ORIGINAL ARTICLE

# Altered dopamine $D_1$ and $D_2$ receptor mRNA expression in mesencephalon from mice exposed to repeated treatments with methamphetamine and cannabinoid $CB_1$ agonist methanandamide

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## Abstract

**OBJECTIVES:** In our previous studies we found that both acute administration of $CB_1$ receptor agonist methanandamide and repeated methanandamide pre-treatment prior to methamphetamine challenge dose elicited increase in the $CB_1$ receptor mRNA expression in the mouse mesencephalon. As a reciprocal cross-talk is reported between the cannabinoid $CB_1$ and dopamine receptors, that are highly co-localized on brain neurones, we targeted possible changes in relative expression of dopamine $D_1$ and $D_2$ receptor mRNA in mesencephalon in mice sensitized by repeated treatments to methamphetamine stimulatory effects and cross-sensitized to methamphetamine by cannabinoid $CB_1$ receptor agonist methanandamide pre-treatment.

**METHODS:** To confirm development of behavioural sensitization or cross-sensitization, respectively, we observed changes in locomotion using the open field test. Mice were treated repeatedly with either methamphetamine or methamphetamine after repeated pre-treatment with methanandamide. After each measurement of locomotion one third of animals were sacrificed and the brain was stored. RNA was isolated from the midbrain and used for reverse transcription and subsequent real-time PCR.

**RESULTS AND CONCLUSION:** As in many of our earlier studies with the same dosage regimen we found in the behavioural part both development of sensitization to methamphetamine stimulatory effects after repeated treatment and cross-sensitization to them by pre-treatment with cannabinoid receptor $CB_1$ agonist methanandamide. Real-time PCR analyses showed an increase in $D_1$ receptor mRNA expression after the first dose of methamphetamine (that persisted also after the last dose of methamphetamine) and after the first dose of methanandamide (which also persisted after the methamphetamine challenge dose). In opposite a significant decrease in $D_2$ receptor mRNA expression both after the first dose of methamphetamine and methanandamide (that persisted also after

the methamphetamine challenge doses) was registered. Thus, our results suggest that both methamphetmine and methanandamide treatment can provoke changes in dopamine receptor density in mouse mesenpcephalon, the increase in $D_1$ and decrease in $D_2$ receptor subtypes.

**Abbreviations:**

| | |
|---|---|
| CAN | - mice after the 1st dose of methanandamide |
| CAN/M | - mice sensitized with methanandamide after the challenge dose of methamphetamine |
| GAPDH | - glyceraldehyde-3-phosphate dehydrogenase |
| ISHH | - *in situ* hybridization histochemistry |
| M | - mice after the 1st dose of methamphetamine |
| M/M | - mice sensitized with methamphetamine after the challenge dose of methamphetamine |
| PET | - positron emission tomography |
| V | - mice after the dose of vehicle |
| VTA | - ventral tegmental area |

## INTRODUCTION

Increased behavioural response to certain drug conditioned by its previous repeated administration is well-known as behavioural sensitization (Robinson & Berridge, 1993). It has been manifested for the whole range of psychotropic drugs such as amphetamines (Wang *et al.* 2010), cannabinoids (Rubino *et al.* 2003) or opiods (Bailey *et al.* 2010; Liang *et al.* 2010). Moreover, an increased response to a drug tested elicited by previous repeated pre-exposure to another drug is recognized as cross-sensitization; e.g. cross-sensitization between metylphenidate and amphetamine was observed (Yang *et al.* 2011), cross-sensitization with cannabinoid agonist WIN 55,2122 to morphine has been described (Manzanedo *et al.* 2004) or animals pre-treated with amphetamine displayed behavioural cross-sensitization to nicotine and vice versa animals pre-treated with nicotine showed sensitized locomotor response to amphetamine (Santos *et al.* 2009).

