; Neuroactive amino acid; Neurotoxicity; Caudate-putamen; Microdialysis

1. Introduction

Psychomotor stimulants, once in general clinical use in the treatment of psychiatric disorders and physical and mental fatigue and in counteracting of sedation induced by depressants, are no longer frequently administered in medical practice. The primary reasons for reduced clinical use are the tolerance and dependence which develop with repeated administrations and profound neurotoxic effects. 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).

Amphetamines produce behavioral changes through activation of the mesolimbic and mesocortical dopaminergic systems. The glutamatergic afferents to the caudate-putamen have been held to modulate psychostimulant-induced locomotor activation (Ohmori et al., 1996; Rockhold, 1998). There is no conclusive evidence, however, as to whether acute administration of moderate doses of D-amphetamine increases the extracellular levels of excitatory amino acids. The mechanism by which endogenous glutamate may exacerbate the stimulatory action of amphetamines is thus still a matter of debate.

The abundance of glutamatergic nerve endings in the caudate-putamen renders it likely that excitotoxicity is involved in neuronal damage caused by psychostimulants. 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. Suggestive evidence

* Corresponding author. Brain Research Center, Medical School, FIN-33014 University of Tampere, Tampere, Finland. Tel.: +358-3-215-6715; fax: +358-3-215-6170.
E-mail address: anderzhanova@hotmail.com (E. Anderzhanova).

0014-2999/01/$ - see front matter
PII: S0014-2999(01)01285-7

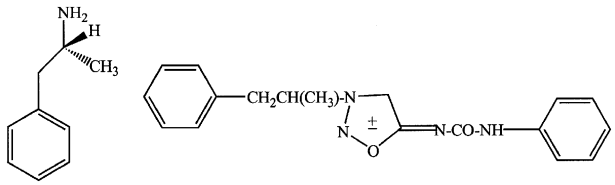

Fig. 1. Structural formulae of D-amphetamine and sydnocarb.

for the involvement of glutamate in the neurotoxicity of systemically administered amphetamines is afforded by the association of monoaminergic neuronal damage with an increased extracellular level of glutamate (Nash and Yamamoto, 1992; Stephans and Yamamoto, 1994; Abekawa et al., 1994; Wolf and Xue, 1998; Burrows et al., 2000). Systemic administration of psychostimulants increases the core body temperature and this effect also seems to be an important factor (Bowyer et al., 1992, 1993; Colado et al., 1998). The glutamate release and hyperthermia contribute to the metabolic stress and they both may be key mediators in the toxic effects of amphetamines. NMDA receptor antagonists counteract the elevation in temperature and attenuate methamphetamine-induced toxicity in mice (Sonsalla et al., 1991; Bowyer et al., 1994; Weihmuller et al., 1992; 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 temperature (Miller and O'Callaghan, 1994; Albers and Sonsalla, 1995). In addition to the excessive release of glutamate and hyperthermia (Ali et al., 1994), other factors may also be involved in toxicity (e.g., increased dopamine oxidation (LaVoie and Hastings, 1999).

Sydnocarb [3-(β-phenylisopropyl)-*N*-phenylcarbamoylsydnonimine], synthesized in the Russian Center for Drug Chemistry (Moscow), is a psychostimulant used in clinical practice in Russia as primary and adjunct therapy for psychiatric disorders, including schizophrenia and depression (Fig. 1). Like other indirect dopamine receptor antag-

