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Influence of social isolation and 6-OHDA lesion on the effects of quinelorane

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Abstract

The sensitivity of the response to the preferential dopaminergic D3 (DAD3) receptor agonist, quinelorane, was compared in mice housed socially and in mice isolated for 4 weeks. Quinelorane (1, 5, 10, 50 and 100 μg/kg) was administered intraperitoneally. Motor activity was measured for 60 min posttreatment. Rectal temperature was measured prior to and 1 h following the administration of quinelorane (10, 50 and 100 μg/kg ip). Quinelorane significantly and dose-dependently decreased locomotor activity in social and in isolated mice. The locomotor activity of isolated mice was significantly lower than that of social mice, but isolation had no effect on quinelorane-induced hypomotility. Quinelorane decreased dose-dependently rectal temperature in isolated and social mice, but isolation had no effect on quinelorane-induced decrease in rectal temperature. The lesions of dopaminergic terminals with intracerebroventricular administration of 6-OHDA decreased the dopamine (DA) level by 93% in the nucleus accumbens and by 91% in the corpus striatum; these lesions impaired neither the hypolocomotion nor the hypothermia induced by quinelorane. Thus, it may be concluded that social isolation has no influence on the quinelorane-induced decreases in rectal temperature and in locomotor activity and that the DA receptors involved in these effects of quinelorane are located postsynaptically.

Keywords: Social isolation; Quinelorane; Rectal temperature; Locomotor activity; 6-OHDA lesions; Brain dopamine concentration

1. Introduction

In a previous work (Coudereau et al., 1997), we found that isolation of mice for 30 days profoundly blocked the conditioning of a place preference to morphine. A dose of 100 mg/kg failed to induce conditioning in isolated animals, whereas 8 mg/kg induced the conditioning of a place preference in social mice. To explain this difference, several hypotheses were formulated, one of them being a dopaminergic hypothesis, which links the rewarding effects of morphine to central dopamine (DA) (Fibiger, 1978; Wise, 1982). It has, indeed, been shown that isolation reduces the utilisation of DA in the rat brain (Blanc et al., 1980; Jones et al., 1992). Thus, social isolation could have altered the rewarding properties of morphine through an action on the dopaminergic system.

The dopaminergic D3 (DAD3) receptors have been recently described as playing a role in reward. Mallet and Beninger (1994) observed that 7-OH-DPAT, an agonist at DA D3 receptors, produced a place preference, and Caine and Koob (1995) suggested that pretreatment with 7-OH-DPAT enhances the reinforcing properties of cocaine. In addition, the dopaminergic receptor agonist, 7-OH-DPAT, modulates the acquisition and expression of morphine-induced place preference in rats (De Fonseca et al., 1995) and BP 897, which is a partial D3 receptor agonist in vitro and acts, in vivo, as either an agonist or an antagonist, increases the acquisition of morphine-induced place preference in mice (Frances et al., 1999) but inhibits the cocaine-seeking behaviour that depends upon the presentation of drug-associated cues in rats (Pilla et al., 1999).

The aim of the present study was to measure the responsiveness of social and isolated mice to the stimulation of DA D3 receptors. Quinelorane (LY 163502) was chosen

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because it binds preferentially to the DA D3 receptor (Sautel et al., 1995a). The behavioural effect measured was the decrease in locomotor activity and the physiological effect, the decrease in rectal temperature produced by low doses of such drugs. In addition, lesions of dopaminergic terminals were performed using 6-OHDA to assess the pre- or post-synaptic location of the DA receptors involved in quinelorane-induced hypolocomotion and hypothermia.

2. Material and methods

2.1. Animals

Male NMRI mice originating from CERJ, Genest St. Isle 53940 (France) were used. The animals were either housed in groups of six in home cages of $30 \times 20 \times 8$ cm or isolated for 4 weeks in home cages of $24 \times 10 \times 8$ cm. Mice were 4–5 weeks old at the beginning of the isolation period. At the time of experiments, mice, either isolated or not, were 8–9 weeks old. The room was thermostatically maintained at $21 \pm 1°C$ with a 12L/12D schedule (lights on from 08:00 to 20:00 hours). Food and water were freely available. Mice were killed using CO_2 in a special container. The number of animals per cage was in conformity with regulations (Olfert, 1993). The experimental protocols were in compliance with the French regulation extracted from the European communities council directive of 24 November 1986. The authorisation for animal experimentation of the first author has the number 594 (5/04/1989).

