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Intermittent morphine treatment causes long-term desensitization of functional dopamine D_2 receptors in rat striatum

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Abstract

3 weeks following cessation of intermittent morphine administration (10 mg/kg, s.c., once daily for 14 days), [^{3}H]dopamine and [^{14}C]acetylcholine release induced by 10 μM *N*-methyl-D-aspartate (NMDA) from superfused rat striatal slices appeared to be significantly higher than the release from striatal slices from saline-treated rats. A similar adaptive increase of the NMDA-evoked release of these neurotransmitters was observed in slices of the nucleus accumbens, whereas that of [^{3}H]noradrenaline from hippocampal slices remained unchanged. Blockade of dopamine D_2 receptors by 10 μM (−)-sulpiride enhanced NMDA-induced [^{3}H]dopamine and [^{14}C]acetylcholine release from striatal slices from saline-treated animals, but was found to be ineffective in this respect following intermittent morphine treatment. Moreover, morphine administration appeared to cause a profound decrease in the apparent affinity of the full dopamine D_2 receptor agonist LY171555 (quinpirole) for these release-inhibitory dopamine D_2 receptors, indicating the occurrence of dopamine D_2 receptor desensitization. It is suggested that such a desensitization of dopamine D_2 receptors on dopaminergic nerve terminals as well as on cholinergic interneurons may play a pivotal role in the long-lasting nature of behavioural sensitization upon cessation of treatment with morphine and possibly other drugs of abuse.

Keywords: Morphine; Dopamine release; Acetylcholine release; Striatum; Dopamine D_2 receptor

1. Introduction

Dopaminergic neurotransmission in the rat striatum and nucleus accumbens seems to play an important role in the acute and long-term behavioural effects of drugs of abuse. In this respect, repeated administration of drugs of abuse has been shown to lead to a persistent increase in their behavioural effects. This behavioural sensitization is associated with long-lasting changes in pre- and postsynaptic dopaminergic neurotransmission processes, possibly involved in the acquisition and maintenance of drug dependence (for reviews, see Wise and Bozarth, 1987; Kalivas and Stewart, 1991; Di Chiara and North, 1992; Robinson and Berridge, 1993; Stewart and Badiani, 1993). Considering the long-lasting nature of the central neuroadaptative effects of drugs of abuse, we recently showed that intermittent morphine treatment causes an enhanced release of [^{3}H]dopamine from slices of rat striatum, which slowly intensifies upon cessation of drug treatment (Tjon et al., 1994). Moreover, we showed that this enduring increase of dopamine release is associated with an enhanced excitability of cholinergic neurons within the striatum and nucleus accumbens (Tjon et al., 1994, 1995).

A possible explanation for an enhanced neurotransmitter release upon depolarization of dopaminergic nerve terminals and cholinergic interneurons long after repeated treatment with drugs of abuse might be the occurrence of desensitization of release-inhibitory dopamine D_2 receptors. Several studies investigated this possibility in rats repeatedly treated with psycho-

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stimulants. Unfortunately, a decrease (Yi and Johnson, 1990; Yamada et al., 1991), no change (Fitzgerald and Reid, 1991; Gifford and Johnson, 1992; King et al., 1994) and an increase (Dwoskin et al., 1988) in dopamine D_2 receptor sensitivity has been reported in rat striatum and nucleus accumbens following amphetamine or cocaine administration. The inconsistency of these findings may be due to, for instance, differences in drug administration regimens and length of drug withdrawal period. These discrepancies in the literature and the lack of data on the sensitivity of D_2 receptors mediating inhibition of neurotransmitter release following morphine treatment prompted us to carry out the present study. Here we report on the effects of intermittent morphine administration on the functional role of dopamine D_2 receptors mediating inhibition of [^{3}H]dopamine and [^{14}C]acetylcholine release in vitro, 3 weeks after cessation of in vivo drug treatment.

Both the behavioural and neuroadaptive effects of morphine and psychostimulants have been shown to depend on activation of NMDA receptors (Karler et al., 1990; Wolf and Jeziorski, 1993; Jeziorski et al., 1994; Liu et al., 1994; Ohno et al., 1994). Since these receptors primarily mediate the glutamatergic regulation of the activity of dopaminergic and cholinergic neurons within the striatum and nucleus accumbens (Gerfen, 1992; Krebs et al., 1991), NMDA was used as a stimulus to induce Ca^{2+}-dependent [^{3}H]dopamine and [^{14}C]acetylcholine release in vitro. For comparison, NMDA-stimulated [^{3}H]noradrenaline release from hippocampal slices was studied in parallel experiments.