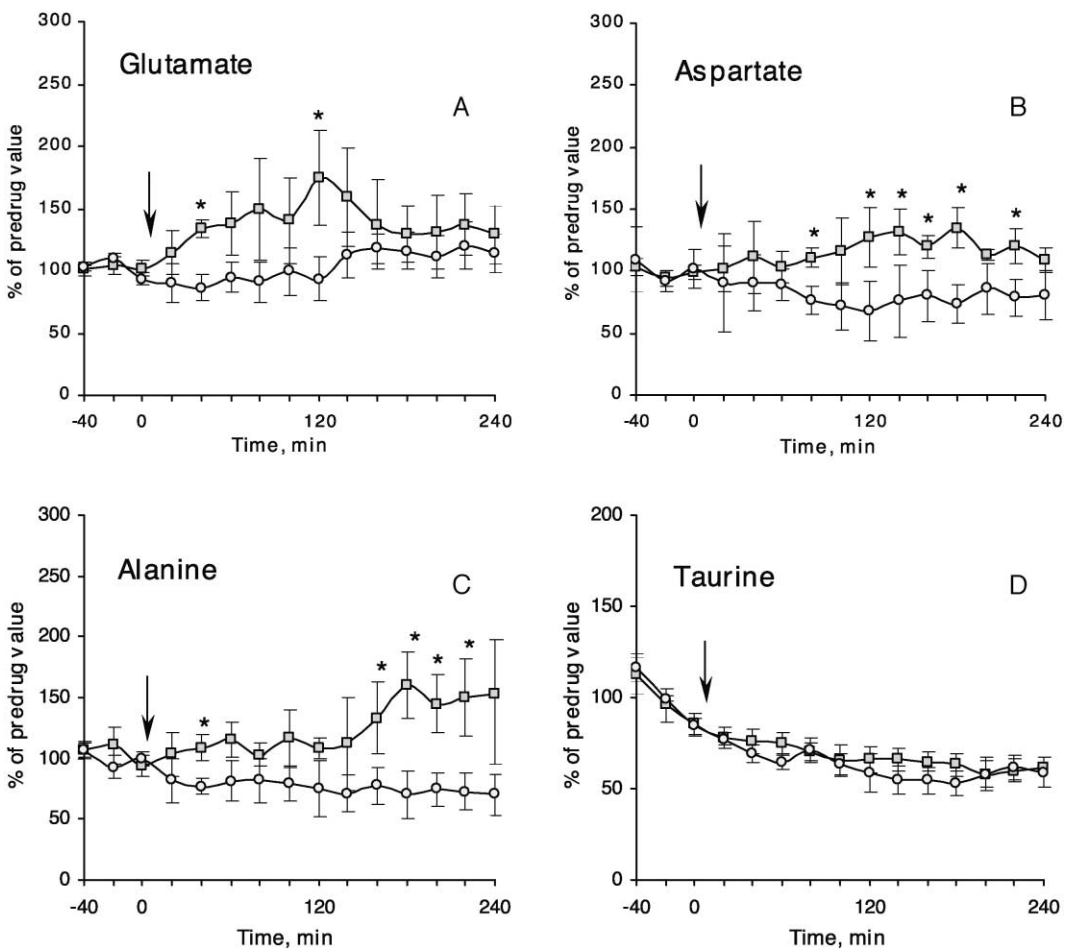

Fig. 2. The effect of acute administration of D-amphetamine on the extracellular levels of (A) glutamate, (B) aspartate, (C) alanine and (D) taurine in the caudate-putamen in halothane-anesthetized rats (-○- 0.85% NaCl × 1, i.p.; -□- D-amphetamine, 5.0 mg/kg × 1, i.p.). * Significant difference from control, $P < 0.05$, $n = 7$. The arrows indicate the moment of drug administration.

onists, sydnocarb evinces a pharmacological profile reminiscent of other stimulants but there is some evidence that the mode of its action is different (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 and last longer, and are accompanied less by stereotypy. There are no peripheral sympathomimetic effects, pronounced euphoria or motor excitation. Sydnocarb has also been characterized as a stimulant with weak addiction liability. Neither behavioral nor physical dependence on sydnocarb has been noted (Mashkovsky et al., 1971; Rudenko and Altshuler, 1978). 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 (Witkin et al., 1999). In contrast to D-amphetamine, sydnocarb does not induce any dramatic increase in the formation of hydroxyl radicals in the rat caudate-putamen upon subchronic treatment (Anderzhanova et al., 2000).

The aim of present study was to estimate the effects of sydnocarb on the levels of glutamate and other neuroactive amino acids in the caudate-putamen and compare them to those induced by D-amphetamine. The changes in the extracellular concentrations of glutamate, aspartate, alanine and taurine were measured by microdialysis during acute and subchronic treatment with potentially neurotoxic doses of D-amphetamine and sydnocarb.

2. Materials and methods

2.1. Animal preparation

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

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

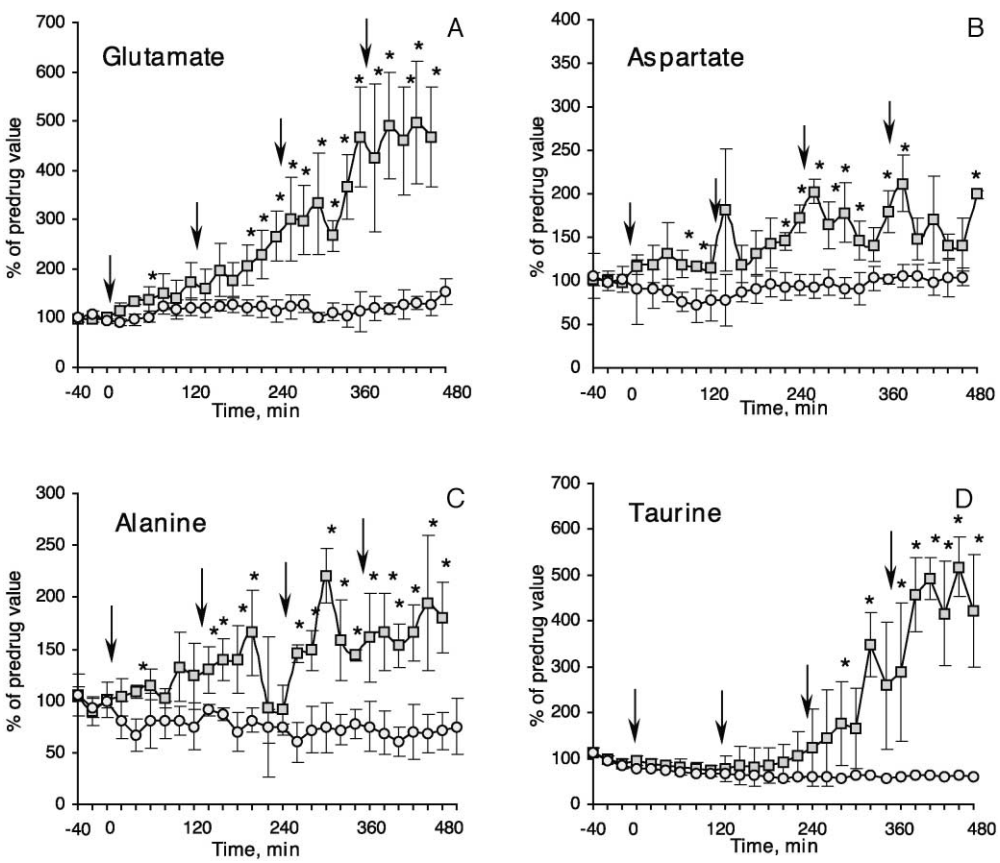

Fig. 3. The effect of subchronic administration of D-amphetamine on the extracellular levels of (A) glutamate, (B) aspartate, (C) alanine and (D) taurine in the caudate-putamen in halothane-anesthetized rats (-○- 0.85% NaCl × 4, i.p.; -□- D-amphetamine, 5.0 mg/kg × 4, i.p.). * Significant difference from control, $P < 0.05$, $n = 8$. The arrows indicate the moments of drug administration.

skull. The holes were drilled for skull screws and the concentric microdialysis probes implanted in the left and right caudate-putamens [coordinates from bregma, AP = 0.5, ML = ±0.3, DV = −6.5, according to the atlas of Paxinos and Watson (1996)].

