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Disruption of $G_{i/o}$ protein signaling in the nucleus accumbens results in a D1 dopamine receptor-mediated hyperactivity

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Abstract

Intra-accumbens infusion of pertussis toxin (PTX) results in a progressive and persistent locomotor hyperactivity and sensitizes rats to the locomotor-activating effects of cocaine. The present study further defined the hyperactivity resulting from inactivation of accumbens G_i/G_o proteins and tested the hypothesis that PTX-induced hyperactivity is mediated by dopamine D1 receptors. PTX (0.15 μg/side) infused bilaterally into the nucleus accumbens of rats resulted in a progressive increase in locomotor activity that peaked at 218% of preinjection activity levels 15 days after injection and persisted for greater than 5 weeks postinjection. Administration of the D1 receptor antagonist SCH23390 16 and 23 days after PTX injections dose dependently attenuated PTX-induced hyperactivity. D1 receptor blockade did not significantly alter activity in sham-injected animals. These findings support the hypothesis that the hyperactivity resulting from PTX-mediated inactivation of $G_{i/o}$ proteins reflects increased nucleus accumbens D1 receptor activation and suggest that striatal D1 receptors are important mediators of activity-related behavior, such as cocaine-induced hyperactivity.

Keywords: G-protein; cAMP; Cocaine; Adenylyl cyclase; Rat; SCH23390

1. Introduction

The dopaminergic projection from the ventral midbrain to the nucleus accumbens is a key component of motor functioning. Numerous studies have demonstrated that both lesioning of dopamine terminals (Kelly and Iversen, 1976) or increasing dopamine levels (Staton and Solomon, 1984; Carr and White, 1987; Delfs et al., 1990) in the nucleus accumbens can have inverse and profound effects on locomotor activity. Motor activity is mediated by two main classes of dopamine receptors (D1- and D2-like) which are expressed in the nucleus accumbens (Gerfen et al., 1990). Attempts to define the relative contributions of D1 versus D2 receptor subtypes to locomotor behavior using intra-accumbens administration of selective agonists and antagonists for D1 or D2 receptor subtypes suggest that both subtypes are important for locomotor behavior (Pijnenburg et al., 1975; Andén, 1977; Molloy and Waddington, 1984; Molloy et al., 1986; Dreher and Jackson, 1989). Several studies have suggested that a synergistic interaction between D1 and D2 receptors is needed for the expression of most dopamine-related behaviors (Braun and Chase, 1986; Walters et al., 1987).

While dopamine receptor-mediated behavior has been extensively investigated, somewhat less is known about the role of D1/D2 receptor signal transduction mechanisms and their relationship to behavior. D1-like receptors are coupled to the stimulatory G-proteins G_s/G_{olf} and increase cAMP production through adenylyl cyclase activation (Stoof and Kebabian, 1981; Sibley et al., 1993; Zhuang et al., 2000). D2-like receptors are coupled to inhibitory G-proteins G_i/G_o and inhibit adenylyl cyclase resulting in a reduction of cAMP levels (Stoof and Kebabian, 1981; Sibley et al., 1993). Because D1 and D2 receptor activation has opposing effects on adenylyl cyclase, the signal transduction mechanisms employed by these receptors in the nucleus accum-

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bens are likely to be of critical importance when considering the neurobiological components of locomotor behavior.