2. Materials and methods

2.1. Drug treatment

Male Wistar rats (140–160 g body weight), purchased from Harlan (Zeist, The Netherlands), were housed in groups of four per cage in a temperature-controlled room with a 12 h light/dark cycle (lights on at 7:00 h) and were given food and water ad libitum. All animal use procedures were in strict accordance with the guidelines of the Law on the Use of Laboratory Animals in the Netherlands and were approved by the Animal Care Committee of the Free University, Amsterdam. 1 week after arrival, rats were randomly assigned to one of two groups and received one daily s.c. injection of either saline or 10 mg/kg morphine hydrochloride for 14 days at 13:00 h.

2.2. Determination of neurotransmitter release

Rats were decapitated 3 weeks after the last injection. Striatum, nucleus accumbens and hippocampus were rapidly dissected from the brain. Brain tissue of two rats was pooled and slices ($0.3 \times 0.3 \times 2$ mm) were prepared using a McIlwain tissue chopper and incubated and superfused essentially as described previously (Schoffelmeer et al., 1988). Slices were washed twice with Mg^{2+}-free Krebs-Ringer bicarbonate medium containing 121 mM NaCl, 1.87 mM KCl, 1.17 mM KH_2PO_4, 25 mM $NaHCO_3$, 1.22 mM $CaCl_2$ and 10 mM D-(+)-glucose, followed by preincubation for 15 min in this medium in a constant atmosphere of 95% O_2-5% CO_2 at 37°C. After preincubation, the slices were rapidly washed with the Mg^{2+}-free Krebs-Ringer and incubated for 15 min in 2.5 ml of this medium containing 5 μCi [^{3}H]dopamine and 2 μCi [^{14}C]choline in an atmosphere of 95% O_2-5% CO_2 at 37°C. Hippocampal slices were incubated with 5 μCi [^{3}H]noradrenaline. Since the nucleus accumbens, in contrast to the striatum, has a dense noradrenergic innervation, 3 μM desipramine was added to the medium during incubation and superfusion of the nucleus accumbens slices, to prevent [^{3}H]dopamine uptake in noradrenergic nerve terminals. After labelling, the slices were rapidly washed and transferred to each of 24 chambers of a superfusion apparatus (approximately 4 mg tissue in 0.2 ml volume) and superfused (0.20 ml/min) with medium gassed with 95% O_2-5% CO_2 at 37°C. In each experiment neurotransmitter release from brain slices from morphine- and saline-treated controls was studied simultaneously in 24 parallel superfusion chambers. The superfusate was collected as 10 min samples after 40 min of superfusion. Stimulation of neurotransmitter release was induced by superfusion of the slices with 10 μM NMDA for 10 min. Drugs were added to the medium 30 min prior to stimulation. The radioactivity remaining at the end of the experiment was extracted from the tissue with 0.1 M HCl. The radioactivity in superfusion fractions and tissue extracts was determined by liquid scintillation counting. Regarding the signal to noise ratio, spontaneous [^{3}H]dopamine, [^{14}C]acetylcholine and [^{3}H]noradrenaline release during the 10 min fraction preceding NMDA receptor activation amounted to about 4.1, 3.1 and 1.9% of total tissue radioactivity, respectively, whereas about 5.5, 4.8 and 6.0% of the radioactivity content was released during the 10 min of NMDA exposure and during the subsequent fraction.

The efflux of radioactivity during each collection period was expressed as a percentage of the amount of radioactivity in the slices at the beginning of the respective collection period. The NMDA-evoked release of neurotransmitter was calculated by subtracting the spontaneous efflux of radioactivity from the total overflow of radioactivity during stimulation and for the next 10 min. A linear decline from the 10 min interval before to that 20–30 min after the start of stimulation was assumed for calculation of the spontaneous efflux

of radioactivity. The release evoked was expressed as percentage of the content of radioactivity of the slices at the start of the stimulation period.

2.3. Radiochemicals and drugs

Morphine hydrochloride and cocaine hydrochloride were purchased from O.P.G. (Utrecht, The Netherlands). [^{3}H]Dopamine (specific activity 50 Ci/mmol), [^{14}C]choline (55 mCi/mmol) and [^{3}H]noradrenaline (41 Ci/mmol) were obtained from the Radiochemical Centre (Amersham, UK). NMDA, desipramine and (−)-sulpiride were obtained from Sigma (St. Louis, USA), LY171555 (quinpirole) from RBI (Natick, MA, USA) and phentolamine from Ciba-Geigy (Arnhem, Netherlands).