Both behavioural sensitization and cross-sensitization represent enduring changes in drug response and although not all neuronal processes involved in these phenomena have been fully elucidated yet, it is clear that the crucial neuronal circuit essential for the development of sensitization involves numerous structures in the central nervous system. Neuroadaptive changes occurred namely in a circuit comprising dopaminergic, GABAergic and glutamatergic interconnections between the ventral tegmental area (VTA), nucleus accumbens, prefrontal cortex and amygdala (Nestler, 2001a; b). Kalivas *et al.* (1993) suggest that the mesolimbic dopaminergic projection from the VTA to nucleus accumbens plays the key role for effects associated with reward properties of abused drugs. In addition, it is well known that dopamine plays a crucial role in the development of behavioural sensitization. This was also confirmed when the established behavioural sensitization to methamphetamine was reversed by administration of dopamine $D_1$ receptor antagonist R-(+)-SKF38393 (Shuto *et al.* 2006) and signs of behavioural sensitization to amphetamine were decreased by the $D_1$ receptor antagonist SCH23390 (stereotypical behaviour) and the $D_2$ receptor antagonist eticlopride (all behavioural activities) (Shi & McGinty, 2011).

An earlier study realized at our laboratory suggested interaction between the endocannabinoid system and methamphetamine brain mechanisms in the rat I.V. drug self-administration model (Vinklerova *et al.* 2002). Furthermore, this finding was confirmed by following research when we provoked behavioural sensitization to psychostimulant methamphetamine and also cross-sensitization to this drug elicited by cannabinoid $CB_1$ receptor agonist methanandamide pre-treatment (Landa *et al.* 2006a; b).

Our recent study concerning behavioural sensitization to methamphetamine was focused on neuroplastic changes on genomic level. We found that repeated pre-treatment with $CB_1$ receptor agonist methanandamide elicited increase in the $CB_1$ receptor mRNA expression in the mouse mesencephalon neurons (Landa *et al.* 2011). Since stimulation of cannabinoid $CB_1$ receptors present on GABAergic and glutamatergic nerve terminals negatively regulated the release of GABA and glutamate and in this manner affected the mesolimbic dopamine functions (Kelley & Berridge, 2002; Chiang & Chen, 2007) and since a reciprocal cross-talk was reported among the cannabinoid $CB_1$ and dopamine $D_1$ and $D_2$ receptors, which are highly co-localized on brain neurones (Glass and Felder, 1997; de Fonseca *et al.* 1998; Beltramo at al. 2000; Hermann *et al.* 2002; Kearn *et al.* 2005; Martín *et al.* 2008; Dalton & Zavitsanou, 2010; Dowie *et al.* 2010; Terzian *et al.* 2011), we decided to extend the above mentioned research project to these dopamine receptors, too.

With reference to results obtained in our pilot studies focusing on relative expression of $D_1$ and $D_2$ receptors (Landa & Jurajda, 2008a; b; c) we designed the present study to reveal possible changes in expression of $D_1$ and $D_2$ receptor mRNA in mouse mesencephalon (that involves VTA) by quantitative polymerase chain reaction (qPCR) during: a) sensitization to methamphetamine and b) cross-sensitization to methamphetamine induced by repeated pre-treatment with $CB_1$ receptor agonist methanandamide.

## MATERIAL AND METHODS

### *Animals*

Male mice (strain ICR, TOP-VELAZ s. r. o., Prague, Czech Republic) with an initial weight of 18–21 g were used. Animals were randomly allocated into two treatment groups. In order to minimise possible variability due to circadian rhythms the behavioural observations were always performed in the same period between 1:00 p.m. and 3:00 p.m. of the controlled light/dark cycles (light on 6:00 a.m. – 6:00 p.m.).

## APPARATUS

Locomotor activity was measured using an open-field equipped with Actitrack (Panlab, S. L., Spain). This device consists of two square-shaped frames that deliver beams of infrared rays into the space inside the square. A plastic box is placed in this square to act as an open-field arena (base 30 x 30 cm, height 20 cm), in which the animal can move freely. The apparatus software records locomotor activity of the animal by registering the beam interruptions caused by movements of the body. Using this equipment we have determined the Distance Travelled (trajectory in cm per 3 minutes).

*Drugs*

Vehicle and all drugs were always given in a volume adequate to drug solutions (10 ml/kg).

(+)Methamphetamine, (d-N,α-Dimethylphenylethylamine; d-Desoxyephedrine), (Sigma Chemical Co.) dissolved in saline.

(R)-(+)-Methanandamide, (R)-N-(2-hydroxy-1-methylethyl)-5Z,8Z,11Z-eicosotetraenamide) supplied pre-dissolved in anhydrous ethanol 5 mg/ml (Tocris Cookson Ltd., UK) was diluted in saline to the concentration giving the chosen dose to be administered to animals in a volume of 10 ml/kg; vehicle therefore contained an adequate part of ethanol (a final concentration in the injection below 1%) to make effects of placebo and the drug comparable.

