Key role of striatal cholinergic interneurons in processes leading to arrest of motor stereotypies

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Motor stereotypy is a key symptom of various disorders such as Tourette’s syndrome and punding. Administration of nicotine or cholinesterase inhibitors is effective in treating some of these symptoms. However, the role of cholinergic transmission in motor stereotypy remains unknown. During strong cocaine-induced motor stereotypy, we showed earlier that increased dopamine release results in decreased acetylcholine release in the territory of the dorsal striatum related to the prefrontal cortex. Here, we investigated the role of striatal cholinergic transmission in the arrest of motor stereotypy. Analysis of N-methyl-D-aspartic acid-evoked release of dopamine and acetylcholine during declining intensity of motor stereotypy revealed a dissociation between dopamine and acetylcholine release. Whereas dopamine release remained increased, the inhibition of acetylcholine release decreased, mirroring the time course of motor stereotypy. Furthermore, pharmacological treatments restoring striatal acetylcholine release (raclopride, dopamine D2 antagonist; intraperitoneal or local injection in prefrontal territory of the dorsal striatum) rapidly stopped motor stereotypy. In contrast, pharmacological treatments that blocked the post-synaptic effects of acetylcholine (scopolamine, muscarinic antagonist; intraperitoneal or striatal local injection) or induced degeneration of cholinergic interneurons (AF64A, cholinergic toxin) in the prefrontal territory of the dorsal striatum robustly prolonged the duration of strong motor stereotypy. Thus, we propose that restoration of cholinergic transmission in the prefrontal territory of the dorsal striatum plays a key role in the arrest of motor stereotypy.

Keywords: cholinergic interneurons; dorsal striatum; dopamine/acetylcholine balance; motor stereotypy; cocaine
Abbreviation: NMDA = N-methyl-D-aspartic acid

Introduction

Stereotypy is a cardinal feature of numerous neurologic and neuropsychiatric disorders such as Tourette’s syndrome and is a major component of the behavioural syndrome provoked by psychomotor stimulants. Parkinsonian patients overtreated with dopamine agents or humans addicted to cocaine exhibit stereotyped behaviour referred to as ‘punding’ and characterized by non-goal directed repetitive activity (Rylander, 1972; Schiørring, 1981; Friedman, 1994; Evans et al., 2004, 2009). In rodents,
cocation-induced motor stereotypy consists essentially of stereotyped movements such as head bobbing, rearing, licking and sniffing. Although the precise pathophysiological basis of stereotyped behaviour is still unknown, the corticobasal ganglia circuits seem to play a key role. Observations both in humans suffering from repetitive and compulsive disorders and in experimental animal models of stereotypy have pointed to a dysfunction in prefronto-corticobasal ganglia circuits (Graybiel and Rauch, 2000; Mallet et al., 2002; Volkow et al., 2004; Van den Heuvel et al., 2005). Accordingly, we recently showed that cocaine-induced motor stereotypes is correlated with strong alterations of the basal ganglia circuits related to the medial prefrontal but not of those related to the sensorimotor cortical areas, resulting in an important imbalance between these circuits (Aliane et al., 2009). In the striatum, the main input structure of the basal ganglia, the dopamine/acetylcholine balance is essential for striatal functions. In line with this balance, we previously found that during the period of strong cocaine-induced motor stereotypy, the high level of extracellular dopamine occurring in the prefrontal territory of the dorsal striatum is associated with a decrease of acetylcholine release (Aliane et al., 2009). If an increase of dopamine is considered determinant in the process leading to motor stereotypes, some clinical observations suggest an involvement of acetylcholine in the arrest of motor stereotypes. Indeed, besides its numerous side-effects, donepezil, a cholinesterase inhibitor, is effective in children suffering from motor stereotypes and Tourette’s syndrome (Cubo et al., 2008). However, an involvement of cholinergic transmission in the arrest of motor stereotypes remains to be demonstrated.