2.2. Pharmacological treatment

D-amphetamine (Sigma, St. Louis, MO, USA) was dissolved in 0.85% NaCl, 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 an intraperitoneal injection. In a series of control experiments the possible effects of both vehicle solutions were tested.

2.3. Microdialysis procedure

Microdialysis probes of a concentric design (0.5 mm o.d., a 2-mm dialysing membrane) were used (CMA 12, CMA/Microdialysis, Sweden). The probes were perfused with artificial cerebrospinal fluid containing (in mM): Na^+ 150; K^+ 3.0; Ca^{2+} 1.2, Mg^{2+} 0.8; $H_2PO_4^-$ 31.0; Cl^- 155; pH 7.4. All probes were perfused at 2 μl/min for 1–2 h before the commencement of sample collection and the same constant flow rate was maintained with a microdialysis pump (CMA/Microdialysis) throughout the experiment.

2.4. High-pressure liquid chromatography of amino acids

Amino acids were assayed in dialysates kept frozen at −70 °C and thawed immediately prior to analysis. The concentrations of glutamate, aspartate, alanine and taurine were measured by high-pressure liquid chromatography with fluorescence detection (Shimadzu Scientific Instruments, Kyoto, Japan) after pre-column derivatization with *o*-phthaldialdehyde (Sigma) (Kendrick et al., 1996). Derivatization was performed by an autoinjector SIL-10AD (Shimadzu Scientific Instruments). The samples in the autoinjector were maintained at 4 °C by a Peltier thermoelectric sample cooler. The samples and 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. × 25 cm, Waters, UK) equipped with a guard column (4 × 20 mm). The mobile phase was 0.075

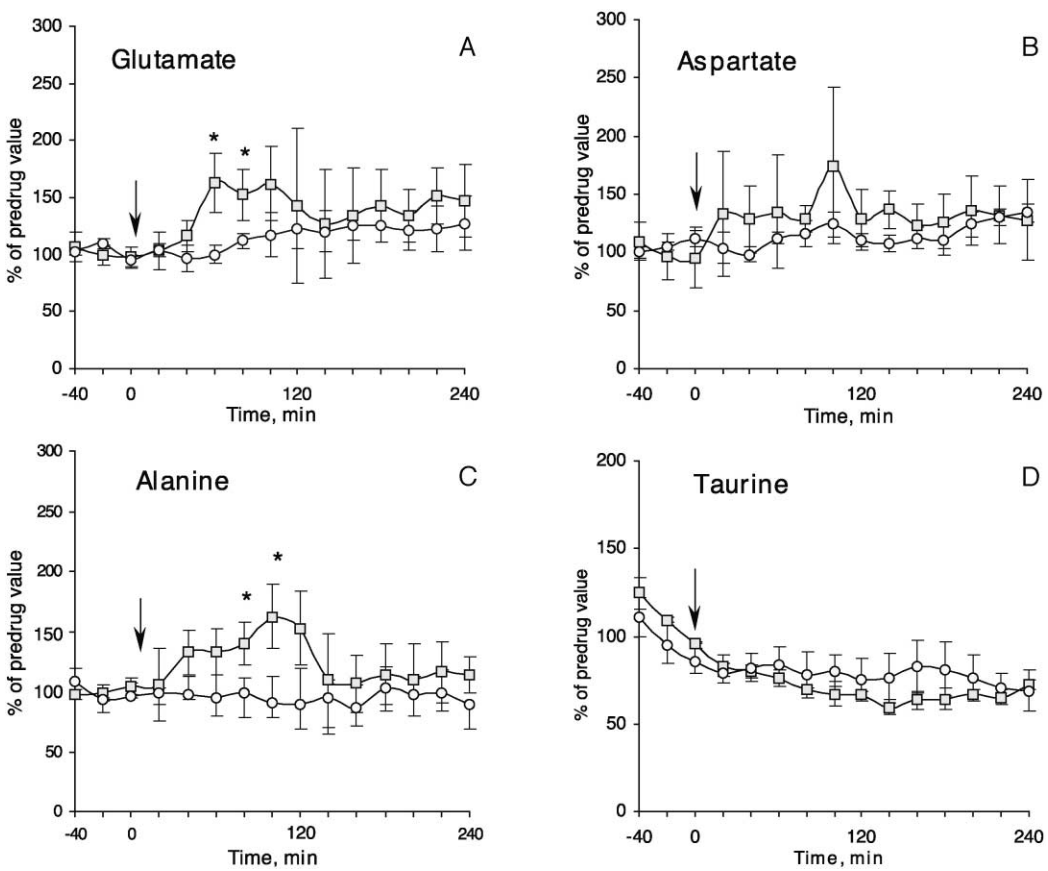

Fig. 4. The effect of acute administration of sydnocarb on the extracellular levels of (A) glutamate, (B) aspartate, (C) alanine and (D) taurine in the caudate-putamen in halothane-anesthetized rats (-○- propyleneglycol/0.85% NaCl × 1, i.p.; -□- sydnocarb, 23.8 mg/kg × 1, i.p.). * Significant difference from control, $P < 0.05$, $n = 6$. The arrows indicate the moment of drug administration.

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 analysed by PC using VPclass5 software and quantified by comparing the peak areas to those of standards.

