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Ontogeny of PFC-related behaviours is sensitive to a single non-invasive dose of methamphetamine in neonatal gerbils (*Meriones unguiculatus*)

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Summary. A single dose of methamphetamine (50 mg/kg; i.p.) was administered to neonatal male gerbils (Meriones unguiculatus) aged 14 days, and adult prefrontal cortex (PFC)-related behaviours were analysed and compared with saline-treated controls at the age of postnatal day 90. For that purpose, animals were tested for open-field activities and y-maze delayed alternation. This solitary and non-invasive drug challenge, which has recently been found to initiate serious restraint in maturation of the mesoprefrontal dopamine (DA)-system (Dawirs et al., 1994), induces a significant delayed alternation impairment as well as significant increases in open-field motor activity and emotionality. Since an undisturbed development of the prefrontal DA-innervation seems to be a precondition for the maturation of normal PFC-related behaviours, a single early methamphetamine impact may be a suitable animal model for further investigation of structural and functional aspects of non-invasively induced behavioural deficits in rodents. The present results are discussed with regard to the assumption that hypofunctional mesoprefrontal DA-systems might be basic to schizophrenic behaviours in man.

Keywords: Prefrontal cortex, ontogeny, open-field, delayed alternation, methamphetamine, schizophrenia, gerbil.

Introduction

The prefrontal cortex (PFC) plays an essential part in organizing complex emotional, cognitive, and social behaviours (Butter and Snyder, 1972; Goldman, 1976; De Bruin et al., 1983; Kolb, 1984; Goldman-Rakic, 1987; Fuster, 1989). In this connection, temporal organization of behaviour appears to be a fundamental function of the PFC (Fuster, 1991) in which working memory (e.g. Funahashi and Kubota, 1994; Granon et al., 1994; Granon and Poucet, 1995) and behavioural inhibition (e.g. Stam et al., 1989; Kalsbeek et

al., 1989a; Bubser and Schmidt, 1990; Sokolowski and Salamone, 1994) are important prerequisites for normal functioning. Experimental animals can be selectively tested for different capacities in working memory and behavioural inhibition using a delayed alternation task and measuring open-field activities respectively (e.g. Bubser et al., 1992; Crawley et al., 1992; De Brabander et al., 1992, 1993; Braun et al., 1993; Diamond et al., 1994). Whereas acquisition of delayed alternation tasks is sensitive primarily to lesions of the medial PFC (homologous to dorsolateral PFC) (Van Haaren et al., 1985; Bubser and Schmidt, 1990), open-field behaviour is frequently impaired by lesions of the orbital PFC (homologous to ventromedial PFC) (Nonneman and Corwin, 1981; De Bruin et al., 1983).

It is now well established that an intact mesoprefrontal dopamine (DA)-system is a precondition for the normal functioning of the PFC (Brozoski et al., 1979; Simon et al., 1980; Bertolucci-D'Angio et al., 1990). Thus, comparable impairments of delayed alternation and open-field activity can be induced by lesions directed against DA-neurons of the ventral tegmental area (VTA) or by local ablation of prefrontal areas (Tassin et al., 1978; Carter and Pycock, 1980; Kessler and Markowitsch, 1981; Stam et al., 1989; Bubser and Schmidt, 1990). Techniques most frequently used to destroy the mesoprefrontal DA-system are, for instance, local application of 6-hydroxydopamine (6-OHDA) or thermal coagulation of the VTA. Nevertheless, these methods have serious disadvantages in common, such as unwanted non-specific lesions due to necessarily invasive handling.

Therefore, we have recently introduced a non-invasive technique in which a single dose of methamphetamine (i.p.) is sufficient to acutely induce selective autotoxic destruction of specific subpopulations of prefrontal DAergic fibres (Teuchert-Noodt and Dawirs, 1991). Further, this single pharmacological challenge was found to be a stimulus strong enough to initiate synaptic and neuronal reorganization in the PFC of adult animals (Dawirs et al., 1991, 1993a). In order to investigate in which way and to what extent neonatal disturbance of prefrontal DA-functions might influence subsequent neurogenesis of the PFC, we have quantitatively evaluated the postnatal maturation of the prefrontal DA innervation both during undisturbed development and following an early single dose of methamphetamine (Dawirs et al., 1993b, 1994). This solitary pharmacological challenge severely restrains the maturation of prefrontal DA innervation resulting in adult innervation densities which were significantly lower than in controls (Dawirs et al., 1994).