2.2. Experimental procedure for measures of rectal temperature and locomotor activity

Mice were brought to the experimental room and the test begun only 1 h later. The rectal temperature of all mice was measured (with a temperature sensitive probe inserted to constant depth — 2 cm; Bailey, USA) on three occasions. The mean of these three measures was, for each mouse, the basal rectal temperature prior to treatment. Then, water or quinelorane was administered intraperitoneally (0.2 ml/20 g body weight) just before the mice were placed in a photocell actimeter (Apelex, 91300 Massy, France). Locomotor activity was recorded for 60 min, and rectal temperature was measured at the point.

2.3. Interaction of quinelorane–nafadotride on locomotor activity

Mice were brought to the experimental room and the test begun 1 h later. Four groups were formed: water + water, water + quinelorane, nafadotride + water and quinelorane + nafadotride. Drugs were administered (ip) successively just before the mice were placed in the photocell actimeter. Locomotor activity was recorded every 5 min for 60 min.

2.4. Intracerebroventricular administration

Nisoxetine (20 mg/kg) was intraperitoneally administered 30 min before 6-OHDA (100 μg/mouse). The neurotoxic drug was administered by intracerebroventricular route using a Hamilton syringe of 100 μl graduated in 1/100ième; the sham mice received the vehicle (ascorbic acid 0.01%) by the same route under the same volume (10 μl/mouse). Mice, without guide cannula implantation, were maintained with one hand; the head of the mouse was firmly held between the thumb and the forefinger placed above the ears. Commercially available needles were cut to obtain bevelled needles, the bevel of which was between 2.5 and 3.5 mm The site of injection was 4 mm behind the line that joins together the posterior sides of the eyes, 2 mm laterally and 3 mm depth (Frances et al., 1979). Nisoxetine was used to make the lesions more specific: nisoxetine inhibits the uptake of the neurotoxin 6-OHDA in noradrenergic neurons. The effect of quinelorane (0.1 mg/kg, ip) on motor activity and on rectal temperature was measured 1 week after performance of the 6-OHDA lesions. The same protocol as described in ‘‘experimental protocol’’ was used.

2.5. Drugs

6-Hydroxydopamine was obtained from RBI (Natick, MA, USA). It was diluted in ascorbic acid 0.01%. Nisoxetine HCl was obtained from Lilly Company (Indianapolis, IN, USA). Nafadotride tartrate and quinelorane HCl were a gift from Dr. P. Sokoloff. The doses are expressed as salts.

2.6. Monoamines determination

2.6.1. Analytical methods: DA and metabolites

Dopamine (3-4 dihydroxyphenylethylamine) and metabolites [3-4 dihydroxyphenyl-acetic acid (DOPAC), homovanillic acid (HVA)] in cerebral structures (nucleus accumbens and corpus striatum) were determined by high-pressure liquid chromatography (HPLC) with coulometric detection (Aymard et al., 1983).

2.6.2. Reagents and chemicals

The reference compounds were: DA and DOPAC from Sigma (St. Louis, MO, USA), HVA and perchloric acid from Fluka (Pouchs, Switzerland), ethylene diamine-tetra-acetic acid (EDTA) and sodium metabisulfite from Sigma, methanol for CLHP from Prolabo (Fontenay-sous-Bois, France), potassium dihydrogenophosphate from Merk (Darmstadt, Germany) and Pic B7 (1 heptane-sulfonic acid) from Waters Assoc. (Milford, MA, USA) and 3-4 dihydroxybenzylamine (DBA) from Sigma infused as internal standard.