2.4. Statistics

One-way analysis of variance was conducted for a set of replicate experiments. If replicate experiments were not significantly different they were considered to represent one population and the observations were pooled for two-tailed Student's t-test analysis. A level of $P < 0.05$ was accepted as evidence of a statistically significant level.

3. Results

The effect of 2 weeks intermittent morphine administration on the 10 μM NMDA-evoked [^{3}H]dopamine and [^{14}C]acetylcholine release from superfused striatal slices was determined 21 days after morphine withdrawal. Preliminary experiments revealed that this concentration of NMDA did not induce neurotransmitter release in the absence of Ca^{2+} in the superfusion medium. Fig. 1 shows that both NMDA-evoked [^{3}H]dopamine and [^{14}C]acetylcholine release were increased by 14% in slices from morphine-treated rats. 10 μM (−)-sulpiride enhanced NMDA-evoked [^{3}H]dopamine and [^{14}C]acetylcholine release from striatal slices from saline-treated rats by 33% and 38%, respectively, whereas in slices from morphine-treated rats, the dopamine D_2 receptor antagonist did not affect the release of these neurotransmitters. The addition of (−)-sulpiride did not change spontaneous neurotransmitter release.

In a subsequent set of experiments, the effect of intermittent morphine administration on the 10 μM NMDA-evoked [^{3}H]dopamine and [^{14}C]acetylcholine release was determined in superfused slices of rat nucleus accumbens. These experiments revealed a similar enduring enhancement of NMDA-evoked neurotransmitter release from slices of this limbic rat brain region as observed in striatal slices (Fig. 2).

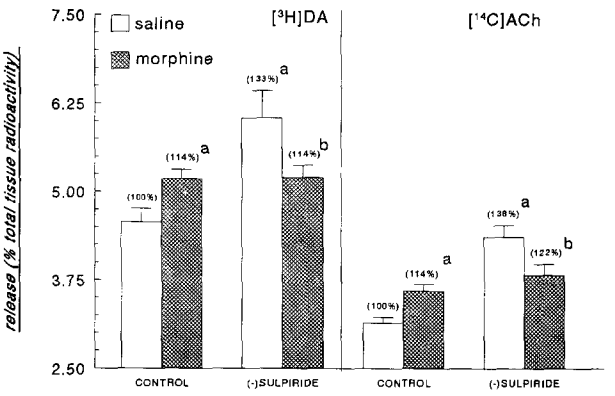

Fig. 1. Effect of intermittent morphine administration on NMDA-evoked [^{3}H]dopamine (left) and [^{14}C]acetylcholine (right) release from rat striatal slices and the effects of D_2 receptor blockade thereon. 3 weeks following cessation of morphine treatment, striatal slices were incubated with [^{3}H]dopamine and [^{14}C]choline and subsequently superfused with medium. 10 μM (−)-sulpiride was added to the medium 30 min prior to stimulation. Ca^{2+}-dependent neurotransmitter release was induced by adding 10 μM NMDA to the superfusion medium for 10 min. Neurotransmitter release is expressed both as a percentage of total tissue radioactivity at the start of the stimulation period and as a percentage of (control) release from slices from saline-pretreated rats in the absence of (−)-sulpiride. Values represent means ± S.E.M. of 9 observations. Triplicate observations were made in each experiment. [a] $P < 0.05$ vs. control release following saline pretreatment. [b] $P < 0.05$ vs. control release following saline pretreatment, but not significantly different from release following morphine pretreatment.

To exclude the involvement of a possible adaptive change in the functionality of the dopamine uptake carrier in the morphine-induced increase in neurotransmitter release, 10 μM cocaine was added to the

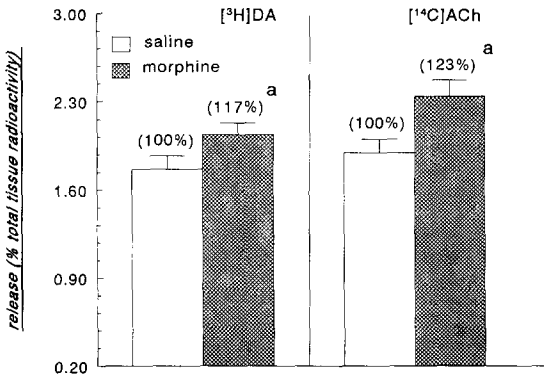

Fig. 2. Effect of intermittent morphine treatment on NMDA-evoked [^{3}H]dopamine (left) and [^{14}C]acetylcholine (right) release from slices of rat nucleus accumbens. The slices were incubated with [^{3}H]dopamine and [^{14}C]choline and subsequently superfused with medium. Neurotransmitter release was induced by adding 10 μM NMDA to the medium for 10 min. Results are expressed both as a percentage of the content of radioactivity of the slices at the start of the stimulation period and as a percentage of (control) release from slices from saline-pretreated rats. Values represent means ± S.E.M. from 16 observations obtained in 4 separate experiments. [a] $P < 0.05$ vs. control.

