Published in final edited form as:
Eur J Pharmacol. 2008 September 11; 592(1-3): 67–72. doi:10.1016/j.ejphar.2008.06.101.

Altered dopamine D_2-like receptor binding in rats with behavioral sensitization to quinpirole: effects of pre-treatment with Ro 41-1049[a]

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Abstract

Repeated treatment with the dopamine D_2/D_3 receptor agonist quinpirole produces a sensitized behavioral response in rats manifested as an increase in locomotor activity. Pre-treatment with certain monoamine oxidase inhibitors, such as Ro 41-1049 [N-(2-aminomethyl)-5-(3-fluorophenyl)-4-thiazolecarboxamide HCl], changes the sensitized response from locomotion to stationary, self-directed mouthing. In this study, the effects of quinpirole sensitization, with and without pre-treatment with Ro 41-1049, were determined on dopamine D_2-like receptors in the nucleus accumbens and the striatum. Long-Evans rats were pre-treated with Ro 41-1049 (1 mg/kg) 90 min prior to administration of quinpirole (0.5 mg/kg, 8 injections, every 3–4 days). Dopamine D_2-like receptor binding was determined 3 days after the last injection by *ex vivo* radioligand assays using [^{3}H]spiperone and [^{3}H]quinpirole. Densities of [^{3}H]spiperone- and [^{3}H]quinpirole-labeled sites were both increased 32% in the nucleus accumbens of rats with demonstrated locomotor sensitization to quinpirole. In contrast, the density of dopamine D_2-like receptors in quinpirole-sensitized rats pre-treated with Ro 41-1049 was not different from saline controls. These findings support the involvement of alterations in dopamine D_2-like receptors in the development of locomotor sensitization to quinpirole and suggest that modification of these alterations in dopamine D_2-like receptors contributes to the change from sensitized locomotion to mouthing observed when rats are pre-treated with Ro 41-1049.

Keywords

Dopamine D_2 receptor; Sensitization; Quinpirole; Striatum; Nucleus accumbens

[a]Supported by the Canadian Institutes of Health Research Grant MOP-64424 (HS), NIH P30 HD02528 (BL), and NIH P20 RR016475 from the INBRE Program of the National Center for Research Resources (BL).

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1. Introduction

Dopaminergic psychostimulants produce sensitized behavioral responses with repeated, intermittent administration in which the response is greater than after a single, acute administration of the same dose (Robinson and Becker, 1986). This long-lasting phenomenon is thought to contribute to the etiology of addiction, with enhanced activation of the mesolimbic dopamine system contributing to the development of drug craving (Di Chiara, 1995; Robinson, 1993). Similarly, sensitization to other stimuli, such as stressors or chemicals, is hypothesized to contribute to the development of neuropsychiatric disorders including mania, psychosis, obsessive-compulsive disorder, post-traumatic stress disorder, and multiple chemical sensitivity (Ellison, 1994; Post and Contel, 1981; Schmidt and Beninger, 2006; Szechtman et al., 1998). Functional changes in the "motive circuit", which includes the mesolimbic dopamine system, and changes in glutamatergic neurotransmission, appear to contribute to the augmented behavioral response; however, the mechanisms underlying sensitization are not yet fully understood (for review see: Pierce and Kalivas, 1997; Steketee, 2003; Vanderschuren and Kalivas, 2000; Vezina, 2004; Wolf, 2002).

Quinpirole, a selective dopamine D_2/D_3 receptor agonist (Levant et al., 1992; Tsuruta et al., 1981), produces a sensitized locomotor response in rats. The quinpirole-sensitized rat is of particular interest as these animals compulsively revisit the same location in the open field, akin to compulsive "checking" behavior of humans with obsessive-compulsive disorder; thus, the quinpirole preparation may represent a putative animal model (Szechtman et al., 1998; 1999; 2001). Altered cortico-striatal-thalamic-cortical activity, and dysregulation of certain serotonergic and dopaminergic systems, are believed to contribute to the pathogenesis of obsessive-compulsive disorder (Stein, 2002); however, the exact neurobiological basis is not fully understood. Serotonin reuptake inhibitors are used in the treatment of obsessive-compulsive disorder, but are not effective in many patients (Piccinelli et al., 1995). Furthermore, it is not understood why the particular obsessions or compulsions of obsessive-compulsive disorder patients vary (McKay et al., 2004) or why the obsession and/or compulsion changes over time in almost two-thirds of patients (Skoog and Skoog, 1999).