2.6.3. Apparatus

Liquid chromatography was carried out using a pump (LC-GA, Shimadzu), a 250×4.6 mm i.d. column packed

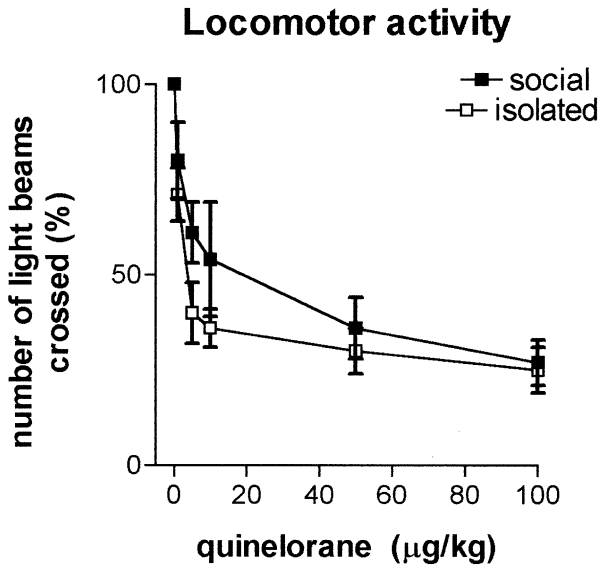

Fig. 1. Effect of quinelorane on locomotor activity (number of light beams crossed, $m \pm$S.E.M.) measured for 60 min in social and isolated mice; $n = 12$ for each dose and each condition.

with nucleosil C_{18} size 5 μm (Waters) with a Brawnlee (RP 18) precolumn and a coulochem II detector (Eurosep) — ($E_1 = 60$ mV $- E_2 = 350$ mV).

2.6.4. Sample preparation

The animals were killed by neck elongation and brain dissected on ice. The structures (nucleus accumbens, corpus striatum) were weighed and immediately frozen in *carboxylic ice* and kept at -80°C. Cerebral structures were homogenized (1 min, ultraturrax) in a perchloric acid 0.1 M, EDTA 2.9 mM and sodium metabisulfite 1.3 mM solution. After centrifugation (10 min, 1300 × *g* at 0°C), the resulting supernatant was filtered through a 0.22-μm filter, added with internal standard and then injected into the chromatographic column. The column was balanced with a mobile phase composed of 4% methanol, 0.1 M phosphate buffer and 5 mM Pic B7 reagent in deionized water (pH 3.6). The flow rate was 1.0 ml/min. The first electrode was fixed at 60 mV and the second at 350 mV. In these conditions, DA, DOPAC and HVA could be quantitatively determined, a standard curve was obtained with increasing concentrations of DA, DOPAC and HVA to obtain concentration ranges of 2–20 ng/ml. The concentrations were expressed in nanograms per gram of fresh brain.

2.6.5. Characteristics of the method

A linear relationship between peak-height ratio (DA, DOPAC or HVA to internal standard) and concentrations of DA (ng/ml) was observed between 1 and 40 ng/ml with a correlation coefficient, *r*, of .9995. The detection limit was estimated at 500 pg/ml for DA, DOPAC and HVA.

The day-to-day reproducibility obtained for 10 determinations for a DA concentration corresponding to 10 ng/ml led to a coefficient of variation (CV) of 6.5%. The within-days reproducibility obtained from 20 determinations for two DA concentrations (5 and 20 ng/ml) gave a CV of 8%.

2.7. Statistical analysis

2.7.1. Motor activity

Two-way analyses of variance were used to compare the effect of quinelorane in isolated and social mice, the effect of quinelorane in lesioned and sham mice and the effect of quinelorane with and without nafadotride.

2.7.2. Rectal temperature

For each mouse, the difference (°C) between the mean rectal temperature before treatment and the temperature 60 min after treatment was calculated. Then, a two-way ANOVA was used to compare the effect of quinelorane in isolated and nonisolated mice, and also to compare the effect of quinelorane in lesioned and sham mice.

The levels of monoamines and of their metabolites were compared in sham and lesioned mice using the one-way ANOVA followed by Dunnett tests.

