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Behavioural and Neurochemical Sensitization of Morphine-Withdrawn Rats to Quinpirole

T. PETTERI PIEPPONEN,* JAANA KATAJAMÄKI,* TOOMAS KIVASTIK,† ALEXANDER ZHARKOVSKY*† AND LIISA AHTEE*[1]

Division of Pharmacology and Toxicology, Department of Pharmacy, P.O. Box 56 (Viikinkaari 5), FIN-00014 University of Helsinki, Finland
†*Department of Pharmacology, Tartu University, EE2400 Tartu, Estonia*

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PIEPPONEN, T. P., J. KATAJAMÄKI, T. KIVASTIK, A. ZHARKOVSKY AND L. AHTEE. *Behavioural and neurochemical sensitization of morphine-withdrawn rats to quinpirole.* PHARMACOL BIOCHEM BEHAV **54**(4) 787–792, 1996.—The sensitivity of dopamine D_2-like receptors in morphine-withdrawn rats was studied using the selective agonist quinpirole. Morphine was administered twice daily increasing the daily dose from 20 to 50 mg/kg during 7 days. Twenty-four hours after the last morphine administration the rats were given quinpirole (0.01–1 mg/kg), and their behaviour was assessed. Withdrawal from repeated morphine treatment enhanced yawning behaviour and penile erections induced by small doses (0.01–0.1 mg/kg) as well as the intensity of stereotypy induced by a large dose (1.0 mg/kg) of quinpirole. In the morphine-withdrawn rats the dose of 1 mg/kg of quinpirole caused less yawning than in the control rats, whereas the number of erections induced by this dose was enhanced as compared with the control animals. In the control rats the striatal and limbic concentrations of dopamine metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA), were not clearly affected by the smallest dose of quinpirole. However, the small dose of quinpirole (0.01 mg/kg) significantly reduced the levels of DOPAC and HVA in the striatum and limbic forebrain of the rats withdrawn from morphine either for 24 or 48 h. These findings indicate that withdrawal from repeated morphine treatment enhances the sensitivity of dopamine D_2-like receptors.

Quinpirole Morphine withdrawal Yawning Penile erections Stereotypy Locomotor activity Cerebral dopamine metabolism

BRAIN dopaminergic systems have been widely implicated in the behavioural effects of opioids (4,14,25). Morphine withdrawal results in a reduction of dopamine (DA) metabolism and release (1,3–5,7), which one would expect to lead to supersensitive dopamine receptors. The sensitization of DA receptors might be reflected by an enhancement of the behavioural effects of DA receptor agonists. However, behavioural studies in morphine-withdrawn animals, where DA receptor agonist apomorphine was used, provided controversial results. While most authors (8,9,13,27,35) found an enhancement of apomorphine-induced stereotypy, climbing, and locomotor activity during morphine withdrawal, some studies (21) failed to detect any changes in apomorphine-induced stereotypy.

The studies of the behavioural supersensitivity to DA receptor agonists in morphine-withdrawn animals are complicated by the existence of the multiple DA receptors within the central nervous system. DA receptors have been classified into two major classes, D_1-like (D_1, D_5) and D_2-like (D_{2A}, D_{2B}, D_3, D_4) receptors (28,30,33,34,36). Postsynaptic DA receptors are represented by D_1- and D_2-like receptors and they are involved in the mediation of behavioural effects of high doses of apomorphine (12,23,26,37). Presynaptic receptors (autoreceptors) are presumably D_2-like and their activation seems to result in the inhibition of DA release and metabolism (2,6,10, 26). There is some evidence suggesting that inhibition of locomotor activity and induction of yawning are also mediated via presynaptic D_2-like receptors (15,16,31,32,39). According to other authors (24,29), yawning behaviour is related to the activation of a distinct subtype of D_2-like receptors located postsynaptically. Functionally, post- and presynaptic DA receptors play an opposite role in the regulation of dopaminergic neurotransmission. Activation of postsynaptic receptors enhances, whereas activation of presynaptic receptors inhibits the activity of the dopaminergic system. Classical DA receptor agonist

