

# Regulation of genes involved in dopamine transporter modulation by acute cocaine in rat striatum

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## ABSTRACT

It is well established that acute administration of psychostimulants alters dopamine transport. However the exact mechanism of this modulation is still unknown. In this study we examined the mRNA levels of several proteins involved in the various proposed processes following cocaine administration. The expression levels of several immediate early genes were also studied. This was performed in rat striatum using real-time quantitative PCR. As expected a marked increase of the immediate early genes *Fos*, *Egr1* and *Egr3* was observed. *Egr2* was also found upregulated. Among the different genes studied only *Synaptotagmin4* in the SNARE family and *Synphilin1* in the synaptic vesicles binding family were modulated by acute cocaine treatment. Interestingly, acute amphetamine treatment did not increase either *Synaptotagmin4* and *Synphilin1* mRNA levels, although increases in early gene expression were noted.

**Keywords :** cocaine, rat, acute, gene expression

A number of lines of evidence supports the critical role played by dopamine in the nucleus accumbens and the striatum in the reinforcing effects of psychostimulants. There are conflicting reports however, concerning changes in the dopamine transporter (DAT) functions following cocaine or amphetamine administration. Some studies have shown changes consistent with reduced activity of DAT, including reduced dopamine (DA) uptake, downregulation of DAT and increase in extracellular concentrations of DA after acute cocaine treatment [18, 21]. In contrast, other groups have reported that a brief exposure to cocaine can rapidly increase DA uptake and the number of DAT at the cell surface [9, 23]. Briegleb and coworkers observed a positive, significant correlation between the levels of [3H]DA uptake and cocaine-induced locomotor activity in individual rats suggesting that DAT activity have direct behavioral implications [6].

The mechanism responsible for this regulation is not yet fully understood but a constitutive internalization and recycling of DAT to the plasma membrane within minutes has been described [24]. DAT redistribution to and from the plasma membrane can also be regulated by various kinases (review in [34]). Moreover DAT trafficking can be diversely altered by its ligands. Inhibitors such as cocaine increase its cell surface expression and activity, conversely substrates such as amphetamine decrease these parameters [9, 12]. Amphetamine-induced internalization of DAT occurs through a clathrin-mediated endocytosis, this effect can be blocked by cocaine suggesting that cocaine-mediated regulation of DAT at the cell surface could share the same pathway [33]. DAT activity is also modulated through direct protein-protein interactions with intracellular modulators such as  $\alpha$ -synuclein (Snca) [37] which interacts with DAT to form a cytoplasmic complex reducing DAT presence at the plasma membrane (review in [34]).

The trafficking of synaptic proteins like DAT is a major determinant of the properties of synaptic transmission. Another determinant is the regulation of proteins involved in the vesicular transport of neurotransmitters. Psychostimulants like cocaine and amphetamine have

been shown to alter the expression of synaptotagmins, members of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) core complex [10, 13] known to be essential for synaptic transmission. An alteration in expression of synaptic vesicle binding proteins in the striatum could be directly implicated in subsequent alterations in synaptic efficacy elicited by cocaine or amphetamine in this region.

In this study we also investigated the regulation of proteins involved in clathrin mediated endocytosis, DAT modulation and synaptic vesicle binding after acute cocaine and amphetamine. The striatum was chosen, as this structure belongs to the mesostriatal dopaminergic system and is one of the most important structures involved in the reinforcing effects of psychostimulants (review in [29]). Rapid and transient induction of immediate early genes which has been extensively studied was used as positive controls of the treatments [11, 16, 26, 28].

Male Sprague–Dawley rats (Charle River, France) weighing an average of 200 g were housed under controlled conditions (12h alternating light/dark cycle at  $21\pm 1^{\circ}\text{C}$ ) with free access to food and water. Care and treatment of animals conformed to the standards and guidelines promulgated by the European Communities Council Directive (86/609/EEC). Acute treatments consisted of intraperitoneal administration of cocaine 20 mg/kg, amphetamine 5mg/kg (Sigma, France) or saline and animals were sacrificed 1 hour after the injection. Chronic cocaine regimen consisted of intraperitoneal injections of cocaine 15 mg/kg, once a day for fourteen consecutive days and animals were sacrificed 24h after the last injection. The dorsal striata were rapidly dissected on ice, frozen in isopentane at  $-50^{\circ}\text{C}$ , and stored at  $-80^{\circ}\text{C}$  until use.