Based on findings that certain monoamine oxidase inhibitors (MAO inhibitors) and related compounds inhibited the *in vitro* binding of [^{3}H]quinpirole, apparently uniquely among dopamine D_2-like receptor radioligands (Levant et al., 1993; 1996; 2001), Culver and colleagues found that pre-treatment of rats with the MAO_A–selective MAO inhibitors clorgyline or Ro 41-1049 [N-(2-aminomethyl)-5-(3-fluorophenyl)-4-thiazolecarboxamide HCl] changed the sensitized behavior produced by quinpirole from locomotion to self-directed "mouthing" activity that included nibbling of paws or tail, and licking of hindquarters or body fur (Culver et al., 2000; Culver and Szechtman, 1997; 2003; Dvorkin et al., 2006). The mechanism underlying the effects of these drugs on quinpirole-induced behaviors remains to be fully determined; however, it appears to be unrelated to inhibition of MAO_A because moclobemide, an MAO_A inhibitor with low affinity in competition with [^{3}H]quinpirole (Levant et al., 1996), produced similar inhibition of MAO_A to clorgyline, but did not alter the sensitized response to quinpirole (Culver et al., 2000). Consistent with *in vitro* findings (Levant et al., 1993; 1996; 2001), modulation of dopamine uptake and interactions with the sigma and imidazoline sites have also been eliminated as potential mediators of clorgyline's or Ro 41-1049's effects on quinpirole-sensitized behaviors (Culver et al., 2000; 2002; Culver and Szechtman, 2003). Furthermore, clorgyline altered quinpirole-sensitized behavior when administered intermittently by injection, continuously by osmotic pump during the sensitizing treatment, or by injection after sensitization had occurred, indicating that the mode of administration and pharmacokinetics were not critical in producing the modification of the sensitized response (Culver et al., 2000; Culver and Szechtman, 2003). Thus, we hypothesize

that these drugs modulate [^{3}H]quinpirole binding to the dopamine D_2 receptor, and in turn, quinpirole-induced behavior, perhaps by an allosteric mechanism (Levant, 2000; 2002).

To further assess mechanisms underlying behavioral sensitization, this study sought to assess changes in dopamine D_2-like receptor binding in rats sensitized to quinpirole. The effects of pre-treatment with the MAO_A inhibitor Ro 41-1049 on behavior and dopamine D_2-like receptor binding were also examined to determine whether the shift in sensitized responding from locomotion to mouthing is related to modulation of D_2-like receptors. Ro 41-1049 was used because, unlike the preponderance of other MAO inhibitors, it has no potentially confounding activities at the sigma or imidazoline sites (Levant et al., 1993). In addition, the effects of these treatments on the ability of Ro 41-1049 to modulate [^{3}H]quinpirole binding *ex vivo* were determined.

2. Materials and Methods

All animal treatments and testing were performed at McMaster University and were conducted in compliance with the guidelines described in the Guide to the Care and Use of Experimental Animals (Canadian Council on Animal Research, 1993).

2.1. Subjects

Experimentally naïve male Long-Evans rats (Charles-River, Canada) weighing 200–230 g at the start of treatment were used. Rats were individually housed in a temperature-controlled colony room (22° C) under a 12-h light-dark cycle (8:00 am to 8:00 pm), with free access to food and water. Rats were allowed to acclimatize to the colony room for 1 week following arrival, and were handled 2 min daily for 7 days before starting experiments. All treatments and testing were conducted during light hours.

2.2. Procedures

Rats (n = 8–10 per group) were pre-treated with Ro 41-1049 (N-(2-aminomethyl)-5-(3-fluorophenyl)-4-thiazolecarboxamide HCl; 1 mg/kg, s.c.; RBI, Natick, MA) or saline 90 min prior to administration of quinpirole (0.5 mg/kg, s.c., RBI, Natick, MA) or saline, twice weekly (3–4 days apart) for a total of eight pairs of injections as previously described (Culver and Szechtman, 2003). An acute quinpirole group was also included, which received eight pairs of saline injections followed by a single saline-quinpirole treatment. All drugs were administered in the testing environment. Rats were returned to the colony room between the pre-treatment and administration of quinpirole. Immediately following each quinpirole or saline injection, rats were placed in Plexiglas locomotor activity chambers (40 × 40 × 35 cm; Accuscan Instruments, Columbus, OH) and their activity recorded for 90 min. Since Ro-1049 sensitizes self-directed mouthing behavior in quinpirole-treated rats, mouthing activity was also measured during the first and last 15 min of the 90-min testing period according to the protocol described in Culver et al. (Culver et al., 2000). Mouthing activity was defined as any contact between the rat's mouth and/or tongue with either an external object (e.g. licking or gnawing Plexiglas chamber) or parts of its own body (e.g., nibbling of paws or tail, licking of hindquarters or body fur) and is reported as total mouthing although externally and self-directed mouthing activity were scored separately. Three days after the last drug treatment, rats were euthanized by decapitation and brains rapidly removed, frozen on dry ice, and stored at −80° C.

