ELSEVIER

Pharmacology, Biochemistry and Behavior 69 (2001) 653–658

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Effects of amphetamine and sydnocarb on dopamine release and free radical generation in rat striatum

Ilya I. Afanas'ev, Elmira A. Anderzhanova, Vladimir S. Kudrin and Kirill S. Rayevsky*

Laboratory of Neurochemical Pharmacology, Research Institute of Pharmacology, Russian Academy of Medical Sciences, Baltiyskaya str., 8, Moscow, 125315 Russia

Received 18 September 2000; received in revised form 26 April 2001; accepted 30 April 2001

Abstract

Microdialysis technique was used to compare the effects of four repeated intraperitoneal administrations of two psychostimulant drugs, D-amphetamine and sydnocarb, at the equimolar doses 5 and 23.8 mg/kg, respectively, on the extracellular level of dopamine (DA), 3,4-dihydroxyphenylacetic acid (DOPAC) and hydroxyl radicals (·OH) in the dorsal striatum of freely moving 3-month-old male Wistar rats 250–300 g in weight. D-Amphetamine caused immediate increase of DA concentration up to 950% with quick decline towards baseline values thereafter, followed by much less increase after further injections. Sydnocarb elicited moderate elevation in DA level achieving 400% after the fourth injection. D-Amphetamine induced deep decrease in DOPAC concentration, while sydnocarb caused its increase after the first and second dosing. Both drugs enhanced generation of ·OH, the effect of D-amphetamine was more pronounced. D-Amphetamine induced more intensive stereotyped behavior in rats compare to sydnocarb. It is concluded that the psychostimulant action of sydnocarb is accompanied by facilitation of the central dopaminergic transmission in rat neostriatum and followed by less pronounced neurotoxic effect than that of D-amphetamine. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Dopamine release; Hydroxyl radicals; Microdialysis; Psychostimulant drug; D-Amphetamine; Sydnocarb

1. Introduction

D-Amphetamine and its analogues have been shown to release dopamine (DA) from nerve terminals by several mechanisms including reversal of the DA uptake transporter (Nakajima et al., 1999) and disruption of DA vesicular stores (Sharp et al., 1986; Sulzer and Rayport, 1990; Weihmuller et al., 1992). It is also known that at the high dose level as well as under repeated administration, D-amphetamine and its congeners are able to produce neurotoxic effects including depletion of endogenous DA from its neuronal stores and enhanced generation of reactive oxygen species (Huang et al., 1997; Robinson and Becker, 1986). A possible role of the DA released as well as hydroxyl radicals (·OH) generated during the action of amphetamine-like drugs on the nerve terminals in the developing of neurotoxicity phenomena has been suggested (Berman et al., 1996; Huang et al., 1997; Yamamoto and Zhu, 1998), however, the exact mechanisms of neurotoxic action of psychostimulants are still poorly understood.

Sydnocarb (3-(β-phenylisopropyl)-*N*-phenyl-carbamoyl-sydnonimine, MW = 322) was introduced to clinical practice in Russia as a psychostimulant drug effective for the treatment of neurasthenia, some forms of depression, narcolepsy, and attention deficit hyperactivity disorder in children (Altshuler et al., 1973). Several important features of sydnocarb, which distinguishes the drug from D-amphetamine, were demonstrated in clinical trials, i.e., gradual developing of mild stimulatory effect, long-lasting action, low abused potential, and lack of peripheral sympathomimetic effects (Rudenko and Altshuler, 1979). The exact mechanisms by which sydnocarb elicits psychostimulant effects remain uncertain, however, some data from animal studies indicate a possible involvement of brain dopaminergic system (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 reuptake of DA and noradrenaline by rat brain synaptosomes (Erdo et al., 1981), and increases

* Corresponding author. Tel.: +7-95-155-4797; fax: +7-95-151-1261.
E-mail address: ksrayevsky@mtu-net.ru (K.S. Rayevsky).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00574-3

the extracellular concentration of DA in the striatum of freely moving rats (Gainetdinov et al., 1997).