superfusion medium 30 min prior to stimulation. In these experiments, no significant differences in the effect of cocaine on NMDA-induced [^{3}H]dopamine release were found between saline- and morphine-treated rats. Cocaine increased NMDA-induced [^{3}H]dopamine release in slices from control animals by 28 ± 4.9% and in those from morphine-treated rats by 23 ± 3.9% (8 observations). Moreover, in slices from saline-treated rats ^{3}H and ^{14}C uptake at the start of superfusion amounted to 142006 ± 9791 and 25635 ± 1781 dpm (12 observations). In morphine-treated rats the uptake amounted to 143910 ± 5890 and 28114 ± 1057 dpm (12 observations) for ^{3}H and ^{14}C, respectively, which was not significantly different from that in the slices from the saline-treated animals.

In superfused striatal slices, the inhibitory effect of the dopamine D_2 receptor-selective agonist LY 171555 on the NMDA-evoked [^{3}H]dopamine and [^{14}C]acetylcholine release was subsequently determined. Fig. 3 shows that intermittent morphine administration caused an almost 10-fold shift to the right of the concentration-effect curves for inhibition by LY 171555.

Whereas dopaminergic and cholinergic nerve terminals in rat striatum and nucleus accumbens appeared to display a long-lasting enhanced sensitivity towards NMDA receptor activation, this did not appear to occur at the level of central noradrenergic nerve terminals. Thus, Table 1 shows that morphine pretreatment did not change [^{3}H]noradrenaline release from hippocampus slices induced by 10 μM NMDA in the absence or in the presence of 3 μM of the α_2-adrenoceptor antagonist phentolamine, which by itself increased release by about 30%.

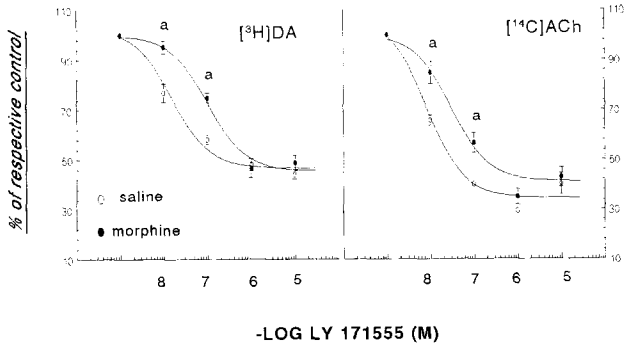

Fig. 3. Effect of LY 171555 on NMDA-evoked [^{3}H]dopamine and [^{14}C]acetylcholine release from rat striatal slices 3 weeks after intermittent morphine administration. Slices were incubated with [^{3}H]dopamine and [^{14}C]choline and subsequently superfused with medium. LY 171555 was added to the medium 30 min prior to stimulation. Neurotransmitter release was induced by superfusion with 10 μM NMDA for 10 min. Results are expressed as percentage of neurotransmitter release in the presence of (−)-sulpiride, i.e. in the absence of D_2 receptor activation. Values represent means ± S.E.M. from 9 observations. Triplicate observations were made in each experiment. Dose-response curves were generated using the ALLFIT program. [a] $P < 0.05$ vs. inhibition found in slices from saline-pretreated rats.

Table 1
Lack of effect of intermittent morphine administration on the NMDA-evoked [^{3}H]noradrenaline release from superfused rat hippocampal slices in the absence and presence of 3 μM phentolamine

Pretreatment	[^{3}H]Noradrenaline release (% total tissue tritium)	
	Control	3 μM phentolamine
Saline	6.35 ± 0.41	8.52 ± 0.63 [a]
Morphine	6.05 ± 0.27	9.10 ± 0.39 [a]

Slices were incubated with [^{3}H]noradrenaline and subsequently superfused with medium. Phentolamine was added to the medium 30 min prior to stimulation. Neurotransmitter release was induced by adding 10 μM NMDA to the medium during 10 min. Results are expressed as a percentage of total tissue tritium at the start of stimulation period. Values represent means ± S.E.M. from 12 observations obtained in 3 separate experiments. [a] $P < 0.01$ vs. control, but no significant differences between slices from saline- and morphine-treated rats.