In this study, we concentrated on the time period of arrest of cocaine-induced motor stereotypy and the suggested involvement of cholinergic transmission in this process. First, the time course of the intensity of cocaine-induced motor stereotypy was compared with the time course of dopamine and acetylcholine release in the prefrontal territory of the dorsal striatum. The result shows that while dopamine transmission remains increased during the decline and arrest of motor stereotypy, cholinergic transmission normalized during this period. Furthermore, the impact of various pharmacological treatments targeting striatal cholinergic transmission, as well as the effect of lesioning cholinergic interneurons of the prefrontal territory of the dorsal striatum on cocaine-induced motor stereotypy, showed that restoration of the cholinergic transmission is a key factor for the arrest of motor stereotypy.

**Materials and methods**

The evaluation of cocaine-induced behaviour as well as in vitro and in vivo neurochemical analyses were performed on cocaine-sensitized Sprague-Dawley male rats, as described earlier (Aliane et al., 2009) and detailed in the online Supplementary Material. Briefly, in vitro (sagittal slices) and in vivo (anaesthetized rats) microsuperfusion, allowing the estimation of [3H]-dopamine and [3H]-acetylcholine release, were performed in the prefrontal territory of the dorsal striatum. For [3H]-dopamine and [3H]-acetylcholine release, the time course of differences between N-methyl-d-aspartic acid (NMDA)-evoked release in rats treated with cocaine or saline were analysed during the periods of strong and decreasing intensity of motor stereotypes leading to the arrest of stereotyped behaviour. For the in vivo studies, rats were anaesthetized using chloral hydrate (420 mg/kg, intraperitoneal; SIGMA, Steinheim, Germany). For canulla implantation or lesioning of cholinergic interneurons, rats were anaesthetized with sodium pentobarbitral (30 mg/kg, intraperitoneal; Ceva Sante Animale, Libourne, France) supplemented by injections of ketamine (27.5 mg/kg, intramuscular; Imalgene 500, Merial, Lyon, France). Neuroleptic or cholinergic antagonist was injected intraperitoneally or locally (through pre-implanted canulla) in the prefrontal or the sensorimotor territory of the dorsal striatum. These injections were performed 15 min after the challenge injection of cocaine (during strong motor stereotypy) or saline. Lesions of cholinergic interneurons in the prefrontal territory of the dorsal striatum were performed using AF64A (Sandberg et al., 1984). Cocaine-induced behaviour was analysed at various time points after the challenge injection, using a 7-point stereotypy scale (MacLennan and Maier, 1983). A score of 0 indicates inactivity, scores of 1 and 2 indicate increased activity and scores of 3–7 correspond to different levels of stereotyped behaviour.

Statistical analyses were performed using SigmaStat 3.1 (Systat Software, San Jose, CA, USA). To allow for multiple comparisons one-way or two-way ANOVAs were applied followed by the Tukey’s post hoc test. Significance level was set at $P < 0.05$.

**Results**

**Time course of dopamine and acetylcholine release in the prefrontal territory of the dorsal striatum in relation to cocaine-induced motor stereotypy**

A challenge injection of cocaine following sensitization and withdrawal induced strong motor stereotypes mainly consisting of head bobbing, sniffing and oral activities such as licking or gnawing. At 15 or 25 mg/kg, the period of strong motor stereotypy (15 or 30 min) was followed by a period of decreasing intensity until the arrest 45 or 60 min after the challenge injection, respectively (Fig. 1).

The time relationships between the intensity of cocaine-induced motor stereotypy and NMDA-evoked release of [3H]-dopamine and [3H]-acetylcholine in the prefrontal territory of the dorsal striatum were examined in striatal slices. As expected, cocaine induced a prominent increase of NMDA-evoked release of [3H]-dopamine [cocaine 15 mg/kg: $F(2,58) = 0.08$, $P = 0.92$, Tukey’s test, 15, 30 and 45 min, $P < 0.001$; cocaine 25 mg/kg $F(2,49) = 0.06$, $P = 0.94$, Tukey’s test, 15, 30 and 60 min, $P < 0.001$]. At variance with the time course of behaviour, the release of dopamine remained at a high level during the entire period of time corresponding to epochs of strong and decreasing intensity of motor stereotypy, i.e. until 45 or 60 min after injection of 15 or 25 mg/kg cocaine, respectively (Fig. 1).