3. Results

3.1. Locomotor activity

Quinelorane decreased locomotor activity in a dose-dependent manner in social and isolated mice (Fig. 1). The statistical analysis (two-way ANOVA) indicates an effect of the drug [$F(5, 131) = 27.24$, $P < .001$], an effect of isolation [$F(1, 131) = 4.403$, $P = .038$] and no interaction

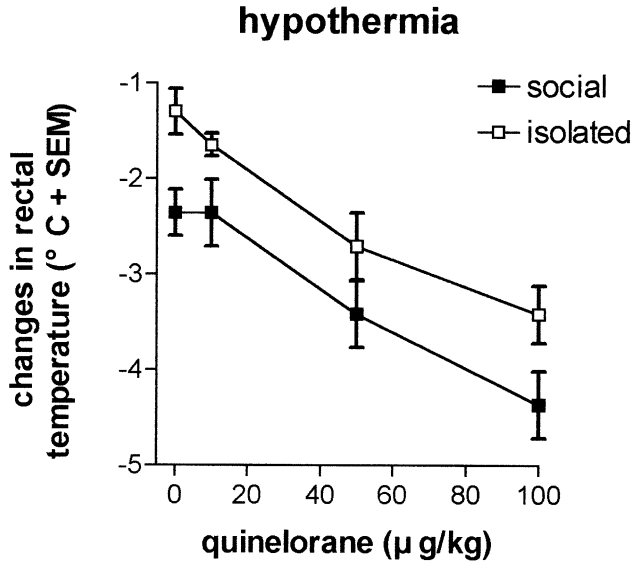

Fig. 2. Effect of quinelorane on rectal temperature in social and isolated mice. Results are expressed as the difference (°C, $m \pm$S.E.M.) between the temperature before and 60 min after drug administration; $n = 12$ mice for each dose and each condition.

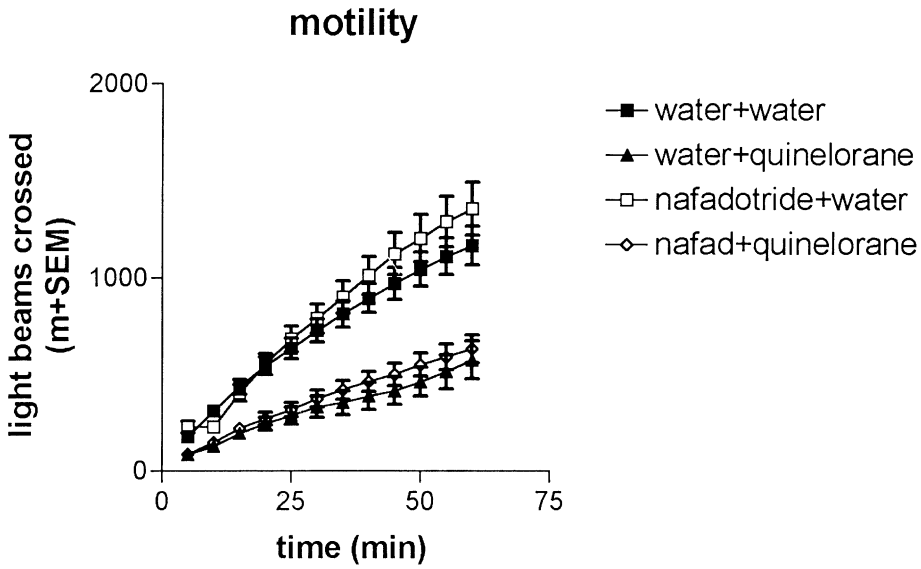

Fig. 3. Effect of nafadotride on locomotor activity ($m \pm$ S.E.M.) of control and quinelorane treated mice; $n = 12$ mice for each combination of treatments.

between isolation and the drug [$F(5, 131) = 0.681$, $P = .425$]. The locomotor activity of isolated mice was lower than that of social mice.

3.2. Rectal temperature

Quinelorane dose-dependently and significantly decreased rectal temperature in both isolated and social mice (Fig. 2). The statistical analysis (two-way ANOVA) indicates an effect of the drug [$F(3, 88) = 19.498$, $P = .001$], an effect of isolation [$F(1, 88) = 16.759$, $P = .001$], but no Isolation × Quinelorane interaction [$F(3, 88) = 0.203$, $P = .894$]. The temperature of isolated mice was higher than that of social mice.