2.5. Data analysis

The relative magnitudes of the evoked effects of different treatments were estimated by expressing them as percentage changes from baseline (100%). The basal levels of amino acids for each rat were defined as the mean of three successive baseline values obtained prior to the injection of drugs or vehicle. Statistical analysis was made with Excel2000 software (Microsoft, USA). Comparisons of different groups were done using two-way analysis of variance (ANOVA), group × time, with the repeated measures as one variable. In all cases, the limit of significance was set at $P < 0.05$.

3. Results

3.1. The basal extracellular levels of amino acids

The basal extracellular levels of amino acids, measured in 69 rats, were in the caudate-putamen 0.384 ± 0.142 μM for glutamate, 0.241 ± 0.094 μM for aspartate, 0.221 ± 0.027 μM for alanine and 1.214 ± 0.218 μM for taurine. These values are not corrected for the recovery in the dialysate samples.

3.2. Effects of single and subchronic D-amphetamine administrations

A single dose of D-amphetamine (5.0 mg/kg × 1, $n = 7$) significantly elevated (ANOVA, $P < 0.05$, when compared to the saline-treated group) the extracellular levels of glutamate in the caudate-putamen (Fig. 2A) at 40 and 120 min after the injection. No immediate increase in glutamate occurred after saline administration due to the possible stress of saline injections. D-amphetamine increased the extracellular levels of aspartate in the same samples (Fig. 2B). The effect remained significant (ANOVA, $P < 0.05$,

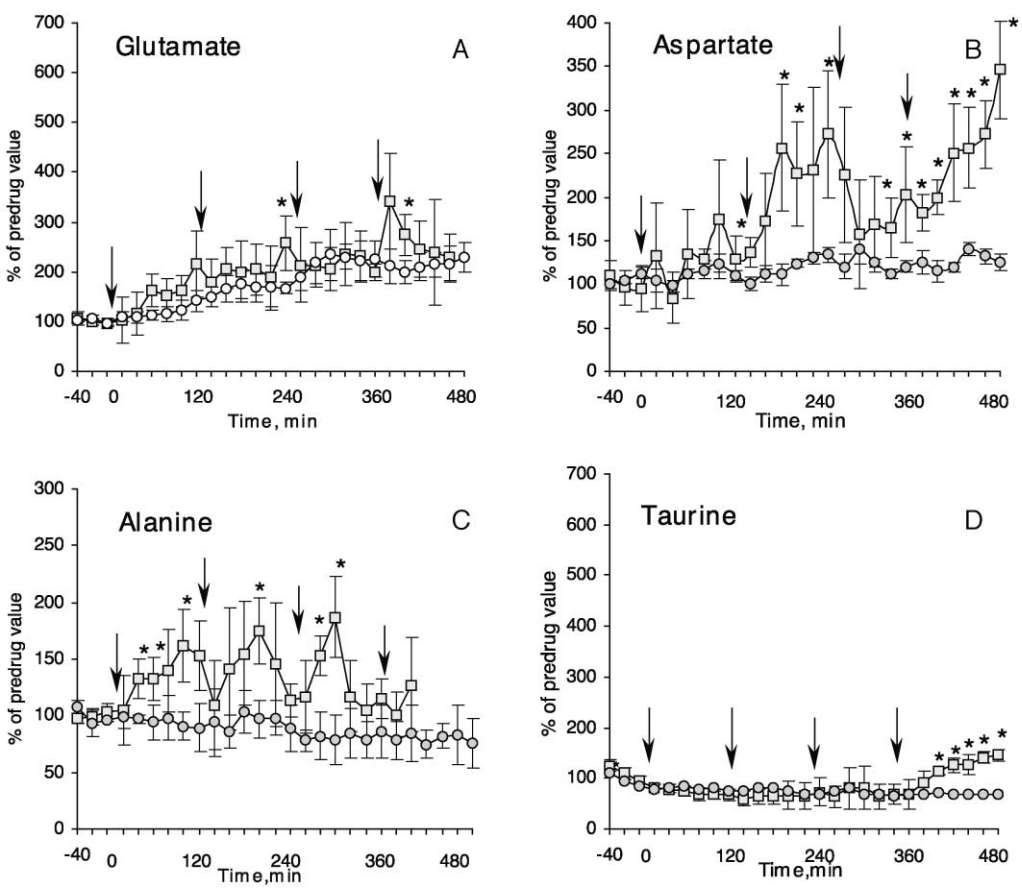

Fig. 5. The effect of subchronic administration of sydnocarb (23.8 mg/kg × 4, i.p.) on the extracellular levels of (A) glutamate, (B) aspartate, (C) alanine and (D) taurine in the caudate-putamen in halothane-anesthetized rats (-○- propyleneglycol/0.85% NaCl × 4, i.p.; -□- sydnocarb, 23.8 mg/kg × 4, i.p.). * Significant difference from control, $P < 0.05$, $n = 6$. The arrows indicate the moments of drug administration.

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 (Fig. 2C). The extracellular level of taurine was not affected by D-amphetamine administration (Fig. 2D).

Subchronic D-amphetamine administration (5.0 mg/kg $\times 4$, $n = 8$) caused a marked gradual increase in the extracellular levels of glutamate and taurine up to 400–550% and 480–580% of controls, respectively (Fig. 3A and D) and a moderate increase in the aspartate and alanine levels up to 170–200% and 140–210%, respectively (Fig. 3B and C). The effect was already discernible in the case of glutamate, aspartate and alanine 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 obtained in the alanine concentration, but the level was quickly restored after the third injection of D-amphetamine (Fig. 3C).

3.3. Effects of single and subchronic sydnocarb administrations

A single sydnocarb injection (23.8 mg/kg $\times 1$, $n = 6$) increased the extracellular glutamate level temporarily (Fig. 4A) and did not change the levels of aspartate and taurine (Fig. 4B and D). A short-lasting but significant increase in the extracellular alanine level was observed during the second hour after the injection (the maximum increase $160 \pm 42\%$ of control at 100 min, ANOVA, $n = 6$). 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 (Fig. 4A).