Consistent with the increase of dopamine, cocaine induced an inhibition of the NMDA-evoked release of [3H]-acetylcholine. This inhibition was prominent during strong motor stereotypy but, in contrast to dopamine, the inhibition of acetylcholine release...
gradually decreased and returned to basal level at 45 or 60 min after the challenge injection of 15 or 25 mg/kg cocaine, respectively [Fig. 1; cocaine challenge 15 mg/kg, F(2,67) = 1.84, P = 0.167, Tukey’s test, 15 and 30 min, P = 0.004, 45 min, P = 0.806; cocaine challenge 25 mg/kg, F(3,101) = 3.63, P = 0.016, Tukey’s test, 15 and 30 min, P < 0.001, 45 min, P = 0.033, 60 min, P = 0.596]. Thus, while the [3H]-dopamine extracellular levels stayed at a high level during strong and decreasing intensity of motor stereotypy, the inhibition of [3H]-acetylcholine release mirrored the time course of motor stereotypy, decreasing when the intensity of motor stereotypy declined until it stopped (Fig. 1).

To further strengthen this latter finding, the NMDA-evoked release of [3H]-acetylcholine in the prefrontal territory of the dorsal striatum was analysed in vivo in anaesthetized rats. As observed in vitro, the challenge injection of cocaine (25 mg/kg) provoked an inhibition of the NMDA-evoked release of [3H]-acetylcholine, which was at its maximum 30 min after cocaine injection and then decreased until reaching its basal level 60 min after the challenge injection, mirroring the decreasing intensity of motor stereotypy [Fig. 2; [3H]-acetylcholine release, F(4,28) = 12.85, P = 0.001, Tukey’s test, 15, 30 and 45 min, P < 0.001, 60 min, P = 0.915].

**Effect of peripheral injection of muscarinic antagonists, raclopride or both on cocaine-induced motor stereotypy**

The time relationship between the level of acetylcholine release and the decrease of intensity of stereotyped behaviour, suggested a major involvement of the cholinergic transmission in the arrest of motor stereotypy. This was further tested by analysing the behavioural consequence of pharmacological treatments interfering directly or indirectly with striatal cholinergic transmission.

A direct blockade of cholinergic transmission was achieved using muscarinic cholinergic antagonists, scopolamine (5 mg/kg),...
The peripheral injections of raclopride and scopolamine did not ascertain that these drugs were acting at the striatal level. Telenzepine M1 antagonist (3 mg/kg) and tropicamide M4 antagonist (10 mg/kg). Muscarinic antagonists or saline were injected (intraperitoneally) 15 min after the challenge injection of cocaine (25 mg/kg, during strong motor stereotypy) or saline. In the control situation (saline), the peripheral injection of muscarinic antagonists induced a slight exploratory behaviour but no motor stereotypy. On the contrary, when injected 15 min after the cocaine challenge, scopolamine, telenzepine, tropicamide or telenzepine and tropicamide together induced a prominent increase of the duration of strong motor stereotypy [Fig. 3, effect of scopolamine: F(21,164) = 69.66, P < 0.001, Tukey’s test, P < 0.004; Fig. 4, effect of telenzepine, tropicamide or telenzepine + tropicamide: F(47,285) = 81.42, P < 0.001, Tukey’s test, P < 0.04].