*Procedure*

Mice were randomly divided into 2 groups ($n_1$=24, $n_2$=24) and all were given vehicle on Day 1 (10 ml/kg). There were no applications from Days 2 to 6. For the next seven days animals were daily treated intraperitoneally as follows: a) $n_1$: methamphetamine at the dose of 2.5 mg/kg/day, b) $n_2$: methanandamide at the dose of 0.5 mg/kg/day. On Day 14 all animals were given intraperitoneally methamphetamine at the dose of 2.5 mg/kg (challenge dose).

Changes in locomotion were measured for the period of 3 minutes in the open field on Days 1, 7 and 14, fifteen minutes after drug application to assess sensitizing phenomenon. After each measurement one third of both groups was decapitated (75 minutes after drug administration) and the brain was stored in RNAlater (Ambion). For RNA isolation we used excised mesencephalon only. The total RNA was isolated by means of RNAEasy Mini Kit (Qiagene) and the subsequent reverse transcription was performed with Omniscript RT Kit (Qiagene) and RNAse OUT Ribonuclease Inhibitor (Invitrogen). Relative expression of $D_1$ and $D_2$ receptors, respectively (assays Mm02620146_s1 and Mm00438541_m1, Life Technologies) was compared to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA (assay Mn99999915_1g, Life Technologies ) using real time cycler ABI SDS 7000 (AppliedBiosystems). All real time PCR reactions were performed using TaqMan Gene Expression Master Mix (Life Technologies).

*Data analysis*

As the data was not normally distributed (according to the Kolmogorov-Smirnov test of normality), non-parametric statistics were used: Mann-Whitney U test, two-tailed (statistical analysis package STATISTICA - StatSoft, Inc., Tulsa, USA).

## RESULTS

The behavioural part of the present study focused on the changes in mouse locomotion fully confirmed our earlier outcomes published elsewhere (Landa *et al.* 2011): a) development of behavioural sensitization to methamphetamine (M) stimulatory effects after repeated M treatment; b) development of cross-sensitization to these effects after repeated pre-treatment with methanadamide (CAN) prior to the M challenge dose.

Real-time PCR results focused on relative expression of $D_1$ receptor mRNA showed in the group $n_1$ a significant increase ($p$<0.05) after the 1st dose of M (see Figure 1; V1 versus M). This increase was even more pronounced ($p$<0.01) after the application of M challenge dose (see Figure 1; V1 versus M/M). The treatments in the group $n_2$ caused significant increase ($p$<0.01) in relative expression of $D_1$ receptor mRNA after the 1st application of CAN compared to the application of vehicle (V2) (see Figure 1; V2 versus CAN). The challenge dose of M produced a non-significant decrease ($p$>0.05) in animals pre-treated repeatedly with CAN when compared to the animals after the 1st application of CAN (see Figure 2; CAN versus CAN/M).

There was no significant change in relative expression of $D_1$ receptor mRNA between animals after the MET challenge dose (those were pre-treated with MET) and animals after the MET challenge dose (those were pre-treated with CAN) – see Figure 1; M/M versus CAN/M.

Real-time PCR results focused on relative expression of $D_2$ receptor mRNA showed in the group $n_1$ a significant decrease ($p$<0.01) after the 1st dose of M (see Figure 2; V1 versus M). There was no significant difference after the application of M challenge dose (see Figure 1; M versus M/M). The treatments in the group $n_2$ caused significant decrease ($p$<0.05) in relative expression of $D_2$ receptor mRNA after the 1st application of CAN compared to the application of vehicle (V2) (see Figure 2; V2 versus CAN). The challenge dose of M produced a non-significant increase ($p$>0.05) in animals pre-treated repeatedly with CAN when compared to the animals after the 1st application of CAN (see Figure 2; CAN versus CAN/M).

There was no significant change in relative expression of $D_2$ receptor mRNA between animals after the MET challenge dose (those were pre-treated with MET) and animals after the MET challenge dose (those were pre-treated with CAN) – see Figure 2; M/M versus CAN/M.