Although the available information is limited, sydnocarb appears to differ from D-amphetamine by its mechanism of action. Unlike the latter, sydnocarb releases DA in a tetrodotoxin-sensitive and Ca^{2+}-dependent manner (Gainetdinov et al., 1997). In the recent neurochemical study, sydnocarb was shown to display psychomotor stimulant effects on mice that are shared by methamphetamine while demonstrating lower potency and toxicity (Witkin et al., 1999). Therefore, neurotoxic potential of this compound needs to be studied in more details.

In this work, we used microdialysis to test effects of repeated administrations of D-amphetamine (5 mg/kg) and an equimolar dose of sydnocarb (23.8 mg/kg) on extracellular levels of DA, its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC), and ·OH in the dorsal striatum of freely moving rats. Experimental protocol of repeated administrations of high doses of the psychostimulant drug was used according to previous studies aimed to estimate neurotoxic effects of drug (O'Dell et al., 1991; Robinson and Camp, 1987; Wolf et al., 1994). To estimate relationship between microdialysis data and behavioral effects of drugs, the pattern of stereotyped behavior was assessed in parallel. The content of DA and its metabolites in the rat striatum was measured ex vivo 7 days after the experiment.

2. Methods and materials

2.1. Intracerebral dialysis

All experiments were carried out in accordance with the Russian Academy of Medical Sciences Animal Research Committee Guide.

The brain dialysis method was used as described elsewhere (Zetterstrom et al., 1984). Briefly, male Wistar rats (250–300 g) were anaesthetized with chloral hydrate (400 mg/kg ip) and placed in a stereotaxic apparatus. Handmade dialysis probes of concentric type (4 mm dialysis membrane, Hospal, Italy, 20 kDa cutoff, outer diameter of 0.5 mm), designed as described elsewhere (Wolf et al., 1994), were implanted into the right striatum (coordinates: anterior +0.5, lateral +3, ventral −7.0, relative to bregma; Paxinos and Watson, 1982). Placement of probes was verified by subsequent morphological examination. Following surgery, animals were returned to their home cages with free access to food and water and were kept there up to 24 h.

The day following surgery, the dialysis probes were connected to a microinfusion system and 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^- 31.0; Cl^- 155; pH 7.4). After 1 h equilibration period, the perfusate was collected every 20 min in small replaceable Eppendorf tubes mounted on the animal head using a lightweight harness. At least three basal samples were taken before the first drug administration. Every animal received four intraperitoneal drug injections each given 2 h apart. Perfusate samples were assayed for DA and its metabolites using high performance liquid chromatography with electrochemical detection (HPLC/ED, BAS LC-4B, Bioanalytical System, West Lafayette, IN). DA and DOPAC were separated on a reverse-phase column (Ultrasphere ODS, 5 μm, 4.6 × 150 mm) using 0.1 M citrate-phosphate mobile phase containing 1.1 mM octane sulfonic acid, 0.1 mM EDTA, and 9% acetonitrile (pH 3.7) and detected by a glassy carbon working electrode set at +0.8 V.

To evaluate the level of hydroxyl radical generation, the salicylate method was used (Huang et al., 1997; Jones et al., 1998). Briefly, sodium salicylate (5 mM) was solved in CSF at pH 7.4 before the perfusion. The formation of 2,3-dihydroxybenzoic acid (2,3-DHBA, a product of reaction between salicylic acid and hydroxyl radicals) was detected by HPLC/ED in the same samples as DA and DOPAC.

2.2. Behavioral tests

In a separate set of experiments, the effects of drugs on stereotyped behavior of rats were studied. Immediately before and at 20-min intervals after drug administration, animals were assessed for stereotyped behavior. For this procedure, each animal was observed individually for a 10-s period every 20 min. Stereotyped behavior was discriminated into stereotyped sniffing (rhythmic movement of the snout and head along the cage wall or floor, accompanied by rapid movements of vibrissae), licking (protrusion of the tongue against the cage wall or floor), and gnawing (Kroph and Kuschinsky, 1993). Further qualification of behavior was performed using a conventional 0–6 point stereotypy rating scale (Havemann et al., 1986): 0 (*no stereotypies*); 1 (*discontinuous sniffing*); 2 (*continuous sniffing*); 3 (*discontinuous licking*); 4 (*continuous licking*); 5 (*discontinuous gnawing*); 6 (*continuous gnawing*).