The bacterial toxin pertussis toxin (PTX) has proven to be a useful tool for examining G-protein-coupled receptor signaling pathways in both cell culture and whole animal preparations. PTX ADP-ribosylates G_i/G_o proteins inactivating and uncoupling them from their receptors (Murayama and Ui, 1983). PTX injected into the ventral tegmental area (VTA) has no significant effect on motor activity alone; however, intra-VTA PTX has profound effects on striatal dopamine levels as well as an animal's behavioral response to the indirect nonselective dopamine receptor agonists cocaine (Steketee et al., 1990, 1992; Striplin and Kalivas, 1992), apomorphine (Narayanan et al., 1997) or amphetamine (Weinstein et al., 1997). Injection of PTX into the striatum interrupts D2 receptor signaling, disinhibiting adenylyl cyclase which results in an increase in cAMP production (Fujita et al., 1985; Olianas and Onali, 1987). While intracranial injection of PTX clearly affects D2 receptor signaling, the behavioral effects of interrupting D2 receptor signaling in the striatum is not as well defined. In a previous study, we demonstrated that intra-accumbens PTX sensitizes rats to the locomotor-activating effects of a single cocaine challenge (Hummel and Unterwald, 2003). The present study sought to further define the hyperactivity resulting from intra-accumbens PTX injection by examining the time course of the development and persistence of PTX's effect. We also sought to determine if PTX-induced hyperactivity was attributed to excess activation of the D1 receptor signaling pathway and hence can be attenuated by the D1 receptor antagonist SCH23390.

2. Materials and methods

2.1. Animals

Eighteen male Fischer rats (150–175 g; Charles River Laboratories, Raleigh, NC) were housed individually and maintained on a 12-h light/dark cycle (lights off at 1900 h, lights on at 0700 h). Animals were acclimatized to the animal facility for 1 week prior to surgery and received food and water ad libitum throughout the experiment. All experiments were conducted according to the guidelines set forth by the Institutional Animal Care and Use Committee at Temple University School of Medicine and the *National Institutes of Health Guide for Care and Use of Laboratory Animals* (Publication No. 85-23, revised 1985).

2.2. Experimental design

Animals were assigned to one of four experimental groups named and defined as follows: PTX-SCH0.5 ($n=5$): animals received bilateral intra-accumbens PTX injections (0.15 μg/side) on Day 0 and intraperitoneal SCH23390 injections (0.5 mg/kg) on Days 16 and 23. PTX-SCH0.1 ($n=5$): animals received bilateral intra-accumbens PTX injections (0.15 μg/side) on Day 0 and intraperitoneal SCH23390 injections (0.1 mg/kg) on Days 16 and 23. PTX-SAL ($n=4$): animals received bilateral intra-accumbens PTX injections (0.15 μg/side) on Day 0 and intraperitoneal saline injections (1 ml/kg) on Days 16 and 23. Sham-SCH0.5 ($n=4$): animals received bilateral intra-accumbens saline injections (1.0 μl/side) on Day 0 and

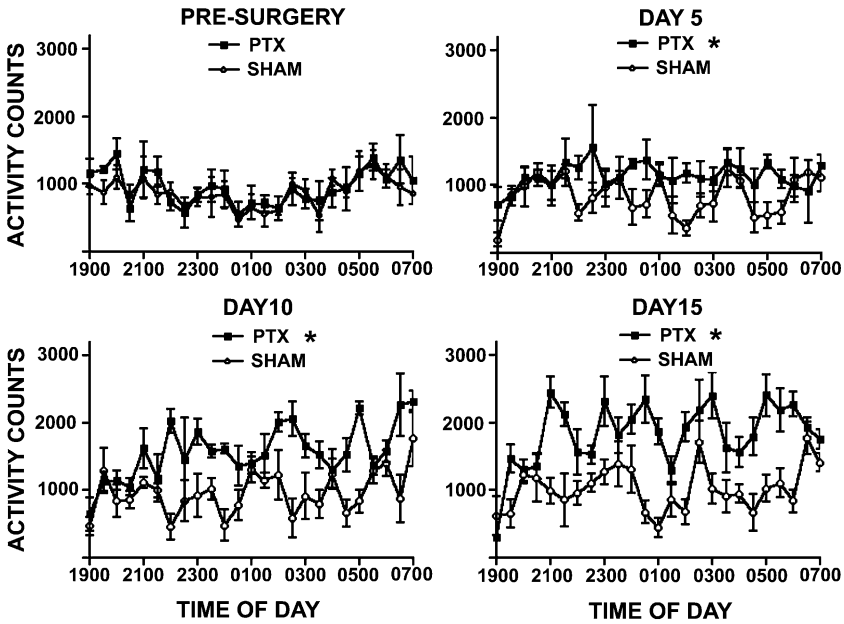

Fig. 1. The effects of a single bilateral intra-accumbens injection of PTX (0.15 μg/side) on motor activity on Days 5, 10 and 15 postinjection. Each graph displays the pattern of activity over the course of 12 h from 1900 to 0700 h during the active portion of the animals' light/dark cycle. Each symbol represents the mean (± S.D.) activity recorded as the total number of beam breaks over a 30-min time period. Significant differences in the mean activity between groups were detected on Days 5, 10 and 15 postinjection (* $P<.0001$, two-way ANOVA).

intraperitoneal SCH23390 injections (0.5 mg/kg) on Days 16 and 23.