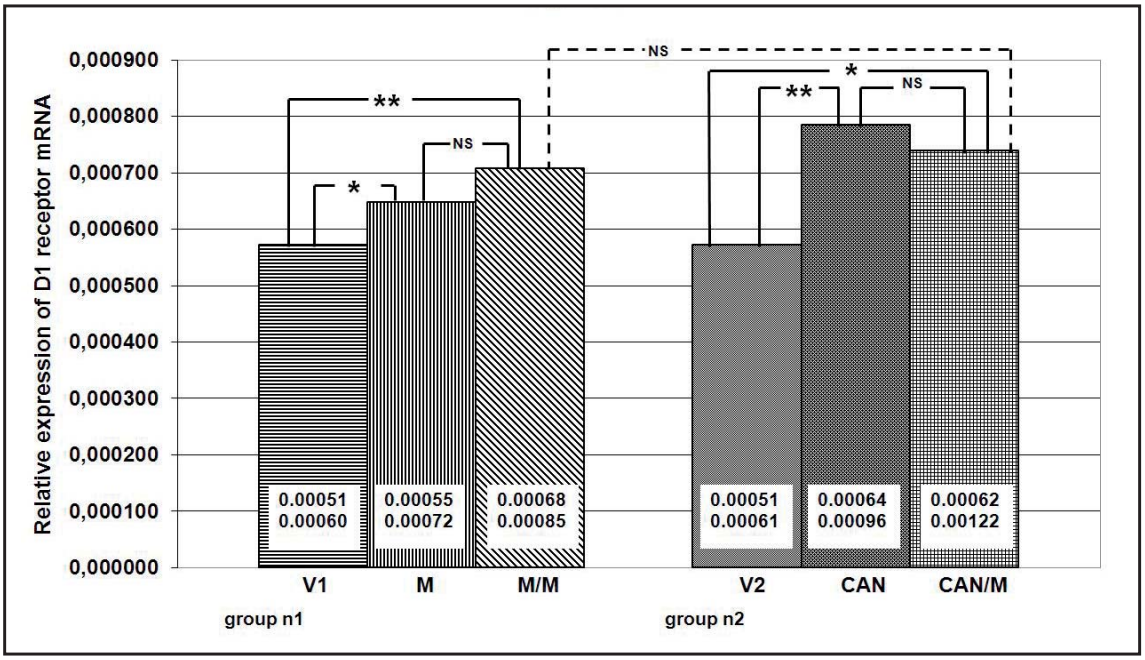


**Fig. 1.** Effects of drug treatments on relative expression of $D_1$ receptor mRNA when compared to GAPDH mRNA shown as median (interquartile range Q1 to Q3):
V1 = mice after the dose of vehicle in the group $n_1$, V2 = mice after the dose of vehicle in the group $n_2$, M = mice after the 1st dose of methamphetamine (2.5 mg/kg), M/M = mice sensitized with methamphetamine after the challenge dose of methamphetamine (2.5 mg/kg), CAN = mice after the 1st dose of methanandamide (0.5 mg/kg), CAN/M = mice sensitized with methanandamide after the challenge dose of methamphetamine (2.5 mg/kg).
*$p$<0.05, **$p$<0.01, NS = non-significant, the nonparametric Mann-Whitney U test, two tailed.

