REVIEW

Does social submissivity or aggressivity influence sensibility of mice to methamphetamine effects?

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Introduction

Violence and aggressive behaviours are important public health problems because of their medical and criminal consequences (Dahlberg 1998; Lederhendler 2003). Aggressive behaviours are quite common among abusers of methamphetamine (Miczek *et al* 1989; Miczek & Tidey 1989; Szuster 1990). Vice versa increased aggressivity in childhood is related to increased drug dependence in adolescence (Halikas *et al* 1990; Martin *et al* 1994). Aggressive behaviours and social interactions can be influenced by methamphetamine in rodents (Miczek & O'Donnell 1978; Shintomi 1975; Sokolov *et al* 2004; Landa *et al* 2006a). Among many neurobiological mechanisms in the process of drug dependence a great importance has development of behavioural sensitization (sometimes it is also called a "reverse tolerance" in contrast to tolerance – a decreasing response after repeated drug administration). This phenomenon is characterized as an increase in behavioural response to repeated administration of various drugs of abuse (Ohmori *et al* 2000; Robinson & Berridge 1993) and in rodents has been considered for a long time as a model of drug craving on withdrawal of drugs of abuse (Di Chiara 1995; Robinson & Berridge 1993). There is increasing evidence indicating that behavioural sensitization can be parcelled into two temporally defined domains called development (or initiation) and expression (Kalivas *et al* 1993). The term "development" of behavioural sensitization refers to the progressive molecular and cellular alterations that culminate in a change in the processing of environmental and pharmacological stimuli by the CNS. These alterations are transient and may not be detected after a few weeks of withdrawal (Kalivas *et al* 1993). The term "expression" of behavioural sensitization is defined as the enduring neural changes, which arise from the process of the development that directly mediate the sensitized behavioural response (Pierce & Kalivas 1997). Under experimental circumstances the sensitization can be elicited to behavioural effects of majority of drugs of abuse in laboratory rodents. Thus, behavioural sensitization has been described for instance in relation to amphetamine (Costa *et al* 2001), cocaine (Elliot 2002), MDMA (Kalivas *et al* 1998), opioids (De Vries *et al* 1999), cannabinoids (Cadoni *et al* 2001) or nicotine (Shoaib *et al* 1994). In our previous works, we shoved methamphetamine behavioural sensitization to stimulatory effects on locomotion in the open field test (Landa *et al* 2006b) and to antiaggressive effects in the model of mouse agonistic behaviour (Landa *et al* 2006a).

Therefore, the question arises if mice with a differential behavioural approach, either aggressive or submissive (occurring as we suppose due to distinct neurobiological basis) to intruding unknown partner of the same gender, express after repeated methamphetamine administration dissimilar behavioural sensitization patterns. This would indicate a possible different susceptibility of those two behavioural phenotypes to methamphetamine abuse.

Methods

The model of agonistic behaviour used for determination of mouse aggressivity or submisssivity (timidity) consists of dyadic social interactions of adult singly-housed male mice with non-aggressive group-housed partners in neutral observational cages. Behavioural changes analyzed are 11 acts of 4 categories: sociable, timid, aggressive and locomotor. Behavioural elements recorded: sociable – social sniffing, following

Table 1. Mean values for the distance traveled in open-field test (see the text), and values of standard error of the mean (SEM).
* Differs from Day 1 in the same group, P<0.01
$ Differs from Day 8 in the same group, P<0.01

Group	Experimental day	Distance run (cm/3 min)	SEM
Aggressive mice	Day 1, drug naive	1190.2	64.3
	Day 8, acute dose	1831.7*	355.0
	Day 14, development of sensitization	2541.9*$	583.9
	Day 21, expression of sensitization	2849.6*$	534.7
Timid mice	Day 1, drug naive	1158.5	90.9
	Day 8, acute dose	1695.1*	148.2
	Day 14, development of sensitization	2531.6*$	242.4
	Day 21, expression of sensitization	3025.0*$	362.6
Controls	Day 1, drug naive	1097.3	154.8
	Day 8, acute dose	2258.3*	154.0
	Day 14, development of sensitization	2756.5*$	205.8
	Day 21, expression of sensitization	2759.5*$	161.7