2.3. Radioligand binding assays

Brains were shipped on dry ice to the University of Kansas Medical Center for assessment of dopamine D_2-like receptor binding.

Binding of the dopamine D_2-like receptor agonist [^{3}H]quinpirole and antagonist [^{3}H]spiperone was performed as previously described in detail (Levant et al., 1992). The nucleus accumbens and striatum were dissected on ice from each brain and homogenized in 20 volumes of assay buffer (50 mM Tris, 5 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$; pH 7.4 at 23° C) and washed twice. The resulting pellets were reconstituted in assay buffer. In order to facilitate the assessment of multiple endpoints in each individual animal, initial binding analysis was performed using a single concentration of each radioligand. Those endpoints exhibiting significant differences between groups were further examined by Scatchard analysis using pooled tissues from all rats in each group.

[^{3}H]Quinpirole (55.5 Ci/mmol; New England Nuclear, Boston, MA) was used at a final concentration of 2 nM for single-point binding studies or five concentrations (0.38 – 10 nM) for Scatchard analysis. The membrane protein concentration was ~200 μg/tube. Non-specific binding was defined in the presence of spiperone (1 μM). MAO inhibitor-inhibitable [^{3}H] quinpirole binding was determined in the presence of Ro 41-1049 (10 μM). Assay tubes were incubated at 23° C for 4 hrs. Binding reactions were terminated by rapid vacuum filtration and bound radioactivity determined using a Beckman 6500 liquid scintillation counter. Membrane homogenate protein concentrations were determined by the BCA method (Pierce, Rockford, IL). Specific binding is expressed as fmol bound/mg protein.

[^{3}H]Spiperone binding was performed as described for [^{3}H]quinpirole except the membrane protein concentration was ~35 μg/tube; [^{3}H]spiperone (24 Ci/mmol; Amersham, Arlington Heights, IL) was used at a final concentration of 0.2 nM for single-point studies or six concentrations (0.02–1.0 nM) for Scatchard analysis; non-specific binding was defined in the presence of (+)-butaclamol (1 μM); and assay tubes were incubated at 23° C for 90 min.

2.4. Analysis

Data are expressed as the mean ± S.E.M. Scatchard binding experiments were analyzed for K_D and B_{max} values using SigmaPlot v.8.0.2. The percentage of receptors in the high affinity state was calculated as the ratio of sites labeled by the agonist [^{3}H]quinpirole to sites labeled by the antagonist [^{3}H]spiperone. The percentage of MAO inhibitor-inhibitable [^{3}H]quinpirole binding (%MQB) was calculated as the percentage of binding inhibited by Ro 41-1049. Binding data was analyzed for statistically significant differences by analysis of variance followed by the Student-Newman-Keuls multiple comparisons tests (GraphPad Instat 3). Statistical significance was set at $P<0.05$.

3. Results

Repeated injections of quinpirole induced behavioral sensitization manifested as an almost 4-fold increase in distance traveled after injection 8 compared to injection 1 ($P<0.01$) (Figure 1). Pretreatment with Ro 41-1049 changed the sensitized behavior induced by quinpirole from locomotion to mouthing activity. Over 90% of the total mouthing activity was directed primarily at the rat's own body and included behaviors such as nibbling and licking of paws, tail, or body fur (Culver and Szechtman, 2003). Total mouthing in the Ro 41-1049 pretreated animals after injection 8 was 7-times higher than in rats treated with saline ($P<0.01$), whereas distance traveled was not different from saline controls. Distance traveled or mouthing by rats treated only with Ro 41-1049 was not different from that of saline controls.