2.3. Ex vivo determination of DA and DOPAC

One week after the treatment with sydnocarb or D-amphetamine (the same schedule and dosage as for microdialysis studies), rats were decapitated and striata were taken. The tissue was homogenized in 0.1 N perchloric acid with 0.5 μM 3,4-dihydroxybenzoic acid (as internal standard) and centrifuged at 10,000 × *g* and 4°C below zero for 10 min. Tissue contents of DA and DOPAC in these supernatants were determined by HPLC/ED method as described above.

2.4. Drugs

In the present study, sydnocarb (Center for Chemistry of Drugs, Moscow, Russia) and D-amphetamine sulphate (Sigma, USA) were used. Sydnocarb was suspended in Tween-60, made up to volume with saline and injected

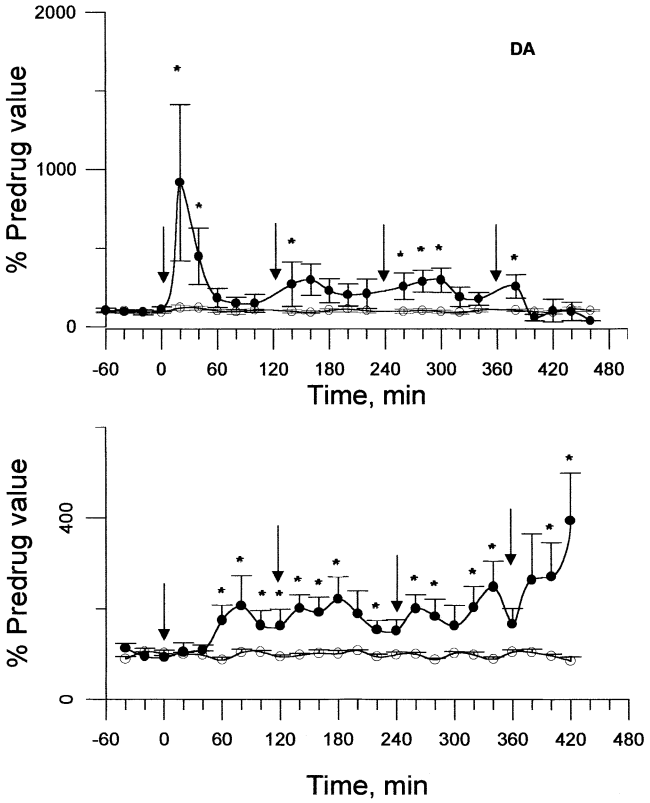

Fig. 1. The effect of D-amphetamine (5 mg/kg ip, upper panel) and sydnocarb (23.8 mg/kg ip, lower panel) on the extracellular concentration of dopamine measured by microdialysis technique in freely moving rats. Arrows indicate the time when the drug (—●—) or saline (—○—) was injected. * Significant difference from the control (saline) group ($P<.05$). Each control and drug-treated group consisted of 10 animals.

intraperitoneally at the dose 23.8 mg/kg equimolar to that of D-amphetamine. D-Amphetamine was dissolved in saline and administered intraperitoneally at the dose 5 mg/kg. The protocol of the drug dosing was used according to that described in the experiments on the assessment of neurotoxic potential of psychomotor stimulant drugs (Jones et al., 1998).

2.5. Data analysis

In microdialysis and behavioral experiments, the average basal values obtained in at least three samples before drug treatment were considered as 100%. Values obtained during drug treatment were expressed as percentage of this basal level. Each point on the time course graphs represents the group mean value ± S.E.M. (the group consisted of 8–10 animals). In ex vivo experiments, the mean contents of DA and DOPAC in striatum of at least eight control rats were considered as 100%, and values obtained after the treatment were expressed as percentage of these levels. Results are presented as the means ± S.E.M. The data obtained in all experiments were analyzed statistically by using the Mann–Whitney U test (two-tailed) or Student's unpaired t test, as well as ANOVA. Significance at the $P<.05$ level and below is reported.