[1]To whom requests for reprints should be addressed.

apomorphine is regarded as a nonselective DA receptor agonist, because in high doses it acts at both D_1 and D_2 receptors, and simultaneous activation of both D_1 and D_2 receptors, located postsynaptically, is required for induction of high grade stereotypy (12,37). In contrast, another DA receptor agonist, quinpirole, possesses rather selective action at D_2-like receptors (28,34). Similarly to small doses of apomorphine, quinpirole inhibits locomotor activity, induces yawning behaviour, and inhibits release and metabolism of DA, but in contrast to apomorphine, it does not induce high grade stereotypy even in high doses (30,34). Therefore, we used quinpirole to study whether the behavioural supersensitivity in morphine-withdrawn rats is associated with supersensitivity of DA D_2-like receptors, and investigated the behavioural and neurochemical effects of quinpirole in rats withdrawn from repeated morphine administration.

METHOD

Male Wistar rats, weighing 200–300 g at the start of the experiments, were housed in groups of four to six, with free access to standard rat diet and tap water, in a room with 12 L:12 D cycle (lights on at 0600 h). Five separate experiments were performed with different groups of animals. In each experiment, animals were randomly assigned to two treatment groups, saline (control) and morphine. Morphine hydrochloride (Ph. Eur. 2nd ed.) was dissolved in 0.9% NaCl solution (saline) so that the salinity of the solution was isotonic with physiological saline. Saline and morphine were given subcutaneously in the back of the neck in the volume of 2 ml/kg body weight. The daily dose of morphine was divided in two parts and administered at 0800 and 1800 h according to the following schedule: day 1: 10 and 10 mg/kg; day 2: 15 and 10 mg/kg; day 3: 15 and 15 mg/kg; day 4: 20 and 15 mg/kg; day 5: 20 and 20 mg/kg; day 6: 25 and 20 mg/kg and day 7: 25 and 25 mg/kg. On day 8, the animals were given only the morning dose (30 mg/kg) of morphine and placed back into their home cages for 24 or 48 h, and were referred to as morphine-withdrawn animals. The doses of morphine refer to the base. Control animals were given repeatedly saline.

Experiment 1

Twenty-four hours after the last saline or morphine administration control (n = 22) and morphine-withdrawn (n = 24) rats were randomly assigned to three groups each, and received quinpirole (quinpirole-HCl, gift of Eli Lilly & Co, Indianapolis, IN) either 0.01, 0.1, or 1.0 mg/kg. Immediately after that animals were placed into Plexiglas observation boxes of 31 × 21 × 20 cm (one rat per box). The number of yawning episodes and number of erections were counted during 30 min. Quinpirole was dissolved in saline and administered subcutaneously in the volume of 1 ml/kg body weight. Quinpirole doses refer to the salt. The rats had no previous experience with the box.

Experiment 2

Twenty-four hours after the last saline or morphine administration control (n = 10) and morphine-withdrawn (n = 12) rats were assigned to two groups each and were given either saline or 0.025 mg/kg quinpirole. Immediately after saline or quinpirole administrations the locomotor activity of the animals was measured by a microcomputer controlled photocell activity monitor containing five activity boxes of 31 × 21 × 20 cm (one rat per box). Locomotor activity was monitored every 5 min over a 20-min period after quinpirole administration. The rats had no previous experience with the box.

Experiment 3

Twenty-four hours after the last saline or morphine administration control (n = 8) and morphine-withdrawn (n = 8) rats were administered quinpirole (1 mg/kg). Immediately after that animals were placed into observation boxes for the assessment of stereotypy. The intensity of stereotypy was rated on a four-point severity scale over a 60-min period after quinpirole administration by two independent observers. The following scoring system was adopted: 0 = no stereotypy; 1 = periodic sniffing with some locomotion; 2 = continuous sniffing; 3 = periodic biting, gnawing or licking; 4 = continuous (1 min) biting, gnawing or licking, no locomotion (11). According to this scoring system scores 1–2 reflect low degree stereotypy and scores 3–4 reflect high degree stereotypy. The rats had no previous experience with the box.