the partner, climbing over the partner; timid – defensive posture, escape, alert posture; aggressive – attack, aggressive unrest (threat), tail rattling; locomotor – walk, rear. Agonistic behaviour was evaluated in singly-housed mice separately in those exhibiting at least one attack (aggressive mice) and those showing a lot of defensive/escape behaviour but no attack (submissive = timid mice). Paired interactions were videotaped and ethological analysis was performed by the observer using the system Observer (Noldus Technology, Holland). For the open-field experiment mice with highest rates of aggressive (N_1=8) or defensive-escape (N_2=8) behavioural acts were chosen. Mice not influenced by social interactions were used as controls (N_3=8). Locomotor behaviour of drug naive mice in the open-field test was assessed on first experimental day. Following five drug free days, acute methamphetamine effects were evaluated in the open-field test 15 minutes after injection of 2.5 mg.kg^{-1} dose, given intraperitoneally on Day 7. Development of behavioural sensitization to the stimulatory effects on locomotion was controlled after next seven daily doses of 2.5 mg.kg^{-1} methamphetamine on Day 14. Expression of behavioural sensitization was also assessed after the same methamphetamine "challenged" dose on Day 21 followed after 6 days without drug administration. For statistical evaluation ANOVA for repeated measures test and Bonferroni post hoc test were used.

Results

The experimental mouse groups – control, aggressive and timid mice did not differ in the exhibition of horizontal locomotor activity in the open field test. Significant stimulatory effects on locomotion registered after acute methamphetamine dose of 2.5 mg/kg did not show any significant differences among all these mouse groups (see ***Table 1***). The development and expression of behavioural sensitization to stimulatory effects of repeated methamphetamine were proven in all groups but again without significant differences between them (see ***Table 1***).

Discussion

In the present study we tested the hypothesis, if the behavioural sensitization to methamphetamine effect in the open-field test is expressed differentially in mice manifesting aggressive or submissive (timid) behaviour on agonistic interactions. We have shown that there is no difference in aggressive, timid or control (with no agonistic interaction experience) mice in sensitivity to acute methamphetamine effects. The repeated administration of methamphetamine also showed no differences in development and expression of behavioural sensitization to this drug.

Various data indicate that processes involved in both development and expression of behavioural sensitization are distinct not only temporally but also anatomically. Development of behavioural sensitization to psychostimulant drugs occurs in the ventral tegmental area and substantia nigra, which are the loci of the dopamine cells in the ventral midbrain that give rise to the mesocorticolimbic and nigrostriatal pathways. In contrast, the neuronal events associated with expression are distributed among several interconnected limbic nuclei that are centred on the nucleus accumbens (Pierce & Kalivas 1997). Mice with alternative behavioural strategies either aggressive or submissive are determined by the features of organization of the mesolimbico-cortical dopaminergic system and emotional state (Dubrovina 2006), and the formation of a neurochemical set is dopaminergic in aggressive mice and serotonergic in submissive ones (Al'perina &

Pavina 1996). Thus, we hypothesised that predominant dopaminergic activity in aggressive mice could support behavioural sensitization to methamphetamine which mechanism of action is dopamine activity modulation in mesolimbic reward pathway. Recent reviews have underlined potential importance of the phenomenon of behavioural sensitization as a model for the intensification of drug craving that characterizes addiction and promotes relapse (Di Chiara 1995; Robinson & Berridge 1993). In the present study however the effect of social behaviour phenotype (aggressive or submissive) on sensitivity to methamphetamine effect in the experimental model of behavioural sensitization was not approved. As the findings in human males and females implicate both variables of conduct behaviour and aggressivity predispose to drug abuse/dependence (Cadoret *et al* 1995), it would be worthwhile to study further a relation between aggressive and submissive behavioural phenotypes and vulnerability to methamphetamine addiction in other experimental models such as e.g. "place preference test".

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