The subject of the present study was to investigate whether a single non-invasive neonatal dose of methamphetamine (i.p.; given on postnatal day 14) might influence subsequent ontogeny of PFC-related behaviours in gerbils. For that purpose, we examined performance of delayed alternation and open-field activity in both drug-treated animals and controls at the age of postnatal day 90.

Material and methods

Twenty eight male gerbils were bred in the laboratory. At the age of postnatal day 14, 14 gerbils received a single dose of methamphetamine (50 mg/kg; i.p.). For this, appropriate

amounts of methamphetamine hydrochloride (Sigma) were diluted in 0.5 ml saline immediately before injection. Fourteen control animals received equivalent volumes of saline. At the age of postnatal day 30, animals were weaned and subsequently kept singly in home cages (30 × 40 cm) under natural day/night cycles. Food and water were provided ad libitum. At the age of postnatal day 90, the animals were tested for y-maze delayed alternation and on open-field activities. Over a period of 2 days before and for the duration of behavioural testing the amount of food provided to individual animals was reduced to 1.5 g of normal food pellets per day.

Open field

On 5 consecutive days the animals were exposed for a 3 minute period in each case to an open-field arena (60 × 70 × 45 cm) which was illuminated by two 60 W light bulbs located 150 cm above. Locomotion, as a total of the distances covered, frequency of inner and outer crossings and number of rearings were recorded with a video camera and analysed with the help of a computer system (Kontron). In order to distinguish between inner and outer crossings, the image of the surface of the open-field arena was divided into 9 equally sized rectangles by covering the screen of the video monitor with transparency marked accordingly. Additionally, the level of anxiety was assessed by counting total numbers of voided faecal pellets during each exposure. Between tests of different animals the whole arena was carefully cleaned with 90% ethanol. The open-field arena has been modified and the tests were carried out in accordance with procedures described in Geyer et al. (1987) and Stam et al. (1989).

Delayed alternation

Ten methamphetamine-treated and 10 control animals were tested using a delayed alternation task on a y-maze which consisted of the following parts: (1) start-room (16 × 16 cm), followed by the (2) choice-room, and the (3) goal-arms (length 31 cm, width 16 cm). The walls of the apparatus were 25 cm high. A guillotine door which was equipped with an electromagnetic mechanism to trigger delayed opening separated the start-room from the choice-room. Likewise, the choice-room could be separated from the goal-arms by movable guillotine doors.

Pretraining

After the animals had been habituated on the y-maze over 5 consecutive days, they were pretrained on the following 8 successive days as follows. Individuals were put into the closed start-room for a 2-minute stay. After that, the guillotine door was raised automatically to give access to the choice-room. Only one of the goal-arms had been previously baited with a food cup. The animals task was to run into the baited goal-arm, pick up one sunflower seed and to return to the start-room. After this, the food cup was immediately removed and the alternative goal-arm was baited. During the next run the animals did not have to repeat the first run but had to choose the alternative goal-arm, find the sunflower seed and take it home into the start-room. Each individual had to go for such runs 20 times a day. On each day the first run was determined by random selection, and the following 19 runs had to be performed in a strictly alternating pattern.

Training

During the next 10 days, the animals were trained in pairs of 10 daily alternation trials per session. In the goal-arms, food cups were hidden behind a blind cover. The first run of each pair-trial was forced by closing one of the two goal-arms. After the animal had found the sunflower seed, returned and consumed it in the start-room, it could start on a second free-choice run without delay (0 sec intertrial interval: ITI 0). During this run, in which both arms were accessible, the animals had to choose the alternative goal-arm to the

forced run. Each forced run of the pair trials was determined by random selection. In those cases where the animals did not alter their course and entered the same goal-arm as during the forced run, they were returned to the start-box and an incorrect response was recorded. Intervals between pair trails were 1 minute. The animals were trained for alternation until the following criterion was fulfilled: there should be 70% or more correct responses during the last 3 training sessions [modified in accordance with Mogensen et al. (1982)].