Total RNA was extracted from individual striatum with RNABle reagent (Eurobio, France) following the manufacturer's protocol. RNA was reverse-transcribed in a final volume of 20  $\mu\text{l}$  as previously described (Marie-Claire et al., 2004). PCR primers were chosen with the assistance of Oligo 6.42 software (MedProbe, Norway). The primer nucleotide sequences used

in this study are listed in table I. Fluorescent PCR analysis was performed using the LightCycler™ instrument (Roche Diagnostics, France). The cDNAs were diluted at 1/100 and 5µl were added to the PCR reaction mix to yield a total volume of 10µl. The PCR reagents were from the FastStart DNA Master SYBR Green I kit (Roche Diagnostics, France). cDNAs from a naive rat brain were used to generate an external standard curve for each gene. We also quantified transcripts of the gene coding for the TATA binding protein (Tbp), a component of the DNA-binding protein complex TFIID, as the endogenous RNA control and normalized each sample on the basis of its Tbp content as previously described [25]. All series of data were analysed with the GraphPad Prism® software (San Diego, USA). Results are displayed as mean  $\pm$  SD of 7-8 animals. Student's test was used for analysis and statistical significance was set at  $P < 0.05$ .

To validate the efficacy of the cocaine treatment we evaluated the modulation of four transcription factors in our conditions. The results are summarized in figure 1. As compared to the saline-treated rats, acute treatment with cocaine led to a significant increase in *Fos* mRNA in the striatum (5.9 fold). This is consistent with the well documented increase in *Fos* expression after acute cocaine [8, 11, 14, 26]. Acute cocaine treatment also induced a significant increase in *Egr1* and *Egr3* mRNA (2.5 and 1.5 fold respectively). *Egr1* and *Egr3* increase after acute cocaine treatment has been previously reported at the mRNA and protein level [3, 17, 20, 28]. *Egr2* is the only member of the family whose expression is restricted to neurons in the central nervous system [15]. A marked increase in *Egr2* mRNA was obtained (7.2 fold) in rats acutely treated with cocaine as compared to controls. Since acute cocaine injection has been shown to induce a dose dependent increase in dopamine extracellular level not only in the nucleus accumbens but also in the striatum of rats [7, 30]. Our finding is in agreement with the previously reported up-regulation of *Egr2* mRNA by dopamine in the striatum of rats [2, 4]. Members of Egr family are known to play an important role in neuronal plasticity and a critical role in the transition from short to long term synaptic plasticity has

been shown for *Egr1* [19]. The modulation of 3 members of the *Egr* family observed here probably participate in mediating long-term adaptations produced by cocaine in the striatum.

DAT has been shown to be constitutively internalized through clathrin-mediated endocytosis *in vitro* [33, 35]. The effects of acute cocaine treatment on the expression of two genes encoding major proteins involved in this process was examined. As shown in figure 2A neither the mRNA of Dynamin1 (*Dnm1*) nor Clathrin (*Cltc*) were regulated by acute cocaine treatment. These results suggests that the redistribution of DAT at the cell surface after acute cocaine treatment does not require modification of the level of mRNA of this two proteins at this time point. Moreover, the mRNA level of *Cltc* and *Dnm1* were still not affected after a 14 days chronic cocaine treatment (Figure 2B).

The binding and functional coupling of *Snca* to DAT increases dopamine uptake leading to a negative regulation of dopamine neurotransmission [22]. A concentration dependent modulation of this protein on the trafficking of DAT has been suggested in mice, and the direct interaction between the two proteins has been demonstrated *in vitro* [32, 37].  $\alpha$  and  $\gamma$ -synucleins have been found upregulated after a high dose cocaine regimen in the dorsal striatum of rats [5]. Moreover, an overexpression of *Snca* in dopamine neurons of cocaine abusers has been observed raising the question of an elevated risk for degenerative changes in dopamine neurons of cocaine addicts [27]. Synphilin-1 (*Sncap*) is highly enriched in presynaptic nerve terminals where it interacts with synaptic vesicles [31]. This interaction can be abolished *in vitro* by *Snca*, the two proteins may therefore play a role in synaptic function [1]. We therefore studied the regulation of the mRNA of these two proteins by acute cocaine treatment and found that *Sncap* mRNA showed a slight but significant 1.3 fold increase one hour after a single cocaine injection (Figure 2C). *Snca* expression level was not affected by cocaine in these conditions. Acute amphetamine treatment, at a dose (5mg/kg) able to increased *Fos* and *Egr1* mRNA levels (data not shown) in agreement with other studies [13,

36], did not modify the expression of neither Snca or Sncaip (data not shown) indicating that the mechanism leading to this upregulation is not common to the two psychostimulants. Interestingly the increase in Sncaip mRNA was still significant after a chronic cocaine treatment while a slight but not significant increase of Snca mRNA could be detected (Figure 2 D). This slight upregulation probably results from the heterogeneity of the sample since the increase of Snca has been shown to be specific to dopamine containing cells of the midbrain in cocaine abusers [27] and/or the dose used since an upregulation of Snca has been described in rat striatum after a high-dose cocaine treatment [5]. Further experiments using in situ hybridization and subcellular localization are required to determine if this cocaine regimen may constitute a model to study the impact of Snca and Sncaip upregulation on the neurodegeneration of dopaminergic neurons.