3. Results

Basal concentrations of DA, DOPAC, and 2,3-DHBA in the rat dialysates from dorsal striatum were 111.2 ± 5.6 fmol/20 min/20 μl, 15 ± 2 pmol/20 min/20 μl, and 10 ± 3.5 pmol/20 min/20 μl, respectively (mean ± S.E.M., $n=15$).

D-Amphetamine (5 mg/kg ip) caused an immediate dramatic increase in DA concentration in the striatal perfusates up to 950 ± 450% (Fig. 1, upper panel). This effect was most pronounced 20 min postdrug and quickly reduced towards nearly baseline value thereafter. Subsequent D-amphetamine injections were followed by much less but significant increase of extracellular DA concentration (about 300 ± 80%) gradually declining and becoming nonsignificant 80–100 min after the injection. Sydnocarb at the dose of 23.8 mg/kg (equimolar to 5 mg/kg D-amphetamine) elicited a moderate increase in the extracellular level of DA (Fig. 1, lower panel), which was up to 200 ± 30% after the first dose. Unlike the effect of D-amphetamine, this enhancement persisted at least 4 h with further increase after that. The maximal DA level reached 400 ± 70% of the basal at the end of the experiment.

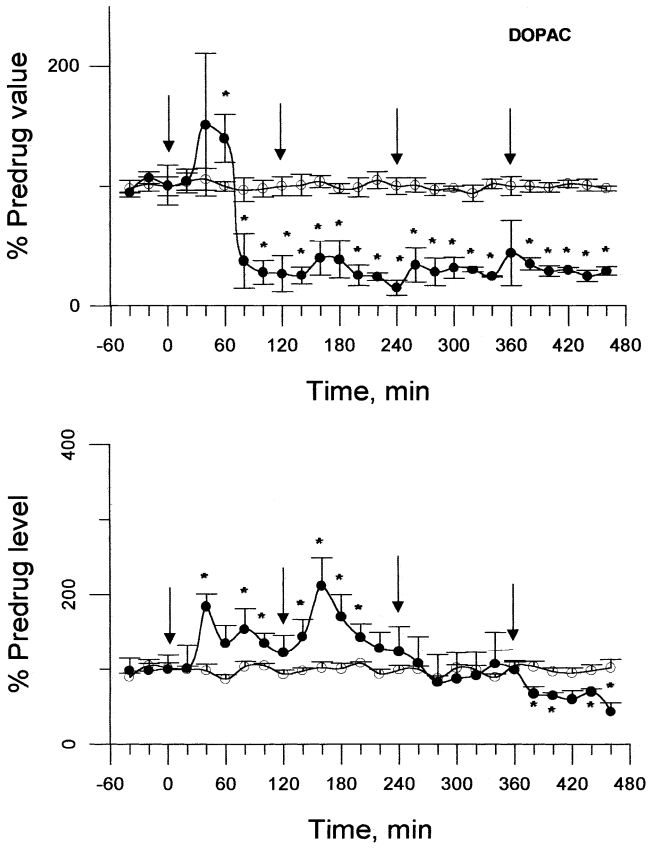

Fig. 2. The effect of D-amphetamine (5 mg/kg ip, upper panel) and sydnocarb (23.8 mg/kg ip, lower panel) on the extracellular concentration of DOPAC measured by microdialysis technique in freely moving rats. Arrows indicate the time when the drug (—●—) or saline (—○—) was injected. * Significant differences from control (saline) group ($P<.05$). Each control and drug-treated group consisted of 10 animals.

DOPAC concentration appeared to be decreased in about 1 h after the first dose of D-amphetamine (Fig. 2, upper panel). The lowered level of this metabolite as compared to control was sustained until the end of experiment (about 40 ± 20%). Unlike D-amphetamine, sydnocarb was found to exert a slight increase in DOPAC extracellular level after the first and second injections (up to 200 ± 50%) followed by a gradual decrease of the latter, which became significantly lower than control level (50 ± 15%) 6 h after the beginning of the experiment (Fig. 2, lower panel).