Test

Immediately after the training-period, acquisition of delayed alternation was tested over 7 consecutive days. In this task, a 15-second delay was introduced between the forced run and the free-choice run (ITI 15). During this delay the animals were placed in the start-room. Individual animals had to perform 10 pair runs in a delayed session [modified in accordance with Yamazaki et al. (1989)].

Statistics

Mean values were computed as arithmetic means ± standard deviation, and compared by t-test with preceding F-test. Data from delayed alternation tasks were analysed with multivariante analysis of variance (MANOVA) with repeated measurements (Sachs, 1974).

Results

Open field

Data of the open-field activities are presented in Table 1. All behavioural parameters analysed reveal significant differences between saline- and methamphetamine-treated animals. The total distance covered was approximately 19% longer in animals which had received a single neonatal dose of methamphetamine when compared to saline-treated controls ($p < 0.001$). At the same time methamphetamine-treated animals performed less inner crossings ($p < 0.001$) but more outer crossings ($p < 0.01$). Ratios between either inner or outer crossings and total number of crossings indicate a 10% difference. Further, methamphetamine-treated animals performed about 36% more

Table 1. Open field activity in adult male gerbils after a single neonatal dose of either saline or methamphetamine (Meth); 14 animals each (n = 14); locomotion as total mean distance covered in five 3-minute sessions in meters (m); other parameters as counted mean numbers; mean values ($\bar{x}$) ± standard deviation (SD); level of significance (p)

	Open field						
	Saline(n = 14)			Meth(n = 14)			
	$\bar{x}$		SD	$\bar{x}$		SD	p<
Distance(m)	95.5	±	12.0	112.3	±	12.2	0.001
Outer crossing	322.9	±	37.2	390.9	±	61.6	0.01
Inner crossing	145.7	±	25.5	106.2	±	29.0	0.001
Rearing	248.5	±	44.6	288.8	±	35.1	0.001
Faecal pellets	14.1	±	8.8	23.5	±	5.5	0.01

Table 2. Delayed alternation task of adult gerbils on a y-maze after a single neonatal dose of either saline or methamphetamine (Meth); total mean errors ($\bar{x}$) ± standard deviation (SD) with 10 individuals per session (n = 10) on 8, 10, and 7 days during pretraining training and test respectively

	Delayed alternation							
Day	Pretraining		Training		Test			
	Saline (n = 10)	Meth (n = 10)	Saline (n = 10)	Meth (n = 10)	Saline (n = 10)	Meth (n = 10)		
	$\bar{x}$ SD	$\bar{x}$ SD	$\bar{x}$ SD	$\bar{x}$ SD	$\bar{x}$ SD	$\bar{x}$ SD		
1	9.2 ± 2.9	7.4 ± 1.4	2.9 ± 1.1	4.1 ± 1.5	3.8 ± 1.8	4.0 ± 1.2		
2	9.5 ± 2.7	8.7 ± 2.5	2.2 ± 1.2	2.9 ± 1.4	3.4 ± 1.7	3.9 ± 1.6		
3	5.9 ± 2.0	7.8 ± 2.4	3.8 ± 0.6	3.7 ± 2.1	2.2 ± 1.6	4.3 ± 2.4		
4	6.8 ± 2.1	7.7 ± 2.8	2.2 ± 1.1	2.5 ± 1.4	2.7 ± 0.5	3.9 ± 1.3		
5	6.7 ± 3.2	6.8 ± 3.0	1.8 ± 1.0	2.9 ± 0.9	1.5 ± 1.1	3.1 ± 1.1		
6	6.0 ± 2.6	6.8 ± 3.1	2.4 ± 1.4	2.6 ± 0.8	2.9 ± 1.2	4.3 ± 1.8		
7	4.0 ± 1.9	7.1 ± 4.6	3.1 ± 1.0	3.0 ± 2.1	1.6 ± 0.8	4.2 ± 1.7		
8	2.9 ± 1.6	6.0 ± 3.6	2.2 ± 1.1	2.5 ± 1.1				
9			2.0 ± 1.3	2.3 ± 1.0				
10			1.3 ± 0.8	1.9 ± 1.2				

rearings ($p < 0.001$) and voided about 67% more faecal pellets ($p < 0.01$) than saline controls.