Experiment 4

Twenty-four hours after the last saline or morphine administration control (n = 22) and morphine-withdrawn rats (n = 26) were assigned to three groups of 5–11 animals each and were administered either saline or 0.01 or 0.1 mg/kg of quinpirole. Animals were decapitated 30 min after quinpirole. The striatum and the limbic forebrain were dissected as described in detail previously (5). Shortly, beginning at the dorsal surface of the rat brain a transverse vertical cut was made 2 mm from the pole, just exposing the rostral ends of caudate nuclei. From the resulting small piece the area ventral to the rhinal fissure was removed and saved as a part of the limbic forebrain. On the ventral side of the brain the borders of the olfactory tubercle were cut to a depth of 2 mm, and the brain was turned to expose the dorsal surface. Cortical hemispheres were spread apart and separated by cutting the corpus callosum, and the hippocampi were peeled away from adjacent cortical tissue and discarded. The area bordered by the anterior commissure and stria terminalis was cut; these cuts continued those made earlier around the olfactory tubercle, and the resulting block of tissue was removed as the main part of the limbic forebrain. The medial borders of the striata were cut free, and the striata removed without the underlying cortex. The brain was then turned to expose the ventral surface and the amygdalae, situated on either side of the diencephalon, were pinched off and added to the limbic forebrain sample. The weights of striata and limbic forebrains were 71.2 ± 8.6 and 172.0 ± 20.9 mg, respectively (n = 48, mean ± SD). Each sample was frozen immediately on dry ice and stored at −80°C. The concentrations of DA and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were estimated by HPLC with electrochemical detection as described by Haikala (18).

Experiment 5

Forty-eight hours after the last saline or morphine administration control (n = 15) and morphine-withdrawn rats (n = 15) were assigned to two groups of seven to eight animals each and were administered either saline or 0.01 mg/kg of quinpirole. Animals were decapitated 30 min after quinpirole. The striatum and limbic forebrain were dissected as described previously (19) with the difference that amygdaloid nuclei from the third rostral slice were discarded. Shortly described, the brain was placed on brain mold (RBM-4000C, ASI Instru-

ments, USA) and sectioned coronally at 2.7, −0.3 and −4.6 mm from bregma (22). The striata were punched from the second rostral slice (2.7 to −0.3) with needle (inner diameter 3 mm), and the limbic forebrain (containing the nucleus accumbens and the olfactory tubercle) was dissected from the tissue ventral to the striata. The weights of striata and limbic forebrains were 23.2 ± 2.2 and 53.6 ± 7.3 mg, respectively (n = 30, mean ± SD). The smaller tissue weights in Experiment 5 than in Experiment 4 are due to the fact that only 3 mm-thick section of the striata was dissected out in Experiment 5 as compared to the whole striata in Experiment 4, and the amygdaloid nuclei were discarded from the limbic forebrain sample. Further, the samples in Experiment 5 obviously contain less surrounding cortical tissues. The concentrations of DA and its metabolites were estimated as described above. In spite of the different weights of the limbic areas in the two experiments, the amounts of limbic DOPAC and HVA per sample were similar in both experiments.

Statistics

The yawning and penile erections data were analyzed by the Kruskall–Wallis analysis of variance. If it was significant, individual group comparisons were made using Mann–Whitney U-test at each dose used. The stereotypy data were analyzed by the Mann–Whitney U-test at each time point. Locomotor activity data were analyzed by multifactor repeated-measures ANOVA [morphine, quinpirole, and time (repeated factor) as independent variables]. Concentrations of DA metabolites were analyzed by the two-way ANOVA followed by the Newman–Keuls test. As the test for interaction in the two-way ANOVA at the ordinary significance levels is known to be of weak power (17), the significance level of 0.15 was considered to be appropriate to indicate morphine withdrawal × quinpirole interaction (38).