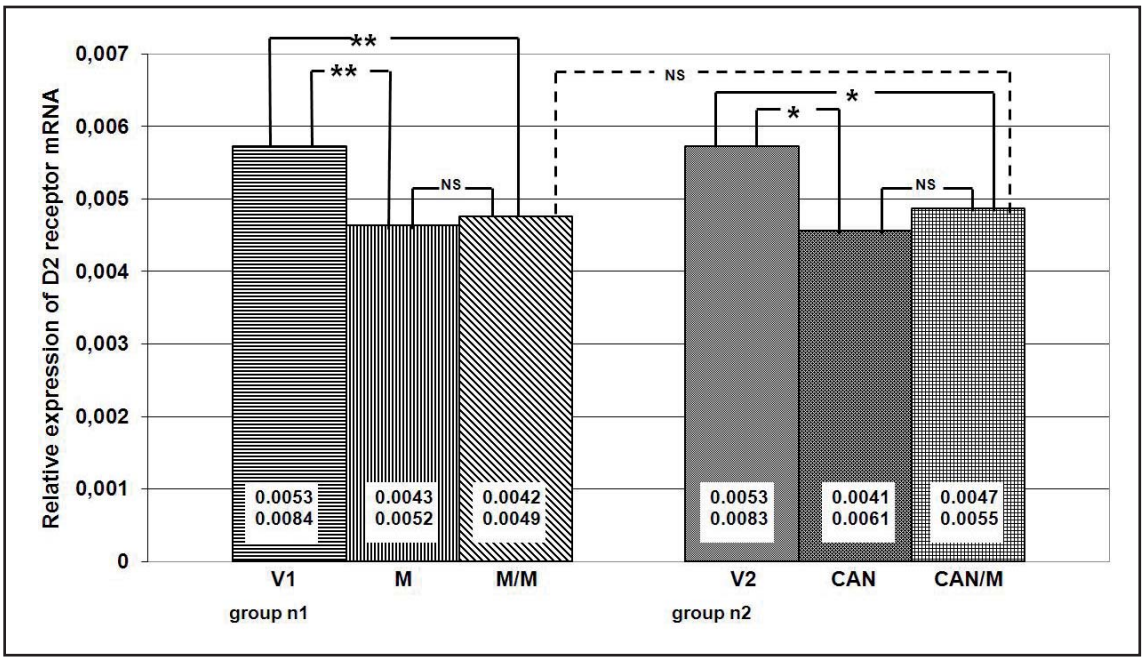


**Fig. 2.** Effects of drug treatments on relative expression of $D_2$ receptor mRNA when compared to GAPDH mRNA shown as median (interquartile range Q1 to Q3):
V1 = mice after the dose of vehicle in the group $n_1$, V2 = mice after the dose of vehicle in the group $n_2$, M = mice after the 1st dose of methamphetamine (2.5 mg/kg), M/M = mice sensitized with methamphetamine after the challenge dose of methamphetamine (2.5 mg/kg), CAN = mice after the 1st dose of methanandamide (0.5 mg/kg), CAN/M = mice sensitized with methanandamide after the challenge dose of methamphetamine (2.5 mg/kg).
*$p$<0.05, **$p$<0.01, NS = non-significant, the nonparametric Mann-Whitney U test, two tailed.

## DISCUSSION

The start-up behavioural assessment confirmed presence of both sensitization to methamphetamine stimulatory effects and cross-sensitization to methamphetamine induced by pre-treatment with cannabinoid $CB_1$ receptor agonist methanandamide, which was completely in accordance with our previous experiments (Landa *et al.* 2006a; 2006b; 2011).

Methamphetamine and methanandamide are believed to elicit increase in dopamine activation in the mesolimbic reward pathway. This pathway primarily connects the VTA and nucleus accumbens and both are central to the brain reward system. Increased dopamine activity in the dopamine reward system is associated with neuroadaptive changes, among others in the density of appropriate receptor systems, especially of $D_1$ and $D_2$ receptors cooperating in dopamine reward processes (Ikemoto *et al.* 1997).

It is known, that the reinforcing/rewarding effects are common for both methamphetamine and methanadamide (dela Peña *et al.* 2010; Justinova *et al.* 2011) we have tested. Results of Ikemoto *et al.* (1997) indicated that concurrent activation of dopamine $D_1$ and $D_2$ receptor subtypes in the shell of nucleus accumbens had a cooperative effect on dopamine-mediated reward processes, which corresponds with our primary hypothesis that both receptor subtypes are involved in the mechanisms of reward. However, despite that also other data attribute to the important role of $D_2$ and particularly $D_1$ receptors in the process of reward (including neuroplastic changes underlying behavioural sensitization) not even all of them are completely consistent (Hasbi *et al.* 2011; Bachtell *et al.* 2005; Dias *et al.* 2004; Maneuf *et al.* 1997; Hamamura et al., 1991).

Our present experiments concerning relationship between methamphetamine and cannabinoid $CB_1$ agonist methanandamide influences on the relative $D_1$ and $D_2$ receptor mRNA expression provided quite controversial findings, too. Real-time PCR analyses showed an increase in $D_1$ receptor mRNA expression after the acute administration of methamphetamine at the dose of 2.5 mg/kg (that persisted also after the last dose of methamphetamine) and also an increase after the acute dose of methanandamide at the dose of 0.5 mg/kg (persisting after the methamphetamine challenge dose). Interestingly, there was a significant decrease in $D_2$ receptor mRNA expression both after the acute dose of methamphetamine and methanandamide at the same doses as above (that persisted also after the methamphetamine challenge doses).