Subchronic sydnocarb administration (23.8 mg/kg $\times 4$, $n = 6$) elicited marked increases in the aspartate level after the second and fourth injections (up to 250–350% in both cases) (Fig. 5B). The level of glutamate was practically unaffected when compared to the control group (Fig. 5A). The alanine level increased temporarily after each administration of sydnocarb (Fig. 5C). The taurine level was not altered within the first 6 h and significantly increased only after the last (fourth) injection. The final extracellular level of taurine attained after sydnocarb treatment was three times less than that after D-amphetamine administration (Fig. 5D).

4. Discussion

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, 1999). The neurotoxic consequences of methamphetamine have been associated with an increase in the core temperature (Askew, 1962), metabolic and oxidative stress (Cadet and Brannock, 1998; Burrows et al., 2000) and excessive glutamate release (Nash and Yamamoto, 1992; Stephans and Yamamoto, 1994; Ohmori et al., 1996). Repeated, but not single, systemic administration of amphetamine or methamphetamine leads 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 sites for dopamine and to inhibition of tyrosine hydroxylase and tryptophan hydroxylase 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 current hypotheses is therefore that the excessive release of dopamine from nerve endings mediates the neurotoxic action of amphetamines. Catecholamines have been found to be toxic in vivo and in vitro (Filloux and Townsend, 1993; Hastings et al., 1996; Stokes et al., 1999). However, microdialysis experiments have shown that the reduced toxicity of methamphetamine at low environmental temperature (5 °C) is not the result of decreased dopamine release (LaVoie and Hastings, 1999). The competitive and non-competitive NMDA receptor antagonists attenuate amphetamine- and methamphetamine-induced neurotoxicity (Sonsalla et al., 1991), whereas they do not block the increase in dopamine efflux (Bowyer et al., 1993; Miller and Abercrombie, 1996). 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., 2000).

The mechanism by which amphetamines increase extracellular glutamate is poorly understood. Amphetamines may evoke the release of amino acids either by affecting the release (or uptake) processes or 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). The possible involvement of excitatory amino acids in the mechanism of hyperlocomotion induced by psychostimulants is still not unequivocally proved. However, the D-amphetamine challenge has increased the level of extracellular glutamate in the striatum, implicating the glutamate receptors in behavioral sensitization to D-amphetamine (Wolf and Khasa, 1991; Baldwin et al., 1993; Bickerdike and Abercombie, 1999). A single dose of systemically administered D-amphetamine has been shown likewise to increase the levels of excitatory amino acids in the striatum (Reid et al., 1997, Burrows et al., 2000; Rawls and McGinty, 2000). In our present studies the increases in extracellular glutamate and aspartate after a single dose of systemically administrated D-amphetamine were relatively moderate. 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 striata of freely moving rats Cepeda and Levine, 1998; Exposito

et al., 1999; Vizi, 2000). However, the ability of local or systemic administration of low doses of amphetamine to elevate markedly extracellular glutamate and aspartate seems to depend on the degree of activation of basal ganglia circuits (O'Dell et al., 1994; Abarca and Bustos, 1999; Burrows at al., 2000). This indirect effect was thus a likely cause of the elevation of extracellular glutamate in our experiments. This assumption is also consistent with the partial neuroprotective effects of dopamine receptor antagonists haloperidol, eticloprid and SCH23390 and underlines the importance of dopamine receptor activation in the development of amphetamine-induced neurotoxicity (O'Dell et al., 1993; Albers and Sonsalla, 1995).

There are several possible additional mechanisms underlying the gradual increase in extracellular glutamate after repeated or single high-dose administration of D-amphetamine in other brain structures (Stephans and Yamamoto, 1994; Ohmori et al., 1996; Wolf and Xue, 1999) and the striatum (the present study). One current theory is that the excessive release of dopamine triggers an accumulation of reactive dopamine metabolites and hyperproduction of hydroxyl radicals. We have indeed shown that the production of hydroxyl radicals is intensified during the same D-amphetamine treatment which was applied here (Anderzhanova et al., 2000). 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) or arachidonic acid (Volterra et al., 1994) upon D-amphetamine administration. The slowly incurring effects of these agents could underlie the delayed increase in extracellular glutamate seen in the present experiments.

The energy consumption of the brain is increased after systemic metamphetamine 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). There obtains a possible correlation between the increase in glutamate release and the methamphetamine-induced depletion of energy stores. The activation of NMDA receptors by glutamate activates nitric oxide synthase (Lizasoain et al., 1996) The subsequent enhanced generation of nitric oxide is followed by the formation of reactive oxygen species 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 reactive oxygen species. 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 Nickals, 1993; Bruno et al., 1994).

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 previously 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 neuroprotective and osmoregulatory (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, 1997, 1998). We now show 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 ammonia generated by glutaminase in the former (Waagepetersen et al., 2000). This mechanism could explain the changes in extracellular alanine noted here.

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 (Gainetdinov et al., 1997; Anderzhanova et al., 2000), but its efficacy to elevate 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). In the present experiments, sydnocarb affected the extracellular levels of amino acids markedly less than D-amphetamine at equimolar doses. The elevation in extracellular aspartate upon sydnocarb administration was relatively more pronounced that the increase in glutamate, whereas the effects of D-amphetamine were precisely the opposite. Furthermore, Witkin et al. (1999) have shown that the convulsive effects of cocaine are significantly aggravated by methamphetamine but not by sydnocarb. All these findings indicate that the mechanisms of action of sydnocarb are different from those of D-amphetamine.