4. Discussion

In the present study NMDA-evoked [^{3}H]dopamine and [^{14}C]acetylcholine release in slices of rat striatum and nucleus accumbens was investigated 3 weeks following 14 days of daily 10 mg/kg s.c. morphine administration. This dose regimen is well known to cause a profound locomotor sensitization towards the drug as is also observed with psychostimulants (Jeziorski et al., 1994; Robinson and Becker, 1986; Wise and Bozarth, 1987; Kalivas and Stewart, 1991; Kalivas and Duffy, 1993). Since behavioural sensitization represents a long-lasting phenomenon, and the underlying neuroadaptational changes between short- and long-term sensitization may differ (McDougall et al., 1994), we performed our studies long (3 weeks) after morphine exposure. The glutamatergic input from cortical regions to striatum (Gerfen, 1992; Krebs et al., 1991) and nucleus accumbens (Fuller et al., 1987; Jones et al., 1987; Youngren et al., 1993) plays an important role in the regulation of the activity of dopamine and acetylcholine neurons. Therefore NMDA was used as a quasi-physiological stimulus to induce [^{3}H]dopamine and [^{14}C]acetylcholine release in vitro.

In morphine-treated rats NMDA-evoked [^{3}H]-dopamine and [^{14}C]acetylcholine release were both increased in slices of striatum and nucleus accumbens. These results are fully comparable to data from previous studies, in which neurotransmitter release was evoked electrically (Tjon et al., 1994, 1995). The enhanced sensitivity of dopaminergic nerve terminals and cholinergic interneurons for NMDA receptor stimula-

tion, which was found in rat striatum and nucleus accumbens, does not seem to be a general effect at NMDA-sensitive central nerve terminals, since we were not able to detect significant changes in NMDA-evoked [^{3}H]noradrenaline release in hippocampal slices 3 weeks following morphine administration.

A possible mechanism for the enduring increase in [^{3}H]dopamine and [^{14}C]acetylcholine release might be that intermittent morphine treatment causes a long-lasting desensitization of neurotransmitter release-inhibitory D_2 receptors on dopaminergic nerve terminals and cholinergic interneurons in the rat striatum and nucleus accumbens. Therefore, we examined the sensitivity of these receptors by studying the effects of the dopamine D_2 antagonist (−)-sulpiride and the dopamine D_2 agonist LY171555 in superfused striatal slices. Although these ligands do not discriminate between D_2, D_3, and D_4 receptors, we prefer to denote the release-inhibitory DA receptors as D_2 receptors, until convincing evidence has been presented for their possible D_3/D_4-like character. As expected, 10 μM (−)-sulpiride increased striatal NMDA-stimulated [^{3}H]dopamine and [^{14}C]acetylcholine release. Interestingly, however, (−)-sulpiride had no effect on the release of these neurotransmitters in striatal slices from rats treated with morphine, suggesting a lack of D_2 receptor-mediated inhibition by released endogenous dopamine. Such a decrease of endogenous inhibition could be due either to D_2 receptor desensitization or to an enhancement of dopamine inactivation. The latter possibility, however, seems unlikely in view of the fact that the enhancing effect of cocaine on dopamine release (caused by blocking the reuptake of released dopamine via the dopamine uptake carrier) was unaltered following morphine administration. In order to further investigate the functionality of dopamine D_2 receptors in striatal slices, the effects of the selective D_2 agonist LY171555 were studied. In view of the release-facilitatory effect of the D_2 receptor antagonist (−)-sulpiride, NMDA-stimulated [^{3}H]dopamine and [^{14}C]acetylcholine release appeared to be inhibited by endogenously released dopamine, acting at D_2 receptors. Consequently, the apparent affinity of agonists for D_2 receptors is underestimated when their inhibitory effect is simply expressed as a percentage of release in the absence of drugs. Thus, changes in receptor sensitivity associated with changes in release can only be correctly derived from data expressing the inhibitory effect of an exogenous agonist as a percentage of the release observed in the presence of a drug that blocks presynaptic receptors (for a detailed discussion on this important issue see Wemer et al., 1979; Starke et al., 1989). Therefore, release found in the presence of (−)-sulpiride served as disinhibited control of neurotransmitter release in the present experiments. Taking into account this activation of D_2 receptors by released endogenous dopamine in striatal slices, these experiments showed an approximately 10-fold shift to the right of the concentration-effect curve of LY171555 for its inhibitory effect on neurotransmitter release from rat striatal slices.