RESULTS

Experiment 1. Yawning and Penile Erections

The spontaneous occurrence of yawnings and penile erections in the morphine-withdrawn rats did not significantly differ from that in the control rats. The number of yawns in the control rats was 1.6 ± 0.7 and in the morphine-withdrawn rats 0.9 ± 0.3 (Fig. 1). The number of spontaneous penile erections was 0.3 ± 0.2 in the control, and 0.4 ± 0.2 in the morphine-withdrawn rats (Fig. 2). Quinpirole induced a behavioural syndrome, which consisted of recurrent yawning and intermittent penile erections accompanied by episodes of grooming. The occurrence of yawning episodes and penile erections followed inverted U-shaped curve with the maximum effect at 0.01–0.1 mg/kg of quinpirole, and with a smaller effect at the dose 1.0 mg/kg. Morphine-withdrawal enhanced significantly the yawning induced by 0.01 and 0.1 mg/kg of quinpirole (Fig. 1). Higher dose (1 mg/kg) of quinpirole caused significantly ($p < 0.05$) less yawning in the morphine-withdrawn rats than in the controls (Fig. 1). In contrast, in the morphine-withdrawn animals the number of erections was enhanced after all doses (0.01, 0.1, and 1 mg/kg) of quinpirole (Fig. 2).

Experiment 2. Inhibition of Locomotor Activity

The locomotor responses to quinpirole in the control and in the morphine-withdrawn animals are shown in Fig. 3. Multifactor ANOVA with repeated measures revealed an overall significant inhibitory effect of both quinpirole, $F(1, 28)$ = 10.5, $p < 0.01$, and morphine withdrawal, $F(1, 28) = 10.0$, $p < 0.01$, as well as a significant interaction, $F(1, 28) = 6.8$, $p < 0.05$. Within group analysis showed that only the effect of quinpirole was significantly dependent on time, $F(3, 84) = 7.5$, $p < 0.05$.

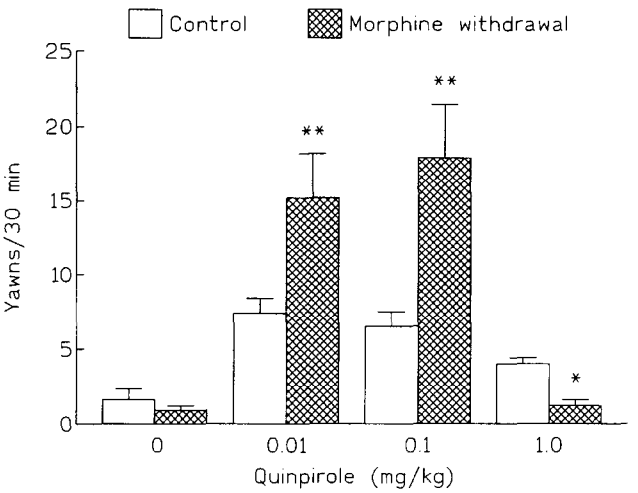

FIG. 1. Quinpirole-induced yawning behaviour in morphine-withdrawn rats. Values are means ± SE, n = 8–10 animals. *$p < 0.05$; **$p < 0.01$ as compared to corresponding control (Mann–Whitney U-test).