We conclude that the increase in the extracellular level of glutamate contributes to excitotoxic damage to neurons caused by D-amphetamine. A massive increase in extracellular taurine reflects the hyperactivation of glutamatergic neurotransmission elicited by D-amphetamine. Extracellular taurine could be a useful biochemical marker of neurotoxicity. The mode of action of sydnocarb differs from that of D-amphetamine and sydnocarb may be less neurotoxic than D-amphetamine, since it elicits less marked changes in extracellular glutamate.

Acknowledgements

This work was supported by grants from the Centre for International Mobility (CIMO) and the Medical Research Fund of Tampere University Hospital, Finland.

References

Abarca, J., Bustos, G., 1999. Differential regulation of glutamate, aspartate and γ-amino-butyrate release by *N*-methyl-D-aspartate receptors in rat striatum after partial and extensive lesions to the nigro-striatal dopamine pathway. Neurochem. Int. 35, 19–33.

Abekawa, T., Ohmori, T., Koyama, T., 1994. Effects of repeated administration of a high dose of methamphetamine on dopamine and glutamate release in rat striatum and nucleus accumbens. Brain Res. 643, 276–281.

Albers, D.S., Sonsalla, P.K., 1995. Methamphetamine-induced hyperthermia and dopaminergic neurotoxicity in mice: pharmacological profile of protective and non-protective agents. J. Pharmacol. Exp. Ther. 275, 1104–1114.

Ali, S.F., Newport, G.D., Holson, R.R., Slikker Jr., W., Bowyer, J.F., 1994. Low environmental temperatures or pharmacologic agents that produce hypothermia decrease methamphetamine neurotoxicity in mice. Brain Res. 658, 33–38.

Anderzhanova, E.A., Afanasèv, I.I., Kudrin, V.S., Rayevsky, K.S., 2000. Effect of D-amphetamine and sydnocarb on the extracellular level of dopamine, 3,4-dihydroxyphenylacetic acid and hydroxyl radicals generation in rat striatum. Ann. N. Y. Acad. Sci. U. S. A. 914, 137–145.

Askew, B.M., 1962. Hyperpyrexia as a contributing factor in the toxicity of amphetamine in aggregated mice. Br. J. Pharmacol. 19, 245–257.

Baldwin, H.A., Colado, M.I., Murray, T.K., De Souza, R.J., Green, A.R., 1993. Striatal dopamine release in vivo following neurotoxic doses of methamphetamine and effect of the neuroprotective drugs, chlormethiazole and dizocilpine. Br. J. Pharmacol. 108, 590–596.

Bickerdike, M.J., Abercrombie, E.D., 1999. Enhanced acetylcholine release in striatum after chronic amphetamine is NMDA-dependent. NeuroReport 10, 77–80.

Bowyer, J.F., Tank, A.W., Newport, G.D., Slikker Jr., W., Ali, S.F., Holson, R.R., 1992. The influence of environmental temperature on the transient effects of methamphetamine on dopamine levels and dopamine release in rat striatum. J. Pharmacol. Exp. Ther. 260, 817–824.

Bowyer, J.F., Gough, B., Slikker Jr., W., Lipe, G.W., Newport, G.D., Holson, R.R., 1993. Effects of the cool environment or age on methamphetamine-induced dopamine release in the caudate-putamen of female rats. Pharmacol. Biochem. Behav. 44, 87–98.

Bowyer, J.F., Davies, D.L., Schmued, L., Broening, H.W., Newport, G.D., Slikker Jr., W., Holson, R.R., 1994. Futher studies of the role of hyperthermia in methamphetamine neurotoxicity. J. Pharmacol. Exp. Ther. 268, 1571–1580.

Bruno, V.M.G., Golberg, M.P., Dugan, L.L., Giffard, R.G., Choi, D.W., 1994. Neuroprotective effect of hypothermia in cortical cultures exposed to oxygen-glucose deprivation or excitatory amino acids. J. Neurochem. 63, 1398–1406.

Burrows, K.B., Nixdorf, W.L., Yamamoto, B.K., 2000. Central administration of methamphetamine synergizes with metabolic inhibition to deplete striatal monoamines. J. Pharmacol. Exp. Ther. 292, 853–860.

Cadet, J.L., Brannock, C., 1998. Free radicals and the pathology of the brain dopamine systems. Neurochem. Int. 32, 117–131.

Cepeda, C., Levine, M.S., 1998. Dopamine and *N*-methyl-D-aspartate receptor interaction in the neostriatum. Dev. Neurosci. 20, 1–18.

Chan, P., Di Monte, D.A., Luo, J.J., DeLanney, L.E., Irwin, I., Langston, J.W., 1994. Rapid ATP loss caused by methamphetamine in the mouse striatum: relationship between energy impairment and dopaminergic neurotoxicity. J. Neurochem. 62, 2484–2487.

Cleeter, M.W., Cooper, J.M., Darley-Usmar, V.M., Moncada, S., Schapira, A.H., 1994. Reversible inhibition of cytochrome *c* oxidase, the terminal enzyme of the mitochondrial respiratory chain, by nitric oxide. Implication for neurodegenerative disorders. FEBS Lett. 345, 50–54.

Colado, M.L., Granados, R., O'Shea, E., Esteban, B., Green, A.R., 1998. Role of hyperthermia in the protective action of clomethiazole against MDMA ('ecstasy')-induced neurodegeneration, comparison with the novel NMDA channel blocker AR-R15896AR. Br. J. Pharmacol. 124, 479–484.

Del Arco, A., Gonzalez-Mora, J.L., Armas, V.R., Mora, F., 1999. Amphetamine increases the extracellular concentration of glutamate in striatum of the awake rat: involvement of high affinity transporter mechanisms. Neuropharmacology 38, 943–954.