Taken together, our data strongly suggest the occurrence of desensitization of the dopamine D_2 receptors mediating inhibition of NMDA-stimulated dopamine and acetylcholine release in rat striatum long after cessation of intermittent morphine treatment. Whether the observed reduction of the apparent affinity of dopamine D_2 receptors is due to a conformational change of D_2 receptors, functional uncoupling from G-proteins or a reduction in receptor expression and number, remains to be examined. In this respect, it should also be noted that Drukarch et al. (1991) suggested that presynaptic dopamine D_2 receptors do not desensitize after sustained in vitro activation with dopamine or the selective D_2 agonist LY 171555. Therefore, the desensitization found in the present study may not be caused by increased activation of D_2 receptors by enhanced levels of dopamine in the striatum in vivo, but rather by a μ-opioid receptor-mediated effect of morphine on e.g. gene expression of D_2 receptor and/or effector proteins in dopaminergic and cholinergic neurons (Liu et al., 1994; Konradi et al., 1994).

Several studies have described changes in the number of dopamine D_2 receptors in striatum and nucleus accumbens after administration of psychostimulants, by means of receptor autoradiographic or binding assays, demonstrating changes in the total D_2 receptor population (see e.g. Unterwald et al., 1994; Kleven et al., 1990). However, the varying results of such studies should not be compared to those of the present study, since the properties of release-inhibitory dopamine D_2 receptors, which represent only a minor proportion of the total number of dopamine D_2 receptors in rat striatum, can only be studied adequately in functional assays. Interestingly, in agreement with the present functional study, Yi and Johnson (1990) and Yamada et al. (1991) found a subsensitivity of dopamine release-inhibitory D_2 receptors 1 week after repeated cocaine and amphetamine administration, respectively, indicating that in this respect psychostimulant treatment has a similar long-lasting effect as morphine administration. As indicated by Gifford and Johnson (1992), the occurrence and extent of D_2 receptor desensitization may be dependent on the in vitro stimulus used to evoke neurotransmitter release, which could explain the negative findings published by others (Dwoskin et al., 1988; King et al., 1994; Fitzgerald and Reid, 1991). Thus, desensitization of D_2 receptors may well be limited to those receptors that mediate inhibition of the excitatory effect of glutamate at NMDA receptors on nerve terminals and cholinergic neurons

in the striatum. Moreover, the phenomenon of D_2 receptor desensitization may become prominent only after relatively long periods of drug withdrawal. In this respect, we recently showed that, in striatal slices from rats withdrawn from intermittent morphine treatment, [^{3}H]dopamine release and dopamine D_1 receptor-stimulated adenylyl cyclase activity is enhanced only after long periods (weeks) of drug withdrawal (Tjon et al., 1994). Thus, desensitization of presynaptic D_2 receptors may represent a drug withdrawal phenomenon that slowly builds up, the time course of which may depend on the experimental protocol of drug treatment.

Regarding the physiological relevance of our present in vitro data, desensitization of D_2 autoreceptors would imply that dopaminergic neurons arising from the substantia nigra and ventral tegmental area release more dopamine upon exposure to various stimuli such as drugs of abuse (Di Chiara and North, 1992) and e.g. stress (Roth et al., 1988; Robinson and Berridge, 1993). Moreover, recent microdialysis studies suggest that in vivo dopamine D_1 receptors (indirectly) mediate an increase in the activity of cholinergic neurons in rat striatum and nucleus accumbens (Di Chiara et al., 1994). Therefore, upon long-term dopamine D_2 receptor desensitization cholinergic neurons would be expected to release more acetylcholine not only upon the release of glutamate (acting primarily on NMDA receptors), but also upon the release of dopamine (acting on D_1 and D_2 receptors) in vivo. Through the activation of primarily muscarinic receptors, cholinergic interneurons are generally thought to play a modulatory role in the regulation of the activity of efferent GABA-ergic neurons of the striatum and nucleus accumbens projecting to the substantia nigra and ventral pallidum (Di Chiara et al., 1994). Therefore, we suggest that desensitization of dopamine D_2 receptors on these cholinergic neurons, just like that of dopamine D_2 autoreceptors, may play an important role in the enduring character of the behavioural (cross)sensitization observed following intermittent exposure to drugs of abuse.

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