Experiment 3. Stereotypy

In the control rats the high dose of quinpirole (1 mg/kg) induced only low intensity stereotypy as indicated by the sniffing episodes. No licking or gnawing could be observed after administration of quinpirole alone. Withdrawal from repeated morphine treatment resulted in an enhancement of the quinpirole-induced stereotypy. In the morphine-with-

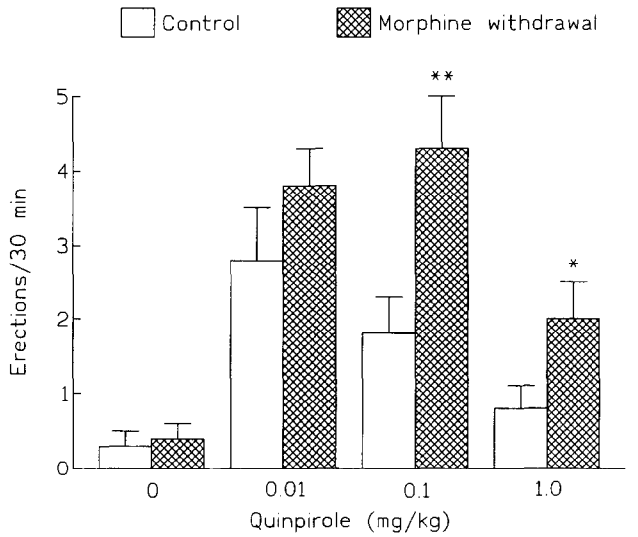

FIG. 2. Quinpirole-induced penile erections in morphine-withdrawn rats. Values are means ± SE, n = 8–10 animals. *$p < 0.05$; **$p < 0.01$ as compared to corresponding control (Mann–Whitney U-test).

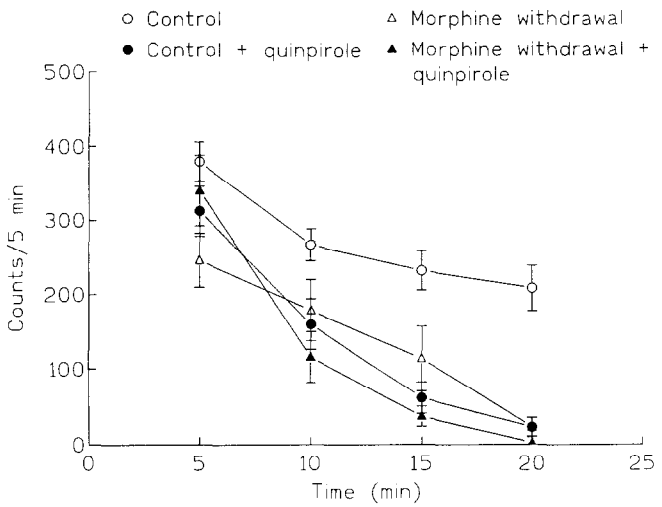

FIG. 3. Effect of quinpirole (0.025 mg/kg SC) on the locomotor activity in morphine-withdrawn rats. Values are means ± SE, $n = 8$ animals.

drawn rats, the stereotyped response was expressed not only by the intense sniffing but also by the appearance of licking and occasional gnawing, which contributed to the stereotypy score (Fig. 4).

Experiments 4 and 5. Dopamine Metabolism

Striatal and limbic DA metabolism was studied in rats withdrawn either for 24 or 48 h from repeated morphine treatment. None of the treatments altered the DA concentrations. The larger concentrations of the limbic DOPAC and HVA in the Experiment 5 than in the Experiment 4 (Table 1) are due to the different dissections of the brains in the two experiments (see the Method section).

Withdrawal from repeated morphine tended to decrease the concentrations of DA metabolites (DOPAC: 1–8%; HVA: 10–17%), but only limbic HVA in Experiment 5 was significantly decreased. In the control animals quinpirole, at the dose of 0.01 mg/kg, did not significantly reduce the levels