Dopamine D_2-like receptor binding was assessed in brains collected three days after the last injection. In the nucleus accumbens, single-point binding assays indicated that [^{3}H]quinpirole and [^{3}H]spiperone binding were both 32% higher in quinpirole-sensitized rats compared to rats treated with saline ($P<0.05$) (Table 1). [^{3}H]Spiperone binding was 38% higher in quinpirole-sensitized rats than in rats pre-treated with Ro 41-1049 prior to administration of

quinpirole ($P<0.05$). [^{3}H]Quinpirole binding was 14% higher in quinpirole-sensitized rats without Ro 41-1409 pre-treatment than in rats pre-treated with Ro 41-1049, but this difference was not statistically significant. Neither treatment with Ro 41-1049 alone, nor an acute injection of quinpirole, altered [^{3}H]quinpirole or [^{3}H]spiperone binding in the nucleus accumbens. None of the treatments altered the percentage of dopamine D_2-like receptors in the high affinity state or the percentage of MAO inhibitor-inhibitable [^{3}H]quinpirole binding (%MQB). Scatchard analysis performed using pooled samples from each treatment group indicated that the increases in [^{3}H]quinpirole and [^{3}H]spiperone binding observed in the quinpirole-sensitized rats resulted from an increase in receptor density (B_{max}), which was higher than Saline-Saline for both [^{3}H]spiperone and [^{3}H]quinpirole (Figure 2). Minor alterations in binding site affinity may also have occurred; however, the single replication of the Scatchard analyses, due to the limited amount of tissue available, affords only qualitative assessment of this data.

In the striatum, single-point binding analysis indicated no alterations in [^{3}H]quinpirole or [^{3}H]spiperone binding, the percentage of dopamine D_2-like receptors in the high affinity state, or the percentage of MAO inhibitor-inhibitable [^{3}H]quinpirole binding (%MQB) (Table 2).

4. Discussion

The effects of sensitization to quinpirole, with and without pretreatment with Ro 41-1049, on the binding properties of dopamine D_2-like receptors were assessed in rats with verified behavioral sensitization.

As evidenced by parallel increases in both [^{3}H]spiperone and [^{3}H]quinpirole binding, sensitizing treatment with quinpirole increased the density of dopamine D_2-like receptors in the nucleus accumbens, but not in striatum. Small changes in dopamine D_2-like receptor affinity in the nucleus accumbens may also contribute to the sensitized behavior, but the presence of such a change in affinity could not be evaluated in the present study due to the limited quantity of tissue available. The increase in the density of dopamine D_2-like sites in the nucleus accumbens after sensitizing treatment with quinpirole was not observed after a single acute injection of the drug, indicating that the increase in receptor density requires multiple injections. The increase in the density of dopamine D_2-like receptors in the nucleus accumbens is consistent with previous studies of the effects of sensitization to quinpirole on quinpirole-stimulated local cerebral glucose utilization in which a decrease in glucose utilization in the nucleus accumbens was observed only in sensitized animals and not those treated acutely (Carpenter et al., 2003). Furthermore a decrease in glucose utilization would be consistent with increased numbers of the inhibitory dopamine D_2-like receptors. This change in dopamine D_2-like receptor density could reflect the increased sensitivity of dopamine D_2-like autoreceptors reported by Dwoskin et al. (1988) in amphetamine- or cocaine-sensitized rats. However, other studies of dopamine receptor changes after amphetamine- or cocaine-induced sensitization report decreased sensitivity (Yi and Johnson, 1990) or no change (Bonhomme et al., 1995; Claye et al., 1995; Farfel et al., 1992; Fitzgerald and Reid, 1991; Gifford and Johnson, 1992; King et al., 1994; Mayfield et al., 1992; Peris et al., 1990; Unterwald et al., 1994), perhaps due to differences in the spectra of activity of these drugs.