Probably simultaneously with our experiments there was run a study (Dalton & Zavitsanou, 2010) examining also influence of single and repeated treatments with cannabinoid receptor agonist on dopamine $D_1$ and $D_2$ receptor densities in adult and adolescent rats. In the adult rats, using in vitro autoradiography they found after the repeated treatment with cannabinoid $CB_1$ receptor agonist HU210 significant increase in $D_1$ and $D_2$ receptor densities. In adolescent rats the increase in the number of receptors was measured only in the case of $D_1$ and not $D_2$ subtypes in the lateral caudate putamen and olfactory tubercle. The authors concluded that the mechanisms stayed unclear to them as previously they registered down-regulation of $D_1$ receptor density in the rat nucleus accumbens, caudate putamen, substantia nigra and olfactory tubercle (Dalton *et al.* 2009). Shishido *et al.* (1997) received similar outcomes to our behavioural results when measuring by in situ hybridization histochemistry (ISHH) dopamine $D_1$ receptor and $D_2$ receptor mRNAs following repeated methamphetamine administration in the dorsal striatum and ventral striatum of rats. Moreover, they revealed, using ISHH, that $D_1$ receptor mRNA levels in the dorsal striatum were significantly increased and in contrast, repeated methamphetamine treatment did not significantly affect the expression of $D_1$ receptor mRNA in ventral striatum or $D_2$ receptor mRNA. Although rather inconsistent, these ISHH-related findings are to certain extent similar to our PCR-results which showed an increase in $D_1$ receptor mRNA expression in methamphetamine sensitized and methanadamide cross-sensitized mice, respectively, and in opposite a decrease in $D_2$ receptor mRNA expression. This latter finding is consistent with results of Nader *et al.* (2006) who found using PET, that $D_2$ receptor availability is decreasing in the brain of rhesus-monkeys by 15–20% within 1 week of initiating cocaine self-administration and remained reduced by similar to 20% during 1 year of exposure.

Vezina (1996) suggested that dopamine $D_1$ receptors in the VTA played a critical role in the development of sensitization to amphetamine effects, whereas activation of $D_2$ receptors is not necessary for the induction of sensitization to amphetamine. Although this is in conflict with suggestions of Ikemoto *et al.* (1997) and also with our working hypothesis, it however corresponds very well with our final results, because the relative expression of dopamine $D_2$ receptor mRNA was decreased in sensitized animals, whereas a significant increase in dopamine $D_1$ receptor mRNA expression occurred after development of sensitization.

It has been described, that both $D_1$ and $D_2$ receptors exist in high- and low-affinity states. High-affinity states of dopamine $D_1$ ($D_1^{High}$) and $D_2$ ($D_2^{High}$) receptors have much higher affinity for dopamine than $D_1$ and $D_2$ receptors in low-affinity states. Dopamine $D_1^{High}$ and $D_2^{High}$ receptors are considered to be the functional state of dopamine receptors and Seeman *et al.* (2002) suggested that the proportion of $D_2^{High}$ receptors was increased in the striatum of amphetamine-sensitized rats, despite of no changes in the density of $D_2$ receptors (for more details see Shuto *et al.* 2008). From this point of view behavioural sensitization to methamphetamine can be explained by the increased proportion of $D_2^{High}$ receptors in the striatum, which results in substantially higher sensitivity to psychostimulants or dopaminergic

drugs (Shuto *et al.* 2008). Despite Seeman *et al.* (2002) reported that in the animals sensitized to amphetamine the entire density of $D_2$ receptors was not altered, the question remains whether PCR method is capable to detect mRNA expression of $D_2$ receptors in both states (high- and low-affinity states), which could explain decrease in the relative $D_2$ receptor expression of sensitized mice in our experiment.

Our present findings showing the decrease in $D_2$ receptor mRNA expression after the acute dose of both methamphetamine and methanadamide support hypotheses of those who suggest that drug dependence is associated with a decrease in $D_2$ receptor availability (Volkow *et al.* 1997; Martinez *et al.* 2004). On the other hand the increase in $D_1$ receptor density in the mesencephalon associated with development of behavioural cross-sensitization to methamphetamine effects after repeated treatment with cannabinoid receptor agonist methanadamide corresponds with conclusion of Worsley *et al.* (2000) that dependence to methamphetamine might be related to reinforced dopamine $D_1$ receptor functioning and can support the cannabinoid gateway hypothesis (e.g. Fergusson *et al.* 2006) increasing risk of use of other drugs of abuse.

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