2.3. Intracranial injections

Animals were anesthetized with Telazol (40 mg/kg ip) and placed in a Kopf stereotaxic frame fitted with a 1-μl Hamilton syringe. The skull was exposed and the needle tip lowered into the nucleus accumbens at the coordinates +1.9 mm anteroposterior, ±1.6 mm lateromedial and −7.5 mm dorsoventral relative to bregma according to the atlas of Paxinos and Watson (1986). PTX (CalBiochem, 0.15 μg dissolved in 1 μl sterile saline) or sterile saline (1 μl) was infused bilaterally by gradually advancing the syringe plunger at a rate of 0.2 μl/min. The needle remained in place after the infusion for 5 min before removal and closure of the wound.

2.4. Behavioral monitoring

Activity was monitored using a Digiscan DMicro System activity monitoring system (Acuscan, Columbus, OH). The animal's home cage complete with food and water was placed into an aluminum frame equipped with 16 computer-monitored infrared photocell beams and detectors. Each animal's activity was monitored every day from 1900 to 0700 h starting 3 days prior to PTX injection until 4 weeks after PTX injection. On Days 16 and 23, animals received an intraperitoneal injection of either saline (1.0 ml/kg) or SCH23390 (0.5 or 0.1 mg/kg) at 2200 h.

3. Results

Preliminary data suggested that PTX-induced hyperactivity was most evident during the dark phase of the light/dark cycle when rats are generally most active. Therefore, we chose to monitor activity from 1900 (lights off) to 0700 (lights on) h. Bilateral intra-accumbens PTX injections resulted in a progressive and persistent increase in activity that developed over the course of 2 weeks and peaked 15 days after PTX administration. Fig. 1 shows a comparison of the activity of all rats that received bilateral PTX injections at