The increase in the density of dopamine D_2-like receptors in the nucleus accumbens produced by sensitizing treatment with quinpirole was not observed in rat pre-treated with the MAO inhibitor Ro 41-1049. This supports a role for the increase in dopamine D_2-like receptor density in the nucleus accumbens in the augmented locomotor response and suggests that the attenuation of this effect, at least in part, underlies the change in sensitized behavior from locomotion to mouthing. Since dopamine D_2-like receptor binding in the nucleus accumbens was at control levels in these animals, neurobiological changes beyond altered accumbal dopamine D_2 receptor density must contribute to the expression of sensitized mouthing. Indeed,

quinpirole-sensitized rats, with and without pretreatment with an MAO inhibitor, exhibited differences in quinpirole-stimulated glucose utilization in the locus coeruleus, raphe magnus nucleus, piriform cortex, and septum, whereas glucose utilization in the nucleus accumbens was not different between these groups (Richards et al., 2007). This suggests that altered activity in the neuronal circuits involving one or more of these regions could be involved in mediating the change in sensitized behavior and perhaps also affect the density of dopamine D_2-like receptors in the nucleus accumbens. However, the present findings cannot rule out the possibility that discretely localized changes in dopamine D_2-like receptor expression in sub-regions of the nucleus accumbens or striatum, which would not be detectable using radioligand binding assays in homogenized grossly-dissected brain regions, may contribute to the particular sensitized behavioral response.

In this study, the ratio of sites labeled by the agonist [^{3}H]quinpirole to those labeled by the antagonist [^{3}H]spiperone was interpreted as representing the proportion of dopamine D_2-like receptors in the high affinity state. However, [^{3}H]quinpirole labels both dopamine D_2 and D_3 sites with roughly equal affinity in our *in vitro* assay (Levant et al., 1992). Thus, some of the [^{3}H]quinpirole binding in the nucleus accumbens represents the dopamine D_3 receptor, though the dopamine D_3 receptor comprises only about 10% of dopamine D_2-like sites in that region (Levant, 1997). Accordingly, dopamine D_3 receptors in the nucleus accumbens certainly contribute to the [^{3}H]quinpirole binding detected in that brain region in this study, and thus the percentage of dopamine D_2-like receptors in the high affinity state. The dopamine D_3 receptor has been proposed as a mediator of the sensitized behavioral response to psychostimulants, with desensitization of the receptor, which inhibits locomotion, contributing to the augmented locomotor response (Richtand, 2006). This study did not assess the specific contribution of the dopamine D_3 receptor due to the limited amount of tissue available. The density of [^{3}H]PD 128907-labeled dopamine D_3 receptor in ventral striatum (nucleus accumbens and olfactory tubercle) was not altered in rats with amphetamine sensitization (Richtand et al., 2003); however, when the specific contribution of dopamine D_3 receptors was measured in quinpirole-sensitized rats, an increase in percent of dopamine D_2 and D_3 receptors in the high affinity state was found in the nucleus accumbens and the striatum (Perreault et al., 2007; Seeman et al., 2006), Thus, while the dopamine D_3 receptor represents only a small fraction of the [^{3}H]quinpirole binding observed in this study, changes in expression level or regulation of that receptor subtype may be functionally consequential.

The literature on dopamine receptor changes after psychostimulant sensitization is conflicting, though most typically negative (see above). One factor contributing to these variable findings is the use of the widely abused psychostimulants amphetamine and cocaine. Although clinically-relevant, the pharmacology of these drugs is quite complex, involving both pre-synaptic actions resulting in post-synaptic effects at a multitude of dopaminergic, noradrenergic, serotonergic receptors (Jaffe, 1993). This spectrum of activity may obscure the detection of key mediators of sensitization. In this context, quinpirole, which produces sufficient stimulation of dopamine D_2/D_3 receptors to induce a sensitized behavioral response, represents a tool that may facilitate elucidation of mechanisms of sensitization that may also occur, perhaps transiently, with other psychostimulants. Alternatively, the effects observed in this study may be specific to quinpirole.

The shift from locomotion to self-directing mouthing produced in quinpirole sensitized rats by some MAO inhibitors may provide a model of neurobiological mechanisms underlying specific symptom changes observed during chronic drug intake or in some psychiatric disorders. As described by Ellinwood (1967), amphetamine users pass through several behavioral stages during the course of chronic drug intake. The stages are characterized by different psychological pre-occupations: At onset of drug-taking there is an expansion of the scope of attention as users become hyper-responsive to distal stimuli and are interested in the wide

environment and broad issues. With chronic intake, the scope of attention narrows progressively as users focus on proximal stimuli and detailed examinations of the immediate environment; ultimately they may become pre-occupied with every minutiae of their own body and self. A parallel shift in the focus of attention from distal to proximal stimuli had been described for the behavior of apomorphine-treated rats (Szechtman et al., 1985) and the observed shift in the present study from locomotor behavior to a focus on the rat's own body may be considered as a behavioral manifestation of a similar change in the rat's focus of attention and pre-occupation. Along the same lines, considering that quinpirole-sensitized rats may constitute an animal model of obsessive-compulsive disorder (Szechtman et al 1998), the shift in behavior produced by Ro 41-1049 may prove revealing as to the neurobiological mechanisms underlying a change in obsessive-compulsive disorder symptoms from compulsive checking to compulsive washing observed in some patients (Besiroglu et al., 2007).