Raclopride, a dopamine D2 antagonist, or saline was injected (intraperitoneally) 15 min after the challenge injection of cocaine (25 mg/kg, during strong motor stereotypy) or saline. After saline injection, raclopride (0.05–0.4 mg/kg) affected neither the NMDA-evoked release of [3H]-acetylcholine in the prefrontal territory of the dorsal striatum nor the rat’s motor activity. In contrast, after the cocaine challenge, raclopride (0.1 or 0.4 mg/kg) totally suppressed the cocaine-induced inhibition of NMDA-evoked release of [3H]-acetylcholine [Table 1, F(7,79) = 4.47, P < 0.001, Tukey’s test, P < 0.05] as well as motor stereotypy within 10 or 5 min, respectively [Fig. 3; F(43,285) = 126.68, P < 0.001, Tukey’s test, P < 0.05]. At a concentration of 0.05 mg/kg raclopride was inefficient (Table 1, Fig. 3).

To verify that the effect of raclopride was linked to cholinergic transmission and thus to its action on dopamine D2 receptors present on cholinergic interneurons (Aubry et al., 1993), the effect of raclopride (0.4 mg/kg) was analysed in the presence of scopolamine (5 mg/kg). When injected 15 min after the cocaine challenge, the simultaneous administration of both scopolamine and raclopride resulted in a prominent increase (2.5-fold) of the duration of strong motor stereotypy when compared with saline injection. Indeed, the time course of motor stereotypy after the administration of raclopride in the presence of scopolamine was similar to that observed in the presence of scopolamine alone. Thus, in the presence of scopolamine, raclopride was not able to suppress the cocaine-induced motor stereotypy [Fig. 3; F(32,186) = 62.29, P < 0.001, Tukey’s test, P < 0.001 effect of raclopride + scopolamine compared with raclopride alone].

**Effect of raclopride or scopolamine injected in the prefrontal or sensorimotor territory of the dorsal striatum on cocaine-induced motor stereotypy**

The peripheral injections of raclopride and scopolamine did not ascertain that these drugs were acting at the striatal level.
Thus, local injections of raclopride (5 µg) or scopolamine (15 µg) were performed either in the prefrontal or the sensorimotor territory of the dorsal striatum. In these experiments, each rat was its own control. Indeed, after verifying that challenge injections of cocaine performed three times at 4 day intervals provoked the same time course of intensity of motor stereotypies, rats received three challenge injections of cocaine or saline (at intervals of 4 days) associated with striatal injections of saline, raclopride or scopolamine interchanging the order of treatments.

In the control situation, when applied 15 min after the challenge injection of saline, raclopride or scopolamine was without overt effect on rat behaviour. When injected bilaterally in the prefrontal territory of the dorsal striatum and during strong cocaine-induced motor stereotypy, raclopride provoked a rapid reduction and arrest of motor stereotypy 10 min after the end of the raclopride injection [$F(21,130) = 80.48$, $P < 0.001$, Tukey’s test, $P < 0.001$]. Conversely, scopolamine induced a prominent increase (2.5-fold) in the duration of strong motor stereotypy [$F(21,130) = 80.17$, $P < 0.001$, Tukey’s test, $P < 0.001$]. Importantly, these effects were observed only if raclopride or scopolamine was injected in the prefrontal territory but not if injected in the sensorimotor territory of the dorsal striatum (Fig. 5). In this latter case, injection of raclopride or scopolamine had no effect on cocaine-induced motor stereotypy [raclopride, $F(21,131) = 85.97$, $P < 0.001$, Tukey’s test, not significant, scopolamine, $F(21,130) = 85.67$, $P < 0.001$, Tukey’s test, not significant] (Fig. 5).

Impact of lesioning cholinergic interneurons in the prefrontal territory of the dorsal striatum on cocaine-induced motor stereotypy

The involvement of cholinergic interneurons of the prefrontal territory of the dorsal striatum was further analysed by performing lesion of these neurons using AF64A, a cholinergic toxin (Sandberg, 1984). AF64A injected in the prefrontal territory of the dorsal striatum induced the loss of anti-choline acetyltransferase-immunolabelled cell bodies in the prefrontal but not in the sensorimotor territory of the dorsal striatum (Supplementary Fig. 1). This lesion did not modify the NMDA-evoked release of [³H]-dopamine in the prefrontal territory. It also did not modify the NMDA-evoked release of [³H]-acetylcholine in the sensorimotor territory of the dorsal striatum (Supplementary Fig. 2). Similar to the effect induced by scopolamine injected either at the periphery or locally in the prefrontal territory of the dorsal striatum, the lesion of cholinergic interneurons considerably prolonged (2.5-fold) the duration of strong motor stereotypy (Fig. 6) [$F(21,164) = 45.24$, $P < 0.001$, Tukey’s test, $P < 0.001$].