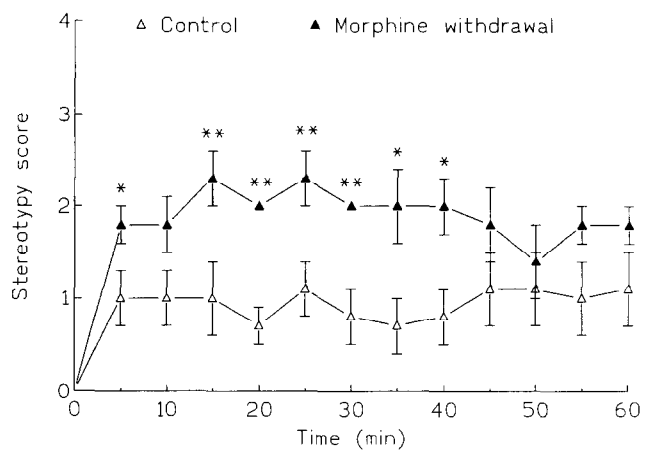

FIG. 4. Quinpirole (1.0 mg/kg SC)-induced stereotypy in morphine-withdrawn rats. Values are means ± SE, $n = 8$ animals. $^{*}p < 0.05$; $^{**}p < 0.01$ (Mann–Whitney U-test).

DOPAC (5–11%) and HVA (3–6%) except striatal DOPAC in Experiment 4 (by 27%; Table 1). The larger dose of quinpirole (0.1 mg/kg) significantly reduced DOPAC (26–32%) and HVA (33–35%) in the control animals. The larger dose of quinpirole reduced the DA metabolites in the morphine-withdrawn rats to about same degree as in the control rats (DOPAC: 32–46%; HVA 38–40%). When the smaller dose of quinpirole (0.01 mg/kg) was given to rats withdrawn from morphine for 24 or 48 h the concentrations of striatal (DOPAC: 20–29%; HVA: 18–23%) and limbic (DOPAC: 15–26%; HVA: 16–26%) DA metabolites were reduced significantly as compared with those of morphine-withdrawn rats not given quinpirole (Table 1). Furthermore, in the rats withdrawn from morphine for 48 h and given quinpirole (0.01 mg/kg) the concentrations of limbic and striatal DOPAC and HVA were significantly smaller than in the control rats given the same dose of quinpirole. However, two-way ANOVA did not reveal significant morphine withdrawal × quinpirole interactions using the ordinary significance level of 0.05. Because both the morphine-withdrawal and quinpirole affected DA metabolism in the same direction, the test for interaction in the two-way ANOVA at the ordinary significance levels is known to be of weak power (17). Still, there was a strong tendency of interaction in the levels of limbic HVA at 24 h withdrawal [0.01 mg/kg quinpirole; $F(1, 32) = 2.3$, $p = 0.14$] and of striatal and limbic DOPAC at 48 h withdrawal, $F(1, 26) = 3.1$, $p = 0.09$; $F(1, 26) = 2.4$, $p = 0.14$, respectively], indicating that quinpirole's effect was enhanced by withdrawal from morphine.

DISCUSSION

The present study shows that withdrawal from repeated morphine treatment enhances yawning behaviour and penile erections induced by small doses of quinpirole in rats. Thus, withdrawal from repeated morphine administration apparently results in hypersensitivity of DA D_2-like receptors involved in the mediation of yawning and penile erections. There is some controversy concerning the precise location of DA receptors mediating yawning response. While some authors (16,23,39) think that yawning is mediated via presynaptic receptors (autoreceptors), others suggest a postsynaptic location for the receptors mediating yawning (24,29).

An enhancement of yawning in the morphine-withdrawn rats could be observed only after small doses of quinpirole. A large dose (1.0 mg/kg) of quinpirole reduced the yawning response in the morphine-withdrawn animals as compared with the controls. This observation might be explained by the finding of Protais et al. (23), who demonstrated that the appearance of stereotypy results in the reduction of yawning because these two behaviours are mutually exclusive in rats. Thus, the enhancement of stereotyped response observed in the morphine-withdrawn rats after a large dose of quinpirole might result in the reduction of yawning. In contrast, penile erections do not seem to be dependent on the intensity of stereotypy because even 1 mg/kg of quinpirole induced more penile erections in the morphine-withdrawn animals than in the controls.