In summary, the present data demonstrate an increase in the density of dopamine D_2-like receptors in the nucleus accumbens of rats with locomotor sensitization to quinpirole. The increase in dopamine D_2-like receptors was not present in quinpirole-sensitized rats that were pre-treated with the MAO inhibitor Ro 41-1049, a treatment regimen which changes the sensitized behavioral response from locomotion to self-directed mouthing. These findings support the involvement of alterations in dopamine D_2-like receptors in the nucleus accumbens in the development of locomotor sensitization to quinpirole and suggest that modification of these alterations contributes to the change from sensitized locomotion to mouthing observed when rats are pre-treated with Ro 41-1049. Further studies must elucidate how these effects on dopamine D_2-like receptors interact with other neurobiological sequelae of intermittent psychostimulant treatment to produce a particular sensitized behavioral response.

Acknowledgements

Supported by the Canadian Institutes of Health Research Grant MOP-64424 (HS), NIH P30 HD02528 (BL), and NIH P20 RR016475 from the INBRE Program of the National Center for Research Resources (BL).

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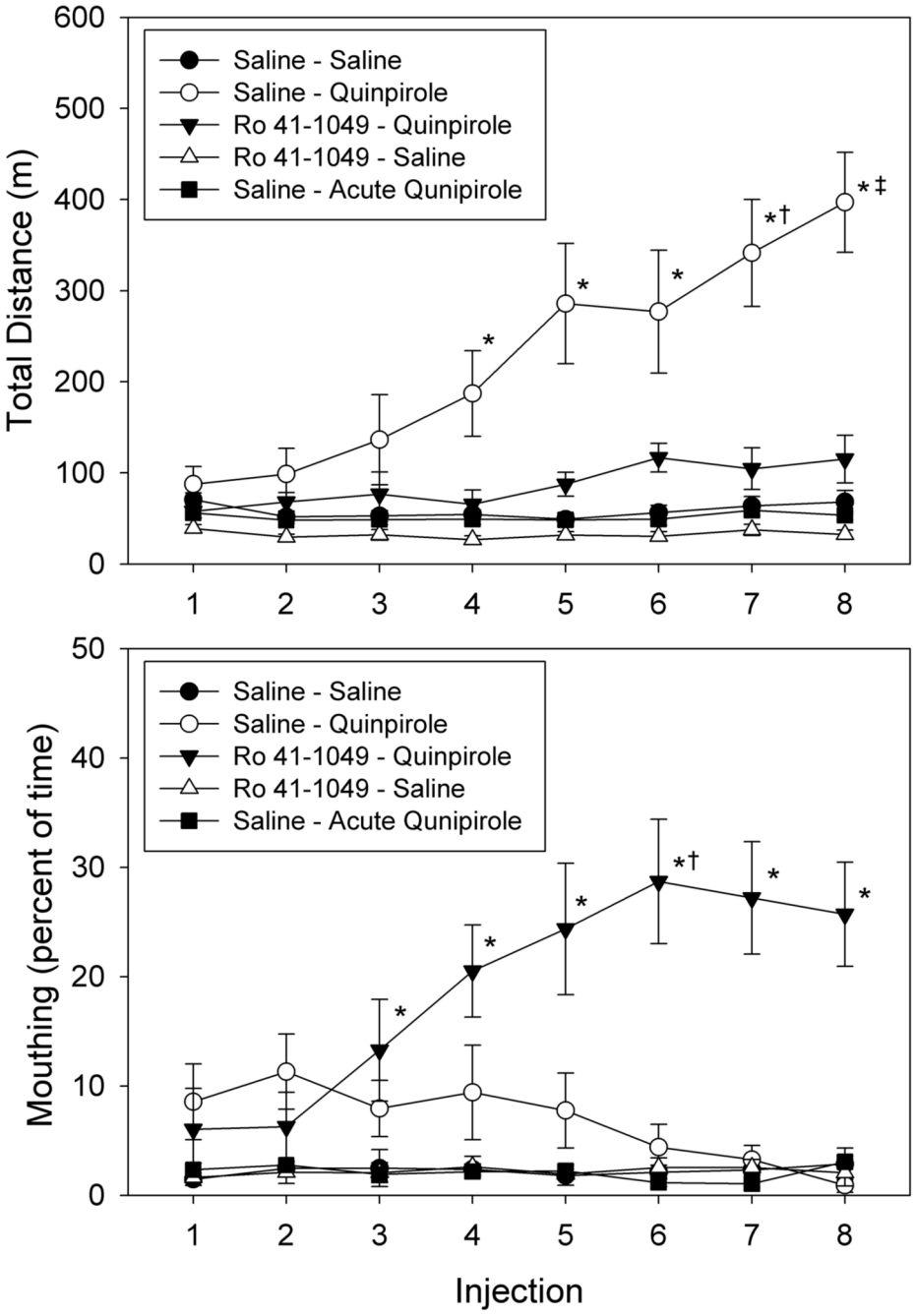