3.3. Interaction of quinelorane–nafadotride on locomotor activity

The results of the multivariate repeated-measures analysis indicate an effect of quinelorane [$F(2, 42) = 75.25$, $P < .0001$], no effect of nafadotride [$F(2, 42) = 0.008$, $P = .928$] and no Quinelorane × Nafadotride interaction [$F(2, 42) = 0.696$, $P = .409$]. Nafadotride at the dose used (1 mg/kg) had no effect and did not antagonize the quinelorane-induced decrease in motor activity (Fig. 3).

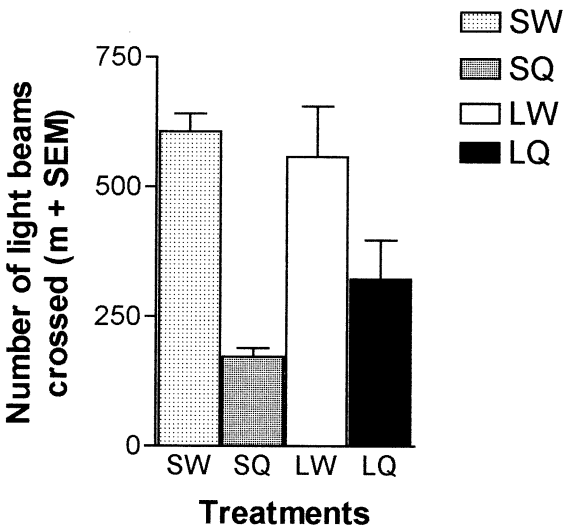

Fig. 4. Effect of the 6-OHDA lesion of the dopaminergic terminals on quinelorane-induced decrease in locomotor activity. S = sham, L = lesioned, W = water, Q = quinelorane (0.1 mg/kg ip); $n = 12$ mice for each condition and each treatment.

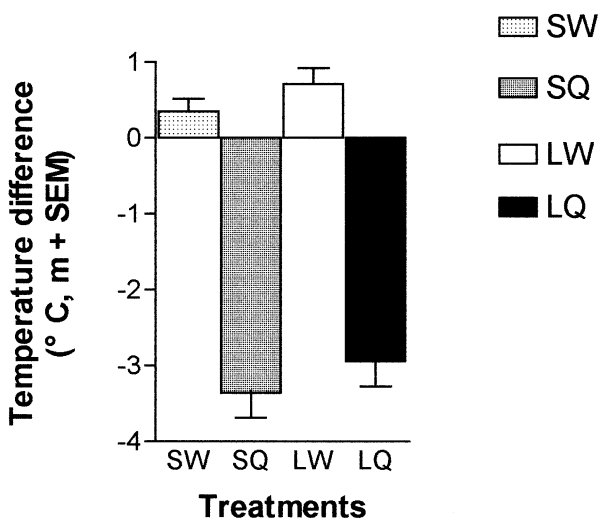

Fig. 5. Effect of the 6-OHDA lesion of the dopaminergic terminals on quinelorane-induced decrease in rectal temperature. S = sham, L = lesioned, W = water, Q = quinelorane (0.1 mg/kg ip); $n = 11$ or 12 for each condition and each treatment.

3.4. Behavioural and physiological effects of quinelorane after 6-OHDA lesions

After lesions of the dopaminergic system with intracerebroventricular administration of 6-OHDA, the quinelorane-induced decrease in locomotor activity did not disappear. The results (Fig. 4) were analyzed with a two-way ANOVA: There is a significant effect of quinelorane [$F(1, 44) = 27.12$, $P < .001$], there is no effect of the lesion [$F(1, 44) = 0.627$, $P = .433$] and there is no Lesion × Quinelorane interaction [$F(1, 44) = 2.42$, $P = .127$].

The mice with 6-OHDA lesions did not present with an unusual rectal temperature. The mean basal rectal temperature (three measures) was (°C, $m \pm$ S.E.M.) in the subgroups used for water administration is 37.7 ± 0.15 ($n = 12$) and for quinelorane treatment is 37.6 ± 0.15 ($n = 12$).