The increased score of the stereotyped responses in the morphine-withdrawn rats was due to the appearance of the elements of high degree stereotypy, licking and gnawing, which were not seen in the control rats. Previous studies have demonstrated that high degree stereotypy (e.g., continuous licking, biting, and gnawing) is induced by coadministration of D_1 receptor agonist SKF 38393 with quinpirole (12,37). This suggests that activation of D_1 receptor plays a permissive role

TABLE 1

EFFECT OF QUINPIROLE ON THE STRIATAL AND LIMBIC CONCENTRATIONS OF DOPAC AND HVA OF RATS WITHDRAWN FROM REPEATED SALINE OR MORPHINE TREATMENT

	DOPAC (ng/g)		HVA (ng/g)	
Quinpirole mg/kg	Control	Morphine Withdrawal	Control	Morphine Withdrawal
Experiment 4 (24 h)				
Striatum				
0	1015 ± 50	944 ± 39	808 ± 62	696 ± 48
0.01	744 ± 53*	672 ± 36*	784 ± 51	570 ± 29*
0.1	796 ± 49*	642 ± 54*	523 ± 90*	433 ± 37*
Limbic forebrain				
0	268 ± 12	247 ± 7	233 ± 15	195 ± 13
0.01	254 ± 7	210 ± 11*	226 ± 11	143 ± 7*‡
0.1	183 ± 21†	133 ± 11†§	156 ± 45*	117 ± 15*
Experiment 5 (48 h)				
Striatum				
0	1269 ± 69	1253 ± 60	849 ± 50	768 ± 70
0.01	1211 ± 56	1003 ± 31†‡	800 ± 50	592 ± 32*‡
Limbic forebrain				
0	949 ± 35	877 ± 39	530 ± 31	438 ± 31‡
0.01	841 ± 43	651 ± 35†§	497 ± 26	369 ± 17§

Quinpirole (0.01 or 0.1 mg/kg SC) was administered at 24 h (Experiment 4) or 48 h (Experiment 5) after the last saline or morphine administration, and the rats were decapitated 30 min later. Given are means ± SE, n = 5–13.

*$p < 0.05$, †$p < 0.01$ as compared with corresponding nonquinpirole group (repeated saline or repeated morphine).

‡$p < 0.05$, §$p < 0.01$ as compared with corresponding control (repeated saline + acute saline or quinpirole) group (Newman-Keuls test).

in the expression of the intense stereotypy induced by D_2 receptor agonists. The appearance of high degree stereotypy in the morphine-withdrawn rats was rather unexpected and suggested an additional activation of D_1 receptor.

The withdrawal from repeated morphine clearly reduced the locomotor activity. Although quinpirole significantly inhibited locomotor activity in the control rats, it failed to further reduce the locomotor activity in the morphine-withdrawn rats. This, however, might be explained by the fact that the locomotor activity in these rats was nearly maximally reduced due to the morphine withdrawal. Thus, the locomotor activity cannot be considered as a good indicator of the changes in DA receptor sensitivity under our experimental conditions.

Further, our results suggest that there is an enhancement of the effect of quinpirole on the cerebral DA metabolism in the morphine withdrawn rats. This enhancement was most clearly seen in the rats withdrawn from morphine for 48 h. Thus, these findings show that sufficiently long withdrawal from morphine augments the effects of quinpirole, and suggest that the sensitivity of DA receptors involved in the inhibitory action of quinpirole on the DA release and metabolism increases during morphine withdrawal. The findings that the D_2-like receptors involved in the regulation of DA metabolism seem to be sensitized later after morphine withdrawal than the receptors involved in the behavioural actions, agree with the time courses of behavioural and neurochemical sensitization after withdrawal from psychostimulants (20).

In conclusion, our data demonstrate that withdrawal from repeated morphine treatment induces behavioural supersensitivity to the D_2-like agonist quinpirole as reflected by an increase in the number of yawnings and penile erections. Further, our data suggest that the DA receptors controlling the release and metabolism of the striatal and limbic DA are sensitized as well in the morphine-withdrawn rats.

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