Figure 1. Locomotor and mouthing responses to quinpirole, with and without pretreatment with Ro 41-1049

Rats were pretreated with with Ro 41-1049 (1 mg/kg, s.c) or saline 90 min prior to administration of quinpirole (0.5 mg/kg, s.c.) or saline twice weekly (3–4 days apart) for a total of 8 pairs of injections. Data are presented as the mean ± SEM (n = 8 for Saline-Saline, n = 10 for all other groups). *P<0.05 vs. Saline-Saline, same injection by ANOVA and Student-Newman-Keuls test. †P<0.05 vs. injections 1 and 2, same treatment. ‡P<0.05 vs. injections 1–4, same treatment. These data were previously reported in Culver and Szechtman (2003).

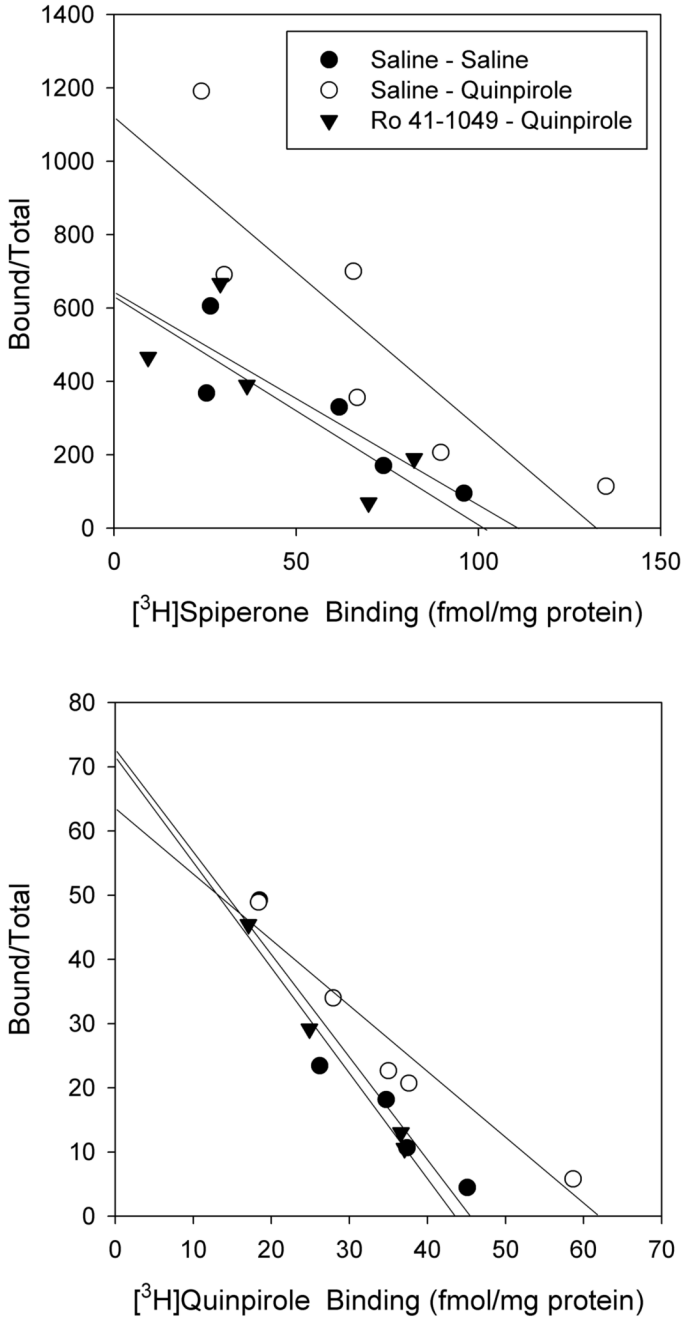

Figure 2. Rosenthal plots of [^{3}H]spiperone and [^{3}H]quinpirole binding in the nucleus accumbens of quinpirole-sensitized rats, with or without pretreatment with Ro 41-1049

Data represent a single determination performed using pooled samples from all individual animals in each treatment group that were used for the single-point analyses presented in Table 1. For [^{3}H]spiperone binding, K_D values were 0.17, 0.12, and 0.16 nM; B_{max} values were 112, 133, and 102 fmol/mg protein for the Saline-Saline, Saline-Quinpirole, and Ro 41-1049-Quinpirole groups, respectively. For [^{3}H]quinpirole binding, K_D values were 0.63, 0.94, and 0.60 nM and B_{max} values were 46, 59, and 44 fmol/mg protein for the Saline-Saline, Saline-Quinpirole, and Ro 41-1049-Quinpirole groups, respectively. For clarity, data for the Ro 41-1049–Saline and Saline-Acute Quinpirole groups are not shown.

Table 1

Effects of sensitization to quinpirole, with and without pre-treatment with Ro 41-1049, on [^{3}H]spiperone and [^{3}H]quinpirole binding in the nucleus accumbens.

Pre-treatment/Treatment		[^{3}H]Spiperone (fmol/mg protein)	[^{3}H]Quinpirole (fmol/mg protein)	% High Affinity	%MQB