D-Amphetamine produced a marked increase of 2,3-DHBA level (Fig. 3, upper panel), 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. 2,3-DHBA extracellular concentration in rats treated with sydnocarb appeared to be increased in much less degree (up to 200 ± 25%) as compared to that produced by D-amphetamine at the equimolar dose schedule (Fig. 3, lower panel). The most pronounced effect of sydnocarb took place within the period of 120 and 180 min after the beginning of the experiment with the following decline.

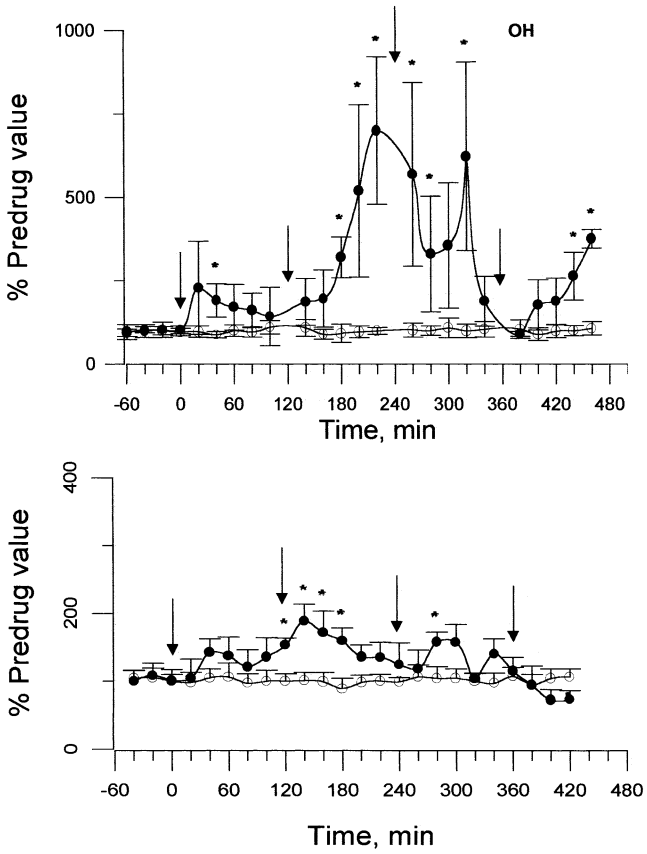

Fig. 3. The effect of D-amphetamine (5 mg/kg ip, upper panel) and sydnocarb (23.8 mg/kg ip, lower panel) on the concentration of 2,3-DHBA measured by microdialysis technique in freely moving rats. Arrows indicate the time when the drug (—●—) or saline (—○—) was injected. * Significant differences from control ($P < .05$). Each control and drug-treated group consisted of 10 animals.

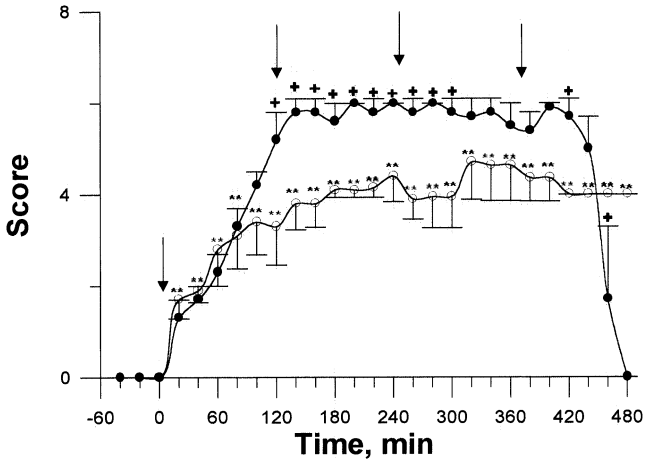

Fig. 4. The effect of D-amphetamine (5 mg/kg ip) and sydnocarb (23.8 mg/kg) on the stereotyped behavior in rats. Arrows indicate the time when D-amphetamine (—●—) or sydnocarb (—○—) was injected. ** Significant differences from the control (saline) group ($P < .01$). + Significant differences between groups of rats treated with sydnocarb and D-amphetamine ($P < .05$). Control and drug-treated group consisted of 10 animals.