Discussion

Dopamine transmission in the dorsal striatum is known to play a determinant role in psychomotor stimulant-induced stereotyped behaviour. Lesion of dopamine innervation of the dorsal striatum prevents stereotypy induction by amphetamine (Kelly et al., 1975). Moreover, we recently demonstrated that during the period of strong motor stereotypy induced by cocaine, an increase of dopamine release associated with a decrease of acetylcholine

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### Table 1 Effect of peripheral injection of raclopride on the cocaine-induced inhibition of NMDA-evoked release of [³H]-acetylcholine in the prefrontal territory of the dorsal striatum

<table>
<thead>
<tr>
<th>NMDA-evoked release of [³H]-acetylcholine (%)</th>
<th>Saline</th>
<th>Raclopride 0.05 mg/kg</th>
<th>Raclopride 0.1 mg/kg</th>
<th>Raclopride 0.4 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>141 ± 9</td>
<td>142 ± 9</td>
<td>138 ± 10</td>
<td>121 ± 13</td>
</tr>
<tr>
<td>Cocaine 25 mg/kg</td>
<td>91 ± 11*</td>
<td>81 ± 9*</td>
<td>137 ± 14</td>
<td>135 ± 17</td>
</tr>
</tbody>
</table>

Sensitized rats received a challenge injection of cocaine or saline followed (15 min later) by an injection (intraperitoneally) of raclopride (0.05–0.4 mg/kg) or saline. The NMDA-evoked [³H]-acetylcholine release was analysed in the prefrontal territory of the dorsal striatum ($n = 6–11$ corresponding to 3–5 rats per group). One-way ANOVAs were followed by Tukey’s post hoc test for multiple comparisons: *$P < 0.05$, effect of cocaine injection compared with saline injection, in the presence of various doses of raclopride.
release occurs in the prefrontal but not in the sensorimotor territory of the dorsal striatum. Here, we focused on the process involved in the arrest of cocaine-induced motor stereotypy and demonstrated that restoration of cholinergic transmission in the prefrontal territory of the dorsal striatum plays a key role. Indeed, contrasting the period of strong motor stereotypy during which striatal dopamine/acyetylcholine balance is operational, during declining intensity of cocaine-induced motor stereotypy leading to its arrest, the dopamine/acyetylcholine balance becomes dissociated. Whereas dopamine release remains at a high level, acetylcholine release returns to its basal level, mirroring the time course of the intensity of motor stereotypy. Moreover, pharmacological treatments that restored striatal levels of acetylcholine in the prefrontal territory simultaneously provoked the arrest of strong motor stereotypy. In contrast, those blocking the post-synaptic effects of acetylcholine or inducing degeneration of cholinergic interneurons robustly prolonged the duration of strong motor stereotypy. Therefore, restoration of extracellular levels of acetylcholine in the prefrontal territory of the dorsal striatum plays a key role in the arrest of cocaine-induced motor stereotypy.

**Dopamine and acetylcholine release in the prefrontal territory of the dorsal striatum during strong motor stereotypy and its arrest**

The challenge injection of cocaine provokes motor stereotypy with a time course of intensity displaying two periods, a period of strong motor stereotypy followed by a period of gradually decreasing intensity until its complete arrest. We have earlier shown that strong cocaine-induced motor stereotypy is linked to increased dopamine release in the prefrontal territory of the dorsal striatum (Aliane et al., 2009). In the striatum, increased dopamine release induces inhibition of the tonic firing of cholinergic interneurons and inhibition of acetylcholine release (Blanchet et al., 1997; Ding et al., 2000; Kemel et al., 2002; Wang et al., 2006; Pisani et al., 2007). In physiological conditions, the predominant effect of dopamine on cholinergic transmission is an inhibition mediated by dopamine D2 receptors expressed by cholinergic interneurons (DeBoer et al., 1996; Ding et al., 2000; Deng et al., 2007; Pisani et al., 2007). In line with these findings, the cocaine-induced increase of dopamine release provoked an inhibition of acetylcholine release via dopamine D2 receptors, this effect being suppressed by a very low dose of the dopamine D2 antagonist raclopride.