Exposito, I., Del Arco, A., Segovia, G., Mora, F., 1999. Endogenous dopamine increases extracellular concentrations of glutamate and GABA in striatum of the freely moving rat: involvement of D1 and D2 dopamine receptors. Neurochem. Res. 24, 849–856.

Farfel, G.M., Seiden, L.S., 1995. Role of hypothermia in the mechanism of protection against serotonergic toxicity: II. Experiments with methamphetamine, p-chloroamphetamine, fenfluramine, dizocilpine and dextromethorphan. J. Pharmacol. Exp. Ther. 272, 868–875.

Fibiger, H.C., McGeer, E.G., 1971. Effect of acute and chronic methamphetamine treatment on tyrosine hydroxylase activity in brain and adrenal medulla. Eur. J. Pharmacol. 16, 176–180.

Filloux, F., Townsend, J.J., 1993. Pre- and postsynaptic neurotoxic effects of dopamine demonstrated by intrastriatal injections. Exp. Neurol. 119, 79–88.

Gainetdinov, R.R., Sotnikova, T.D., Grekhova, T.V., Rayevsky, K.S., 1997. Effects of a psychostimulant drug sydnocarb on rat brain dopaminergic transmission in vivo. Eur. J. Pharmacol. 340, 53–58.

Hastings, T.G., Lewis, D.A., Zigmond, M.J., 1996. Role of oxidation in the neurotoxic effect of the intrastriatal dopamine injection. Proc. Natl. Acad. Sci. U. S. A. 93, 1956–1961.

Hotchkiss, A.J., Gibb, J.W., 1980. Long-term effects of multiple doses of methamphetamine on tryptophan hydroxylase and tyrosine hydroxylase activity in rat brain. J. Pharmacol. Exp. Ther. 214, 257–262.

Johnston, L.D., O'Malley, P.M., Bachman, J.G., 1997. National Survey Results on Drug use from the Monitoring the Future Study, 1975–1994. US Department of Health and Human Services, Rockville, MD.

Kendrick, K.M., Guevara-Guzman, R., de la Riva, C., Christensen, J., Ostergaard, K., Emson, P.C., 1996. NMDA and kainate-evoked release of nitric oxide and classical transmitters in the rat striatum: in vivo evidence that nitric oxide may play a neuroprotective role. Eur. J. Neurosci. 8, 2619–2634.

LaVoie, M.J., Hastings, T.G., 1999. Dopamine quinone formation and protein modification associated with the striatal neurotoxicity of methamphetamine: evidence against a role for extracellular dopamine. J. Neurosci. 19, 1484–1491.

Lizasoain, I., Moro, M.A., Knowles, R.G., Darley-Usmar, V., Moncada, S., 1996. Nitric oxide and peroxynitrite exert distinct effect on the mitochondrial respiration which are differentially blocked by glutathione or glucose. Biochem. J. 314, 877–880.

Mashkovsky, M.D., Altshuler, R.A., Avrutsky, G.Ya., Aleksandrovich, Yu.A., Smulevich, R.A., 1971. Experimental and clinical study on new psychostimulator sydnocarb. Korsakov J. Neurol. Psychiatry 71, 1704–1709.

Miller, D.W., Abercrombie, E.D., 1996. Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. Brain Res. Bull. 40, 57–62.

Miller, D.B., O'Callaghan, J.P., 1997. Environment-, drug- and stress-induced alterations in body temperature affect the neurotoxicity of substituted amphetamines in the C57BL/6J mouse. J. Pharmacol. Exp. Ther. 270, 752–760.

Nash, J.F., Yamamoto, B.K., 1992. Methamphetamine neurotoxicity and striatal glutamate release: comparison to 3,4-methylenedioxymethamphetamine. Brain Res. 581, 237–243.

O'Dell, S.J., Weihmuller, F.B., Marshall, J.F., 1993. Methamphetamine-induced dopamine overflow and injury to striatal dopamine terminals: attenuation by dopamine D_1 and D_2 antagonists. J. Neurochem. 60, 1792–1799.

O'Dell, S.J., Weihmuller, F.B., McPherson, R.J., Marshall, J.F., 1994. Excitotoxic striatal lesions protect against subsequent methamphetamine-induced dopamine depletions. J. Pharmacol. Exp. Ther. 269, 1319–1325.

Ohmori, T., Abekawa, T., Koyama, T., 1996. The role of glutamate in behavioral and neurotoxic effects of methamphetamine. Neurochem. Int. 29, 301–307.

Oja, S.S., Saransaari, P., 1996. Taurine as osmoregulator and neuromodulator in the brain. Metab. Brain Dis. 11, 153–164.

Oja, S.S., Saransaari, P., 2000. Modulation of taurine release by glutamate receptors and nitric oxide. Prog. Neurobiol. 62, 407–425.

Paxinos, G., Watson, C., 1996. The Rat Brain Sterotaxic Coordinates. 2nd edn. Academic Press, Sydney.

Rawls, S.M., McGinty, J.F., 2000. Delta opioid receptors regulate calcium-dependent, amphetamine-evoked glutamate levels in the rat striatum: an in vivo microdialysis study. Brain Res. 861, 296–304.

Reid, M.S., Hsu Jr., K., Berger, S.P., 1997. Cocaine and amphetamine preferentially stimulate glutamate release in the limbic system: studies on the involvement of dopamine. Synapse 27, 95–105.

Ricaurte, G.A., Schuster, C.R., Seiden, L.S., Miller, R.J., Westley, J., 1980. Long term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in rat brains: a regional study. Brain Res. 193, 153–163.

Ricaurte, G.A., Guillery, R.W., Seiden, L.S., Schuster, C.R., Moore, R.Y., 1982. Dopamine nerve terminals degeneration produced by high doses of methylamphetamine in the rat brain. Brain Res. 235, 93–103.