D-Amphetamine produced a specific pattern of stereotyped behavior observed shortly after the first injection of the drug and achieved almost 6 points intensity 2 h after the beginning of experiment. This pattern persisted at the same level for about 5 h and quickly decreased thereafter. At the end of the experiment, rats became exhausted and practically could not move. Sydnocarb was also able to elicit stereotyped behavior but in less degree than D-amphetamine. The maximal intensity of abnormal movements achieved 4 ± 0.7 points 3 h after the beginning of the experiment and maintained at this level until the end of the session (Fig. 4). Rats were not exhausted and some signs of stereotyped behavior were obvious even 5–6 h after the end of the experiment.

When measured 1 week after the treatment with sydnocarb, a slight (not significant) depletion of DA content in rat striatum was found. No changes of striatal DOPAC content were observed (data are not shown).

4. Discussion

The clinical use of psychomotor stimulants is restricted by their side effects, the most important of them are neurotoxicity and dependence liability which may develop after repeated intake of the drugs. Therefore, a possibility of introduction of nonabused, low-toxic, psychomotor stimulant drug into clinical practice has been expected for a number of years, but such an agent has yet to be recognized. In this aspect, sydnocarb might be considered as a candidate for being a potential therapeutic agent because of lower toxic effects compared to other amphetamine-like drugs.

Although the exact mechanism by which D-amphetamine induces dopaminergic neurotoxicity is still unclear, the prevention of this toxicity by DA-depleting pretreatment (Seiden et al., 1988) suggests that D-amphetamine-induced overflow of DA into the extracellular space might play a critical role in the mechanisms of cell damage. From the other side, reactive oxygen species (ROS) generating during the autoxidation of DA might also be implicated (Hastings and Zigmond, 1992; Ramassamy et al., 1994). An enhanced generation of such species, i.e., hydroxyl radicals (·OH), in the striatum of amphetamine-treated rats was recently reported (Huang et al., 1997). We now found that repeated injections of D-amphetamine resulted in the dramatic enhancement of ·OH formation that achieved its maximum 80 min after the second injection of the drug. Our findings are in agreement with the data reported where a delayed increase of ·OH formation was observed in desipramine-treated rats after a single injection of the psychostimulant (Huang et al., 1997). In our experiment, we did not need to limit D-amphetamine metabolism because of repeated schedule of dosing. The most obvious outcome of neurotoxicity is neuronal degeneration that was demonstrated in rat forebrain after the treatment with D-amphetamine according to similar protocol as it was used in this study (Bowyer et al., 1998). Moreover, according to Nakajima et al. (1999), striatal DA depletion observed in a number of investigations after the treatment with D-amphetamine-like drugs (O'Dell et al., 1991; Robinson and Camp, 1987) and enhanced ·OH generation demonstrated in this as well as in other studies (Huang et al., 1997; Jones et al., 1998) might be considered as substantial signs of neurotoxicity.

Sydnocarb at the dose equimolar to that of D-amphetamine significantly increased the extracellular DA content, and the time course of this effect was different from that of D-amphetamine. This finding seems to be in accordance with previously observed differences between the mode of action of this drug and of amphetamine-like compounds (Gainetdinov et al., 1997; Witkin et al., 1999). Here we report that ·OH generation increased by sydnocarb was much less pronounced than that caused by D-amphetamine. This probably reflects much less neurotoxic potential of the former drug.