Surprisingly, while dopamine release remained at a high level until the complete arrest of motor stereotypy, the inhibition of acetylcholine release decreased during the period of declining intensity until it returned to its basal level at the end of motor stereotypy. Thus, the time course of the inhibition of acetylcholine release mirrored the time course of the intensity of motor stereotypy, and the arrest of motor stereotypy was correlated with a dissociation of the dopamine/acyetylcholine balance. As discussed below, this dissociation is essential in the arrest of motor stereotypy. To date, the mechanism involved in the dissociation of dopamine/acyetylcholine balance allowing counteraction of the dopamine D2 inhibitory control of cholinergic interneurons and leading to restoration of acetylcholine release are unknown. It has been suggested that by acting on cholinergic receptors, cocaine might modulate cholinergic efflux (Williams and Addinoff, 2008). Moreover, it is well-known that in the striatum, local circuits involving various neurotransmitters or neuropeptides such as serotonin, tachykinines, opioids and nitric oxide are involved in the regulation of acetylcholine release (Blanchet et al., 1998; Centonze et al., 2001; Kemel et al., 2002; Labourian et al., 2004; Pisani et al., 2007). Therefore, by acting on these local circuits, cocaine might indirectly control the release of acetylcholine in the dorsal striatum. In addition, sensitization to cocaine allowing the challenge injection to produce strong and reproducible motor stereotypy induces modifications of various neurotransmitter systems (Smith et al., 1995; Reid and Berger, 1996; Vanderschuren and Kalivas, 2000). These changes could also be involved in striatal plasticity and regulation of striatal local circuits leading to the restoration of extracellular levels of acetylcholine.

**Cholinergic transmission and arrest of motor stereotypy**

The observation that acetylcholine release mirrors the time course of the intensity of cocaine-induced motor stereotypy suggested that cholinergic transmission might play an important role in the arrest of motor stereotypy. Interestingly, peripheral injection of scopolamine that blocks the post-synaptic effect of acetylcholine considerably prolonged strong motor stereotypy. Importantly, the
specific muscarinic receptor antagonists telenzepine (M1) and tropicamide (M4), applied either alone or together, have a similar effect on motor stereotypy. Altogether, these data nicely demonstrate the involvement of cholinergic muscarinic receptors in the arrest of motor stereotypies. In contrast, peripheral injection of raclopride that restores acetylcholine release in the prefrontal territory of the dorsal striatum, rapidly and dose dependently suppressed cocaine-induced motor stereotypy. The absence of effect of raclopride in the presence of scopolamine shows that the effect of raclopride is linked to the cholinergic transmission and therefore mediated through dopamine D2 receptors located on cholinergic interneurons. Demonstrating the involvement of cholinergic transmission of the prefrontal territory of the dorsal striatum in the arrest of motor stereotypy, intrastriatal injections of raclopride or scopolamine in this territory stopped or prolonged, respectively, strong motor stereotypy. Furthermore, lesion of cholinergic interneurons in the prefrontal territory of the dorsal striatum strengthened the observation that in the absence of cholinergic transmission in this territory, cocaine-induced motor stereotypy is prolonged. Altogether, these observations and the lack of effect of raclopride or scopolamine injections in the sensorimotor territory of the dorsal striatum strongly suggest that cholinergic transmission specifically in the prefrontal territory of the dorsal striatum has a key role in the process of decreasing intensity and arrest of motor stereotypy.