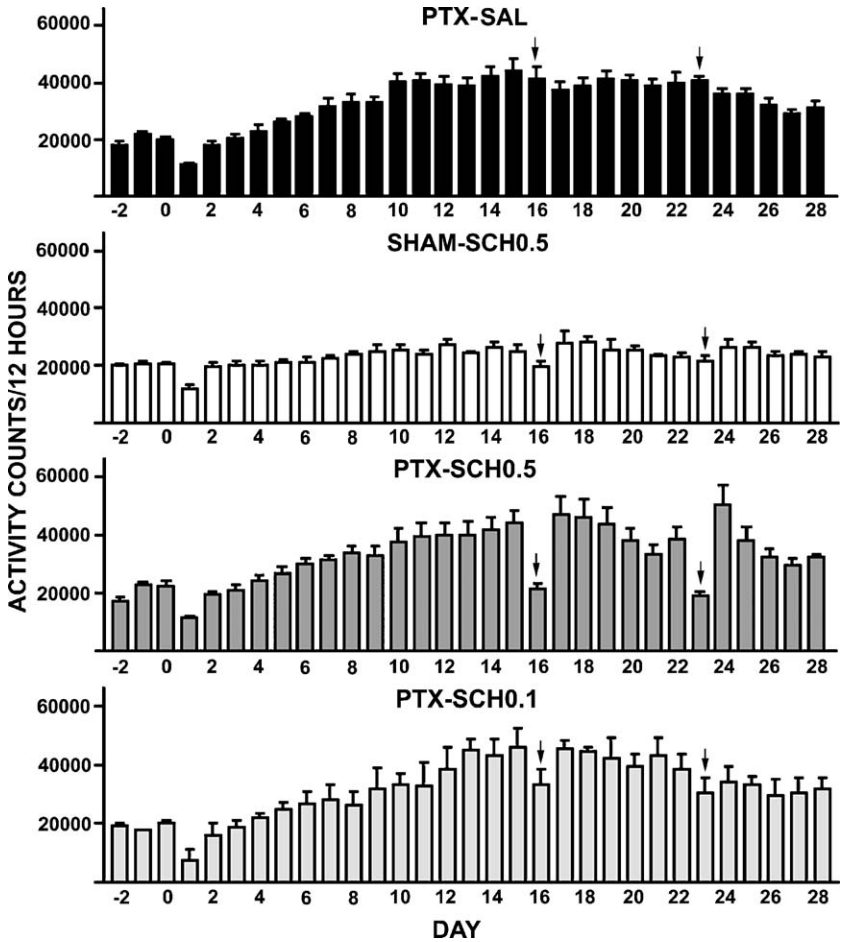

Fig. 2. Time course of the development of PTX-induced hyperactivity. Each graph represents the mean total cumulative activity of animals in one experiment group over the course of 12 h (1900 to 0700 h) beginning 2 days prior to surgery extending to 28 days postsurgery. Rats in the PTX-SCH0.5, PTX-SCH0.1 and PTX-SAL groups received a bilateral intra-accumbens PTX injection (0.15 μg/side) on Day 0. Rats in the SHAM-SCH0.5 group received an intra-accumbens injection of saline (1μl/side) on Day 0. The arrows on each graph indicate that on Days 16 and 23, animals received an intraperitoneal injection of either 1 ml/kg saline (PTX-SAL) at 2200 h, 0.5 mg/kg SCH23390 (PTX-SCH0.5 and SHAM-SCH0.5 groups) or 0.1 mg/kg SCH23390 (PTX-SCH0.1 group).

a dose of 0.15 μg/side (PTX) versus sham-injected (SHAM) rats from 1900 to 0700 h on the day prior to surgery (presurgery) and 5, 10 and 15 days after surgery. Each symbol represents the mean (± S.D.) activity counts recorded over 30-min increments. By Day 5 postinjection, rats that received intra-accumbens PTX displayed a significant increase in mean activity recorded from 1900 to 0700 h compared to rats that received intra-accumbens saline injections [$F(1,24) = 19.63$, $P < .0001$]. PTX-treated rats continued to display significantly elevated levels of activity on Day 10 [$F(1,24) = 74.07$, $P < .0001$] an effect that peaked on Day 15 [$F(1,24) = 76.53$, $P < .0001$] following PTX injection.

Fig. 2 displays the mean cumulative activity from 1900 to 0700 h for each treatment group beginning 2 days prior to surgery until 28 days following surgery. Animals in the PTX-SAL group received an intraperitoneal injection of sterile saline (1 ml/kg) on Days 16 and 23. Rats in the PTX-SCH0.5 and SHAM-SCH0.5 groups received an intraperitoneal injection of SCH23390 (0.5 mg/kg) and rats in the PTX-SCH0.1 group received 0.1 mg/kg SCH23390 on Days 16 and 23. Data were transformed to show the mean percent decrease in activity from Day 15 to Day 16 for each group (Fig. 3A). One-way analysis of variance (ANOVA) revealed a significant main effect of treatment group [$F(3,18) = 9.827$, P=.0008]. Bonferroni posttests showed significant differences in percent decrease in total activity from Day 15 to Day 16 between the PTX-SCH0.5 and SHAM-SCH0.5 groups ($P < .05$), and between the PTX-SCH0.5 and the PTX-SAL groups ($P < .001$). These results demonstrate that SCH23390 at a dose of 0.5 mg/kg can significantly attenuate PTX-induced activity. SCH23390 at a dose of 0.1 mg/kg attenuated PTX-induced hyperactivity; however, this effect was not statistically significant when compared to the PTX-SAL group. Fig. 3B shows the mean percent decrease from Day 22 to Day 23 for each treatment group. One-way ANOVA revealed a significant main effect of treatment group [$F(3,18) = 48.82$, $P < .0001$]. On Day 23, both doses of SCH23390 resulted in significant attenuation of PTX-induced hyperactivity (PTX-SCH0.5 versus PTX-SAL, $P < .001$; PTX-SCH0.1 versus PTX-SAL, $P < .001$). This effect was dose dependent as posttests revealed a significant difference between the activity of the PTX-SCH0.5 and PTX-SCH0.1 groups ($P < .01$). In a separate preliminary study, administration of the selective D2 receptor antagonist eticlopride (1.0 mg/kg) administered 16 days after bilateral intra-accumbens PTX injections in two animals was without effect on PTX-induced hyperactivity (Fig. 3A). A 12-h time-course comparison of the activity of PTX-SCH0.5 versus Sham-SCH0.5 animals on Day 16 is displayed in Fig. 4A. The activity of animals in the PTX-SCH0.5 versus Sham-SCH0.5 groups from 2200 (intraperitoneal injection time) to 0700 h on Day 16 was not significantly different. The activity of animals in the PTX-SCH0.5 group on Day −2