We also examine the modulation of genes encoding for proteins involved in synaptic vesicle binding. SNARE proteins have been implicated as major constitutive vesicular/synaptic proteins responsible for vesicular docking/fusion steps that occur following depolarization and calcium influx in presynaptic terminals. The synaptic SNARE complex consists of the synaptic vesicle proteins Vamp (vesicle associated membrane protein) and the plasma membrane proteins Syntaxins and Snap25 (25 kDa synaptosome-associated protein). Additional factors are required for SNARE-mediated membrane fusion *in vivo*, among these regulators synaptophysin and synaptotagmins are the most studied. The slight but significant upregulation (1.15) of synaptotagmin 4 by acute cocaine administration obtained here (Figure 3) in rat striatum has been described by others [10]. As described by these authors [10] acute treatment with amphetamine had no effect on the mRNA level of synaptotagmin 4 in the striatum of rats (data not shown). None of the other four SNARE or SNARE interacting proteins tested showed a significant regulation by acute cocaine at this time point.

In conclusion, we investigated the regulation of immediate early genes and synaptic vesicles binding genes in the rat striatum of rats after acute cocaine treatment using real time quantitative PCR. We confirmed the previous results showing an increase in *Fos*, *Egr1* and *Egr3* after acute cocaine treatment and extended them to *Egr2*. We could not detect any modulation of the mRNAs of clathrin and dynamin1. We found an up-regulation of the  $\alpha$ -synuclein interacting protein Synphilin 1 in rat striatum after acute cocaine treatment. We also shown that while the mRNA of Synaptotagmin4 is weakly up-regulated after acute cocaine treatment none of the other SNARE complex proteins tested were affected (*Vamp2*, *Syp*, *Snap25* and *Stx1a*) at this time point. The modulatory activities of acute cocaine on the mRNA of these genes, although relatively weak, may be relevant to the synaptic and neuronal plasticity that contribute to cocaine psychomotor activation and addiction. Interestingly, taking into consideration the present results and those from the litterature, it appears that the increases in Synphilin1 and Synaptotagmin4 are specific to cocaine, as the level of these mRNA are not modified following amphetamine administration.



**Table I :** Primer Sequences used for SYBR Green-based real-time quantitative polymerase chain reaction.

Gene	Forward primer	Reverse primer
<i>Tbp</i>	TGCACAGGAGCCAAGAGTGAA	CACATCACAGCTCCCCACCA
<i>Snca</i>	TGGGCAAGGGTGAAGAAG	TAGGCTTCAGGCTCATAGTCT
<i>Cltc</i>	ATCGCCCAGCTGTGTGAGAA	CCACTCGGGGTTGAGAAGATG
<i>Fos</i>	GGCAAAGTAGAGCAGCTATCTCCT	TCAGCTCCCTCCTCCGATTC
<i>Dmn1</i>	CTTGCGGGGACCAGAACAC	GGCATGGGCGTGCTGAC
<i>Sncaip</i>	GGGCGAGCTGGAGCACTAT	GGGGCCAGCTGTTGACTG
<i>Snap25</i>	TCATCCGCAGGGTAACAAAC	CTGGCGATTCTGGGTGTCA
<i>Stx1a</i>	CAGGGGGAGATGATTGACAG	CGTGCCTTGCTCTGGTACT
<i>Vamp2</i>	CAGGGGCCTCCCAGTTTGAA	GGCGCAAATCACTCCCAAGA
<i>Syp</i>	GCCACGGACCCAGAGAACAT	GGAAGCCAAACACCACTGAG
<i>Syt4</i>	TGACGAAACCTTCACATTCTATG	TTTCCCGTCTGACAATTCAAT
<i>Egr1</i>	GAGCCCGCACCCAACAGTG	TGGGGCTCAGGAAAAATGTCA
<i>Egr2</i>	CGCCACACCAAGATCCACC	AGCCCCCAGGACCAGAGG
<i>Egr3</i>	CAACCGCCGCTCACTCTCAA	GCGCAGGTGCCGGGTCAG

## FIGURE LEGENDS

**Figure 1** : Effect of acute cocaine treatment on the mRNA level of immediate early genes by real time RT-PCR analysis. All data have been normalized for levels of Tbp expression within the same sample and represent mean  $\pm$  SD (n= 7-8 rats), \* P<0.05, \*\*P<0.01, (Student's test).

**Figure 2** : Effect of acute (A, C) and chronic (B, D) cocaine treatment on the mRNA level of (A, B) Dynamin1 and clathrin heavy polypeptide and (C, D) Sncaip and Snca by real time RT-PCR analysis. All data have been normalized for levels of Tbp expression within the same sample and represent mean  $\pm$  SD (n= 7-8 rats), \* P<0.05 (Student's test).

**Figure 3** : Effect of acute cocaine treatment on the mRNA level of genes coding for proteins of the SNARE complex by real time RT-PCR analysis. All data have been normalized for levels of Tbp expression within the same sample and represent mean  $\pm$  SD (n= 7-8 rats), \* P<0.05 (Student's test).

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