In lesioned animals, the quinelorane-induced decrease in rectal temperature did not disappear. The results (Fig. 5) analyzed with a two-way ANOVA indicated a significant effect of quinelorane [$F(1, 43) = 197.3$, $P < .001$], no effect of the lesion [$F(1, 43) = 2.16$, $P = .148$] and no Lesion × Quinelorane interaction [$F(1, 43) = 0.011$, $P = .918$].

3.5. Biochemical effect of the 6-OHDA lesion

The analysis of the levels of DA and of its metabolites in the nucleus accumbens and the corpus striatum of sham and lesioned mice is reported in the Table 1. A large and significant decrease in the levels of DA and DOPAC occurred in both structures, as well as a significant increase in the ratios DOPAC/DA and HVA/DA. These results indicate the effectiveness of the lesion. However, it may be noted that the specificity of this lesion was not very high since the level of noradrenaline decreased significantly (Student's t test) in the nucleus accumbens (ng/g, $m \pm$ S.E.M., sham: 229.67 ± 17.4, lesioned: 62.28 ± 26.12, $P < .01$) and in the corpus striatum (ng/g, $m \pm$ S.E.M., sham: 112.05 ± 20.61, lesioned: 22.43 ± 2.15, $P < .01$).

Table 1
Effect of 6-OHDA lesion on the levels of dopamine and its metabolites in the nucleus accumbens and corpus striatum

	Nucleus accumbens		Corpus striatum	
	Sham	Lesion	Sham	Lesion
DA	6156.3 ± 469.5	370.7 ± 104.1*	7793.3 ± 978.7	673.2 ± 113.7*
DOPAC	802.6 ± 48.3	244.8 ± 56.4*	2246.6 ± 373.7	668.6 ± 121.8*
HVA	652.0 ± 49.9	222.6 ± 20.4*	939.5 ± 281.9*	858.2 ± 102.5
DOPAC/DA	0.132 ± 0.006	0.705 ± 0.082*	0.309 ± 0.054	0.999 ± 0.061*
HVA/DA	0.107 ± 0.005	0.736 ± 0.139*	0.138 ± 0.04	1.409 ± 0.197*

The concentrations of DA, DOPAC and HVA were expressed in nanograms per gram of fresh tissue. Results are $m \pm$ S.D. for $n = 6$ mice for each brain structure and condition (sham–lesioned).

* $P < .01$ (vs. sham).

4. Discussion

The present results show that the quinelorane-induced decrease in motor activity is unaltered following social isolation. This effect of quinelorane results probably from the stimulation of postsynaptic dopaminergic receptors since the lesion of dopaminergic terminals did not impair its effect. Our results indicating a postsynaptic action of quinelorane is supported by the results of Svensson et al. (1994) who observed a reduced locomotion induced by pramipexole and 7-OH-DPAT (two preferential DAD3 agonists) at doses that did not affect brain DA synthesis rate (DOPA accumulation) or release (measured in in vivo dialysis experiments). In the same way, Fink-Jensen et al. (1998) showed that *cis*-8-OH-PBZI, a preferential DAD3 agonist in vitro, inhibited spontaneous locomotor activity at doses (6 and 12 mg/kg) that did not affect interstitial levels of DA and DOPAC in the nucleus accumbens or dorsal striatum. The present results also corroborate those of Thorn et al. (1997) in which quinelorane blocked the amphetamine-induced hyperlocomotion without significant effect on amphetamine-induced DA release suggesting that quinelorane acted on postsynaptic dopaminergic receptors.

The quinelorane-induced decrease in rectal temperature is unaffected by social isolation. The quinelorane-induced decrease in rectal temperature probably results from the stimulation of a postsynaptic dopaminergic receptor since it persists after effective lesions of the dopaminergic terminals. We have not observed an influence of isolation on quinelorane-induced hypomotility and hypothermia. However, changes in dopaminergic balance have been described following social isolation (Blanc et al., 1980; Jones et al., 1992) and an isolation-induced increase in the D2-like DA receptor mediation of social emotional reactivity in a mouse model of anxiety has been described (Gendreau et al., 1998). Several questions arise: To what extent is quinelorane preferred by the DAD3 receptors? Are these two effects of quinelorane representative of the stimulation of DAD3 receptors?