Saline	Saline	44 ± 4.3	19 ± 1.7	49 ± 4.7	52 ± 3.0
Saline	Quinpirole	58 ± 4.0[a]	25 ± 1.6 [a]	48 ± 5.0	49 ± 1.9
Ro 41-1049	Quinpirole	40 ± 2.4[b]	22 ± 1.5	55 ± 4.9	44 ± 1.6
Ro 41-1049	Saline	46 ± 2.0 [b]	20 ± 1.4 [b]	43 ± 2.6	47 ± 1.7
Saline	Acute Quinpirole	51 ± 5.4	19 ± 1.9 [b]	45 ± 3.6	47 ± 3.1

Data are presented as the mean ± S.E.M. (n = 8 for Saline-Saline, n = 10 for all other groups). Receptor binding data is from single-point assays using tissue from each individual animal with the concentration of radioligand at the K_D. The percentage of monoamine-displaceable [^{3}H]quinpirole binding (%MQB) was determined in the presence of Ro 41-1049 (10 μM).

[a] P<0.05 v. Saline-Saline;

[b] P<0.05 v. Saline – Quinpirole by analysis of variance and the Student-Newman-Keuls tests.

Table 2

Effects of sensitization to quinpirole, with and without pre-treatment with Ro 41-1049, on [^{3}H]spiperone and [^{3}H]quinpirole binding in the striatum.

Pre-treatment	Treatment	[^{3}H]Spiperone (fmol/mg protein)	[^{3}H]Quinpirole (fmol/mg protein)	% High Affinity	%MQB
Saline	Saline	78 ± 4.3	45 ± 2.4	58 ± 3.7	63 ± 3.5
Saline	Quinpirole	76 ± 5.7	48 ± 3.3	61 ± 3.1	67 ± 3.0
Ro 41-1049	Quinpirole	68 ± 5.4	39 ± 2.9	57 ± 2.2	60 ± 2.7
Ro 41-1049	Saline	64 ± 2.0	39 ± 1.9	62 ± 2.6	56 ± 2.0
Saline	Acute Quinpirole	75 ± 4.9	41 ± 3.2	54 ± 9.8	62 ± 3.5

Data are presented as the mean ± S.E.M. (n = 8 for Saline-Saline, n = 10 for all other groups). Receptor binding data is from single-point assays using tissue from each individual animal with the concentration of radioligand at the K_D. The percentage of monoamine-displaceable [^{3}H]quinpirole binding (%MQB) was determined in the presence of Ro 41-1049 (10 μM). No significant differences between groups were detected by analysis of variance.