Delayed alternation

Data on pretraining, training (ITI 0) and delayed alternation test (ITI 15) are included in Table 2. MANOVA showed a significant influence of a single

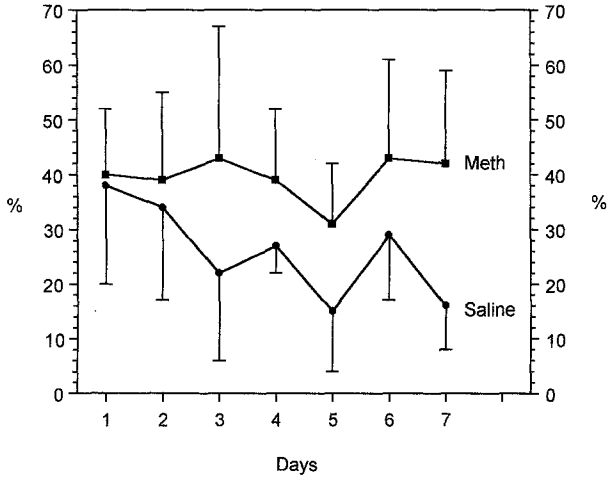

Fig. 1. Percentage numbers of errors (± standard deviation) in a delayed alternation task of adult gerbils on a y-maze after a single neonatal dose of either saline or methamphetamine (Meth); 15 seconds intertrial interval (ITI 15)

neonatal dose of methamphetamine on adult performance of delayed alternation (ITI 15; $p < 0.001$) (Fig.1), whereas the methamphetamine-treated animals did not differ from saline-treated controls during pretraining and training (ITI 0).

Discussion

In the present study we investigated the relationship between an early neonatal single dose of methamphetamine and the performance of PFC-related behaviours in adult gerbils. For that purpose, we analysed motor activity, rearings and number of faecal pellets on an open-field arena and acquisition of delayed alternation was tested on a y-maze. Methamphetamine-treated animals became clearly hyperactive as adults, performing more crossings and rearings in the outer parts of the open-field arena than in the inner parts. Defecation was much higher than in saline controls, indicating an increased level of anxiety, and the animals showed an impressive impairment on delayed alternation. These results show that a single drug challenge during early neonatal life is a stimulus strong enough to significantly impair both open-field activity and delayed alternation in adults, indicating the development of severe deficits in working memory and emotionality (cf. Weinstock et al., 1992; Granon et al., 1995).

In order to discuss the present results, it is necessary to recall that we have recently documented that a single dose of systemically applied methamphetamine induces deafferentiation in the PFC of adult gerbils due to activity-dependent autotoxic degradation of mesoprefrontal DA-fibres (Teuchert-Noodt and Dawirs, 1991). This lesion is permanent and initiates a whole sequence of responses in the PFC, i.e. dynamic structural and physiological changes in postsynaptic prefrontal pyramidal cells, and significant alterations in the afferent input spectrum of these cells in which GABAergic neurons play an important part (Dawirs et al., 1991, 1993a, 1995). Thus, a single dose of methamphetamine is a non-invasive experimental tool to acutely stimulate prefrontal DA-functions which may lead to reorganization of neuronal networks in the PFC. Besides this, a single methamphetamine impact has been proposed as a reliable pharmacological model to simulate stress-induced selective stimulation of the mesoprefrontal DA-system in mammals (for recent discussion see Dawirs et al., 1993a).