Using a functional test to identify DA agonists selective for D3 vs. D2 receptors, Sautel et al. (1995a) showed that (+)-7-OH-DPAT, pramipexole and quinelorane were respectively 7, 15 and 21 times more potent at the DAD3 than at the DAD2 receptors. Therefore, the preference of quinelorane for DAD3 receptors is higher than those of (+)-7-OH-DPAT or pramipexole. Svensson et al. (1994), using five dopaminergic agonists classified according to their relative order of potency to stimulate DAD2 and D3 receptors observed that the two drugs with the greater ratio of potency D3/D2 (*R*-(+)-7-OH-DPAT and pramipexole) were those that reduced locomotor activity to the greater extent. Complementary results have been obtained by Waters et al. (1993) with U 99194A, a dopaminergic antagonist with a ratio of potency D3/D2 of 20, which increased locomotor activity without increasing the DA release. In the same way,

nafadotride, a potent preferential DAD3 receptor antagonist activates locomotion in rodents (Sautel et al., 1995b).

Millan et al. (1995), studying eight dopaminergic agonists, observed a positive correlation between their ability to induce hypothermia and their affinity for D3 (and not D2) receptors. Examining nine dopaminergic receptor antagonists, the same authors found that their potency to inhibit the 7-OH-DPAT induced hypothermia was more highly related to their affinity for D3 than for D2 receptors. Therefore, it is highly likely that the hypothermia induced by quinelorane resulted from the stimulation of DAD3 receptors.

Although several works have shown that quinelorane is a preferential agonist at DAD3 receptors, it cannot be excluded that its effects are due to stimulation of DAD2 receptors. Indeed, recent experiments (Boulay et al., 1999a; Xu et al., 1999) have shown that the decrease in locomotor activity induced by putative DAD3 receptor selective agonists (7-OH-DPAT, quinelorane, PD 128907), as well as increase in locomotor activity produced by the putative DAD3 antagonist (PNU 99194A) are identical in D3 receptor mutant and wild-type mice. In addition, the hypothermia produced by the DAD3 receptor-preferring agonists PD 128907, 7-OH-DPAT and quinelorane are identical in both groups of mice. The present results also show that nafadotride, which is reported as a preferential DAD3 antagonist (Sautel et al., 1995b), did not alter, at the dose used, the effect of quinelorane.

These results raise the question of the involvement of the DAD3 receptor in these behavioural effects and the issue of the in vivo selectivity of these compounds for the DAD3 subtype. In addition, more recent data (Boulay et al., 1999b) have shown that DA D2 receptor knock-out mice are insensitive to the hypolocomotor and hypothermic effects of DAD2/D3 receptor agonists: 7-OH-DPAT and PD 128907. These results show that the presence of DA/D2 receptors is necessary for the expression of the locomotor and core temperature — decreasing effects of DAD2/D3 receptor agonists. In the same way, the morphine-induced CPP does not appear in mice devoid of the DA D2 receptors (Maldonado et al., 1997); that means that the presence of DAD2 receptors is necessary but does not exclude a role for DAD3 receptors.

Nevertheless, the lack of a difference in the responses of isolated and social mice to quinelorane regarding hypothermia and hypolocomotion does not preclude of a lack of difference in reward responses. The central distribution of DAD3 receptors has been extensively studied (Bouthenet et al., 1991). According to these authors, the DAD3 receptor is mainly expressed in the limbic part of the striatum (ventral striatum), as well as in other "limbic" structures such as amygdaloid, septal, medial mamillary or anterior thalamic nuclei and hippocampal formation. These localizations suggest that DAD3 receptors may play a role in cognitive and emotional functions and thus in CPP. Indeed, several studies have shown an influence of DAD3 stimulation on rewarded behaviours (Duaux et al., 1998; Hitchcott et al., 1997; Parsons et al., 1996; Pilla et al., 1999; Sinnott et al., 1999). Further work is required, which will be directed at searching for a difference in isolated and social mice regarding the effect of DAD3 agonists in reward models.

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