Rockhold, R.W., 1998. Glutamatergic involvement in psychomotor stimulant action. Prog. Drug Res. 50, 155–192.

Rudenko, G.M., Altshuler, R.A., 1978. Experimental and clinical study of sydnocarb. Hung. Pharmacother. 124, 150–154.

Saransaari, P., Oja, S.S., 1992. Release of GABA and taurine from brain slices. Prog. Neurobiol. 38, 455–482.

Saransaari, P., Oja, S.S., 1997. Enhanced taurine release in cell-damaging conditions in the developing and ageing mouse hippocampus. Neuroscience 79, 847–854.

Saransaari, P., Oja, S.S., 1998. Release of endogenous glutamate, aspartate, GABA, and taurine from hippocampal slices from adult and developing mice under cell-damaging conditions. Neurochem. Res. 23, 563–570.

Saransaari, P., Oja, S.S., 2000. Taurine and neural cell damage. Amino Acids 19, 509–526.

Sonsalla, P.K., 1995. The role of *N*-methyl-D-aspartate receptors in dopaminergic neuropathology produced by the amphetamines. Drug Alcohol Depend. 37, 101–105.

Sonsalla, P.K., Riordan, D.E., Heikkila, R.E., 1991. Competitive and non-competitive antagonists of *N*-methyl-D-aspartate receptors protect against methamphetamine-induced dopaminergic damage in mice. J. Pharmacol. Exp. Ther. 256, 506–512.

Stephans, S., Yamamoto, B.K., 1994. Methamphetamine-induced neurotoxicity: role for glutamate and dopamine efflux. Synapse 17, 203–209.

Stephans, S.E., Whittingham, T.S., Douglas, A.J., Lust, W.D., Yamamoto, B.K., 1998. Substrates of energy metabolism attenuate methamphetamine-induced neurotoxicity in striatum. J. Neurochem. 71, 613–621.

Stokes, A.H., Hastings, T.G., Vrana, K.E., 1999. Cytotoxic and genotoxic potential of dopamine. J. Neurosci. Res. 55, 659–665.

Trotti, D., Danbolt, N.C., Volterra, A., 1998. Glutamate transporters are oxidant-vulnerable: a molecular link between oxidative and excitotoxic neurodegeneration. Trends Pharmacol. Sci. 19, 328–334.

Vizi, E.S., 2000. Role of high affinity receptors and membrane transporters in nonsynaptic communication and drug action in the central nervous system. Pharmacol. Rev. 52, 63–89.

Volterra, A., Trotti, D., Racagni, G., 1994. Glutamate uptake is inhibited by arachidonic acid and oxygen radicals via two distinct and additive mechanisms. Mol. Pharmacol. 46, 986–992.

Waagepetersen, H.S., Sonnewald, U., Larsson, O.M., Schousboe, A., 2000. A possible role of alanine for ammonia transfer between astrocytes and glutamatergic neurons. J. Neurochem. 75, 471–479.

Wagner, G.C., Ricaurte, G.A., Schuster, C.R., Seiden, L.S., Miller, R.J., Westley, J., 1980. Long lasting depletion of striatal dopamine and loss of dopamine uptake sites following repeated administration of methamphetamine. Brain Res. 181, 1151–1160.

Weihmuller, F.B., O'Dell, S.J., Marshall, J.F., 1992. MK-801 protection against methamphetamine-induced striatal dopamine terminal injury is associated with attenuated dopamine overflow. Synapse 11, 155–163.

Witkin, J.M., Savtchenko, N., Mashkovsky, M., Beekman, M., Munzar, P., Gasior, M., Goldberg, S.R., Ungard, J.T., Kim, J., Shippenberg, T., Chefer, V., 1999. Behavioural, toxic, and neurochemical effects of sydnocarb, a novel psychomotor stimulant: comparisons with methamphetamine. J. Pharmacol. Exp. Ther. 288, 1298–1310.

Wolf, M.E., Khasa, M.R., 1991. Repeated administration of MK-801 produces sensitization to its own locomotor stimulant effects but blocks sensitization to amphetamine. Brain Res. 562, 164–168.

Wolf, M.E., Xue, C.-J., 1998. Amphetamine and D1 dopamine receptor agonists produce biphasic effects on glutamate efflux in rat ventral tegmentum area: modification by repeated amphetamine administration. J. Neurochem. 70, 198–209.

Wolf, M.E., Xue, C.-J., 1999. Amphetamine-induced glutamate efflux in the rat ventral tegmental area is prevented by MK-801, SCH 23390, and ibotenic acid lesion of the prefrontal cortex. J. Neurochem. 73, 1529–1538.

Wolf, M.E., Xue, C.-J., Li, Y., Wavak, D., 2000. Amphetamine increases glutamate efflux in the rat ventral tegmental area by a mechanism involving glutamate transporters and reactive oxygen species. J. Neurochem. 75, 1634–1644.

Ye, Z.C., Sontheimer, H., 1996. Cytokine modulation of glial glutamate uptake: a possible involvement of nitric oxide. NeuroReport 7, 2181–2185.

Zeevalk, G.D., Nicklas, W.J., 1992. Evidence that the loss of the voltage-dependent Mg^{2+} block at the *N*-methyl-D-aspartate receptors underlies receptor activation during inhibition of neuronal metabolism. J. Neurochem. 59, 1211–1220.

Zeevalk, G.D., Nickals, W.J., 1993. Hypothermia, metabolic stress and NMDA-mediated excitotoxicity. J. Neurochem. 31, 1445–1453.

Zeevalk, G.D., Derr-Yellin, E., Nicklas, W.J., 1995. NMDA receptor involvement in toxicity to dopamine neurons in vitro caused by the succinate dehydrogenase inhibitor 3-nitropropionic acid. J. Neurochem. 61, 455–458.