DOPAC extracellular level was significantly decreased after the treatment with D-amphetamine that is consistent with an earlier report (O'Dell et al., 1991). Unlike D-amphetamine, sydnocarb failed to decline DOPAC extracellular level during the first half of the experiment and even increased this parameter that may indicate at a dissimilar mode of action of this drug on the dopaminergic nerve terminals. In contrast to the findings concerning D-amphetamine and its analogues (O'Dell et al., 1991; Robinson and Becker, 1986), in our study, sydnocarb failed to deplete striatal DA and DOPAC content. This also led us to conclude that sydnocarb has less neurotoxic potential compared to D-amphetamine. However, the effect of sydnocarb in the second half of the experiment (last 4 h) differs from that observed during the first half and looks like the effect of amphetamine. Namely, the DA extracellular content increases significantly (up to 400%) while DOPAC level decreases by 50%. This pattern might be explained by an action of possible metabolites of sydnocarb that may inhibit monoamine oxidase (MAO). Sydnocarb itself was reported not to inhibit MAO, but a possible inhibitory effect of its metabolites accumulated in the second part of experiment may not be excluded (Altshuler et al., 1976).

One of the signs of neurotoxicity is stereotyped behavior in rodents. A good correlation between toxic effects of psychostimulant drugs and stereotyped behavior has been reported (Wallace et al., 1999). In our experiments, both D-amphetamine and sydnocarb produced stereotyped behavior in rats, but its severity was different for the two drugs with sydnocarb being less pronounced. As it is shown in Fig. 4, D-amphetamine treatment elicited the most intensive stereotyped behavior that was estimated as score 6 according to the conventional 0–6 point stereotypy rating scale. At the end of experiment, rats became exhausted and practically could not move. On the other hand, sydnocarb elicited less pronounced manifestations of stereotyped behavior.

In principle, the results of this study concerning sydnocarb are in agreement with the findings previously obtained in this laboratory (Gainetdinov et al., 1997). Thus, it might be suggested that the mode of action of sydnocarb differs from that of D-amphetamine. The former substance seems to stimulate brain dopaminergic system and facilitate an enhancement of Ca^{2+}-dependent DA efflux from vesicular stores. From the other hand, D-amphetamine may inhibit the DA reuptake resulting in the decrease of DOPAC extracellular level. Thus, the results of this study provide an evidence that sydnocarb reveals less pronounced neurotoxic effects than D-amphetamine.

In conclusion, sydnocarb, the original psychostimulant drug, at the dose equimolar to that of D-amphetamine, elicited less pronounced effects on DA and DOPAC striatal extracellular level and tissue content, ·OH generation and behavioral stereotypy. In a clinical setting, sydnocarb might have less neurotoxic potential in comparison to D-amphetamine, and, should be given more opportunities to be widely introduced into practice as a mild psychostimulant drug.

Acknowledgments

The work was supported by the grants from INTAS N 96-1502 and RFBR N 98-04-48575.

References

Altshuler RA, Mashkovsky MD, Roschina LF. Sydnocarb — a new stimulator of the central nervous system. Pharmacol Toxicol 1973;1:18–22.

Altshuler RA, Kovalenko TA, Kholodov LE. Study of pharmakokinetic of sydnocarb using the polarography. Khim-Pharm J 1976;2:20–2.

Berman SB, Zigmond MJ, Hastings TG. Modification of dopamine transporter function: effect of reactive oxygen species and dopamine. J Neurochem 1996;67(2):593–600.

Bowyer JF, Peterson SL, Rountree RL, Tor-Agbidye J, Wang GJ. Neuronal degeneration in rat forebrain resulting from D-amphetamine-induced convulsions is dependent on seizure severity and age. Brain Res 1998;809(1):77–90.

Erdo SL, Kiss B, Rosdy B. Inhibition of dopamine uptake by a new psychostimulant mesocarb (Sydnocarb). Pol J Pharmacol Pharm 1981;33: 141–7.

Gainetdinov RR, Sotnikova TD, Grekhova TV, Rayevsky KS. Effects of psychostimulant drug Sydnocarb on rat brain dopaminergic transmission in vivo. Eur J Pharmacol 1997;340:53–8.

Hastings TG., Zigmond MJ.. Prostaglandin synthase-catalyzed oxydation of dopamine. Soc Neurosci Abstr 1992;18:1444.