Cholinergic transmission and corticobasal ganglia information transmission

We earlier showed that cocaine-induced motor stereotypies are related to a functional impairment of the basal ganglia circuits related to the medial prefrontal cortex (Aliane et al., 2009), a result consistent with the role of this cortex in behavioural flexibility (Dalley et al., 2004). Interestingly, cholinergic interneurons of the dorsolateral (prefrontal) striatum are also selectively involved in behavioural flexibility (Ragozzino et al., 2009) and we show here that these interneurons play a key role in the arrest of motor stereotypy. It is well-known that cholinergic interneurons are fundamental in striatal information processing (Apicella, 2002; Tepper and Bolam, 2004; Calabresi et al., 2006; Pisani et al., 2007). They are involved in dynamic modulation of the basal ganglia circuitry through rich synaptic connection with the striatal efferent medium-sized neurons that they directly modulate (Besson et al., 1982; Shen et al., 2005; Pisani et al., 2007). During the period of strong motor stereotypy, the transmission of the cortical information through the direct and indirect striatal circuits is strongly reduced (Aliane et al., 2009). Due to their effect on medium-sized neurons, cholinergic interneurons could be involved in restoration of corticostriatal basal ganglia transmission at the level of the medial prefrontal territory of the dorsal striatum.

In addition to functionally defined prefrontal and sensorimotor territories in the striatum, two compartments, the striosomes and the matrix, can be distinguished in the dorsal striatum (Graybiel, 1990; Desban et al., 1993; Gerfen and Wilson, 1996). They form the striosome- and matrix-based basal ganglia circuits. Indeed, the efferent medium spiny neurons of the striosomes innervate the dopaminergic neurons of the substantia nigra pars compacta that project to the striatum. In contrast, efferent medium spiny neurons of the matrix are at the origin of the direct and indirect pathways sending information to the output structures of the basal ganglia, the substantia nigra pars reticulata and the internal globus pallidus. Interestingly, in monkeys and rodents, cocaine-induced motor stereotypy was correlated with specific patterns of early gene induction in striosomes and matrix indicating an imbalance between striosome- and matrix-based basal ganglia circuits (Canales and Graybiel, 2000; Saka et al., 2004). Cholinergic interneurons could have a major role in the transfer of information between striosome- and matrix-based basal ganglia. Indeed, their dendrites innervate the striosomes and the matrix, but their dense and widespread local axon collateral plexus is largely restricted to the matrix where it primarily targets the medium spiny neurons (Graybiel et al., 1986; Kawaguchi, 1992).

This specific role of cholinergic interneurons in corticobasal ganglia information transmission is most important in the prefrontal territory, since this territory is enriched in striosomes (Desban et al., 1993; Voorn et al., 2004). In line with Saka et al. (2002), during strong motor stereotypy, cocaine-induced increase of dopamine release provoked an inhibition of cholinergic transmission that might lead to the interruption of the connection between striosome- and matrix-based basal ganglia circuits. Progressive restoration of cholinergic transmission could restore this connection that might be essential for the arrest of motor stereotypy.

Conclusion

These findings are in line with clinical observations showing that neuroleptics as well as acetylcholinesterase inhibitors are effective in treating motor and phonic tics in Tourette’s syndrome and stereotyped behaviour in obsessive compulsive disorders (Silver et al., 2001; Cubo et al., 2008; Lombroso and Scahill, 2008; Shprecher and Kurlan, 2009). Indeed, administration of donepezil, a reversible acetylcholinesterase inhibitor, decreases tics in children with Tourette’s syndrome (Cubo et al., 2008). However, administration of acetylcholinesterase inhibitors leads to serious and highly disabling side-effects. Therefore, it is now important to further analyse the mechanisms involved in the restoration of cholinergic transmission in the prefrontal territory of the dorsal striatum leading to the arrest of motor stereotypy. Better knowledge of the neurotransmitters or neuropeptides involved in this process would open new perspectives on possible treatments of stereotyped behaviour with reduced side-effects.

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Supplementary material

Supplementary material is available at Brain online.

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