It is well documented that developing mesoprefrontal DA-fibres are essential in the maturation of the PFC, and that this system has to be intact for the PFC to function normally in adults (Kalsbeek et al., 1989b; Bertolucci-D'Angio et al., 1990; Sokolowski and Salamone, 1994). In mammals, maturation of PFC-related behaviours is remarkably delayed (e.g. Kolb, 1984), running concurrently with clearly retarded development of the prefrontal DA-innervation (Kalsbeek et al., 1990; Dawirs et al., 1993b). Against this background, we are currently analysing disturbances in the structural neurogenesis of the PFC caused by a single neonatal activation of the developing mesoprefrontal DA-system induced by a solitary methamphetamine challenge. This early drug impact leads to a dramatic restraint of the

subsequent maturation of the mesoprefrontal DA-system (Dawirs et al., 1994).

According to what is known as the "Kennard principle", specific lesions of the adult brain may lead to acute and lasting behavioural deficits whereas after comparable lesions in young brains individuals may develop an inconspicuous behavioural repertoire (Kennard, 1938; Kolb and Nonneman, 1978; for discussion see Kolb, 1984). It has been argued that after early disturbance of brain development, sparing of function depends on plasticity of maturing neurons which may be able to realize structural correlates of species-specific behaviours in more than just one way (Kolb and Whishaw, 1989; Vicedomini et al., 1982, 1984). There are a number of reports that mechanical lesioning of the adult PFC may result in acute hyperactivity and impairment on delayed alternation (De Bruin et al., 1983; Bubser and Schmidt, 1990; Verin et al., 1993; De Brabander et al., 1993), whereas PFC-related behaviours were insensitive to neonatal lesioning (Freeman and Stanton, 1992; De Brabander et al., 1992; Carter et al., 1995). Nevertheless, the development of normal PFC-related behaviours becomes severely impaired after the VTA has been invasively destroyed in young immature brains, for instance by local application of 6-OHDA or thermal coagulation (Carter and Pycock, 1980; Stam et al., 1989; Bubser and Schmidt, 1990). Therefore, it seems feasible to conclude that developmental restraint of the mesoprefrontal DA-system, which is primarily affected by a single dose of methamphetamine in juveniles, is responsible for the loss of function in adult PFC-related behaviours.

Nevertheless, although an intact mesoprefrontal DA-system seems to be a "conditio sine qua non" for the development of normal adult PFC-related behaviours, it is not possible to limit the organization of complex behavioural repertoires to a single affected neurotransmitter system. Therefore, it is necessary to investigate further effects of DAergic deafferentiation on prefrontal neurogenesis (cf. Lewis et al., 1992; Dawirs et al., 1993a, 1995). Since mesoprefrontal DA-systems modulate the spontaneous activity of postsynaptic prefrontal pyramidal cells (Mora et al., 1976; Ferron et al., 1984), any change in ontogenesis of these prefrontal target cells, including further afferent systems, might also affect the maturation of prefrontal control over various subcortical systems (cf. Pycock et al., 1980; Simon et al., 1988; Taghzouti et al., 1988; Louilot et al., 1989; Thierry et al., 1990).

Since in man, schizophrenic symptoms seem to be related to deficits in the acquistion of delayed response tasks (e.g. Spitzer, 1993; Park and Holzman, 1992, 1993), the present results on drug-induced impairment on the ontogeny of PFC-related behaviours may provide a fundamental basis for understanding neurobiological correlates of psychotic symptoms. The present experimental device induces severe restraints in the maturation of the prefrontal DA-innervation (hypoinnervation) resulting from a single intensive activation of the juvenile mesoprefrontal DA-system which might equally characterize physiological responses to natural stress (cf.Thierry et al., 1990). Since a hypofunctional mesoprefrontal DA-system might probably be involved in generating psychiatric disorders in man (Davis et al., 1991; Rao and Möller, 1994), it is necessary to further investigate early drug-induced alterations in

prefrontal neurogenesis. Such investigations should take special consideration of the maturation of other neurotransmitter systems as well as the development of neural interconnectivities between the PFC and other cortical and subcortical areas. In this connection, one important aspect of our current interest is to analyse structural and behavioural responses to neuroleptic drugs in adult animals which have been treated with a single dose of methamphetamine as juveniles (cf. Eastwood et al., 1994; Vincent et al., 1994).

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