Havemann U, Magnus B, Moller HG, Kuschinsky K. Individual and morphological differences in the behavioral response to apomorphine in rats. Psychopharmacology 1986;90:40–8.

Huang N-K, Wan F-J, Tseng C-J, Tung C-S. Amphetamine induces hydroxyl radical formation in the striatum of rats. Life Sci 1997;61(22): 2219–29.

Jones SR, Gainetdinov RR, Wightman RM, Caron MG. Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. J Neurosci 1998;18(6):1979–86.

Kroph W, Kuschinsky K. Conditioned effects of apomorphine are manifest in regional EEG of rats both in hippocampus and in striatum. Naunyn-Schmiedeberg's Arch Pharmacol 1993;347:487–93.

Nakajima W, Ishida A, Takada G. Anoxic and hypoxic immature rat model for measurement of monoamine using in vivo microdialysis. Brain Res Protoc 1999;3(3):252–6.

O'Dell SJ, Weihmuller FB, Marshall JF. Multiple metamphetamine injections induce marked increases in extracellular striatal dopamine which correlate with subsequent neurotoxicity. Brain Res 1991;564:256–60.

Paxinos G, Watson C. The rat brain stereotaxic coordinates. 2nd ed. Sydney: Academic Press, 1982.

Ramassamy C, Gibre F, Pincemail J, Christen Y, Costentin J. Modification of the synaptosomal dopamine uptake and release by two systems generating free radicals: ascorbic acid/Fe^{2+} and L-arginine/NADPH. Ann NY Acad Sci 1994;738:141–52.

Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res 1986;396(2): 157–98.

Robinson TE, Camp DM. Long-lasting effects of escalating doses of D-amphetamine on brain monoamines, amphetamine-induced stereotyped behavior and spontaneous nocturnal locomotion. Pharmacol, Biochem Behav 1987;26(4):821–7.

Rudenko GM, Altshuler RA. Peculiarities of clinical activity and pharmakokinetics of sydnocarb (sydnocarbum), an original psychostimulant. Agressologie 1979;20:265–70.

Seiden L, Commins D, Vosmer J, Axt K, Marek G. Neurotoxicity in dopamine and 5-hydroxytryptamine terminal fields: a regional analysis in nigrostriatal and mesolimbic projections. Ann NY Acad Sci 1988;537: 161–72.

Sharp T, Zetterstrom T, Ljungberg T, Ungerstedt U. Effect of sulpiride on amphetamine-induced behavior in relation to changes in striatal dopamine release in vivo. Eur J Pharmacol 1986;129:411–5.

Sulzer D, Rayport S. Amphetamines and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules, a mechanism of action. Neuron 1990;5:797–808.

Wallace TL, Gudelsky GA, Vorhees CV. Methamphetamine-induced neurotoxicity alters locomotor activity, stereotypic behavior, and stimulated dopamine release in the rat. J Neurosci 1999;19(20):9141–8.

Weihmuller FB, O'Dell SJ, Marshall SJ. MK-801 protects against methamphetamine-induced striatal dopamine terminal injury as associated with attenuated dopamine overflow. Synapse 1992;11:155–63.

Witkin JM, Savtchenko N, Mashkovsky M, Beekman M, Munzar P, Gasior M, Goldberg SR, Ungard JT, Kim J, Shippenberg T, Chefer V. Behavioral, toxic and neurochemical effects of sydnocarb, a novel psychomotor stimulant: comparisons with methamphetamine. J Pharmacol Exp Ther 1999;288:1298–310.

Wolf ME, White FS, Hu X-T. MK-801 prevents alterations in the mesoaccumbens dopamine system associated with behavioral sensitization to amphetamine. J Neurosci 1994;14:1735–45.

Yamamoto BK, Zhu W. The effects of methamphetamine on the production of free radicals and oxidative stress. J Pharmacol Exp Ther 1998;287(1):107–14.

Zetterstrom T., Sharp T., Ungerstedt U. Effect of neuroleptic drugs on striatal dopamine release and metabolism in the awake rat studied by intracerebral dialysis. Eur J Pharmacol 1984;106:27.