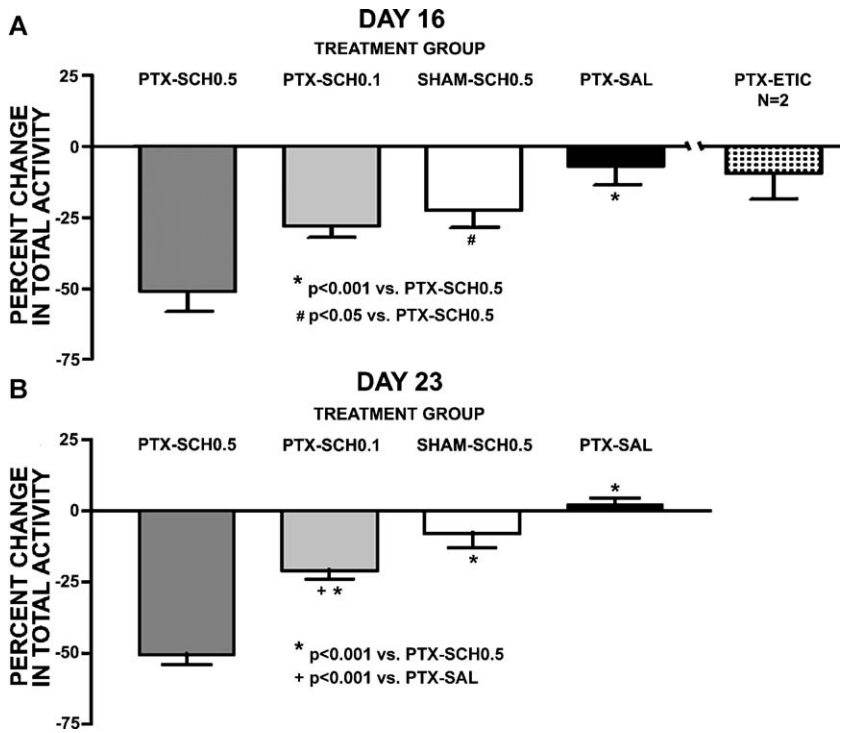

Fig. 3. Mean (± S.D.) percent change in total activity from Day 15 to Day 16 (A) and from Day 22 to Day 23 (B) for each experimental group. On Day 16 (A), PTX-treated rats that received SCH23390 (0.5 mg/kg) displayed a significant attenuation of PTX-induced hyperactivity compared to both the SHAM-SCH0.5 ($^{\#}P < .05$) and PTX-SAL ($^{*}P < .001$) groups. On Day 23 (B), both doses of SCH23390 were effective at attenuating PTX-induced hyperactivity (PTX-SCH0.5 versus PTX-SAL, $^{*}P < .001$; PTX-SCH0.1 versus PTX-SAL, $^{+}P < .001$). In a separate preliminary study, eticlopride (1.0 mg/kg) did not affect PTX-induced hyperactivity 16 days after PTX administration (PTX-ETIC).

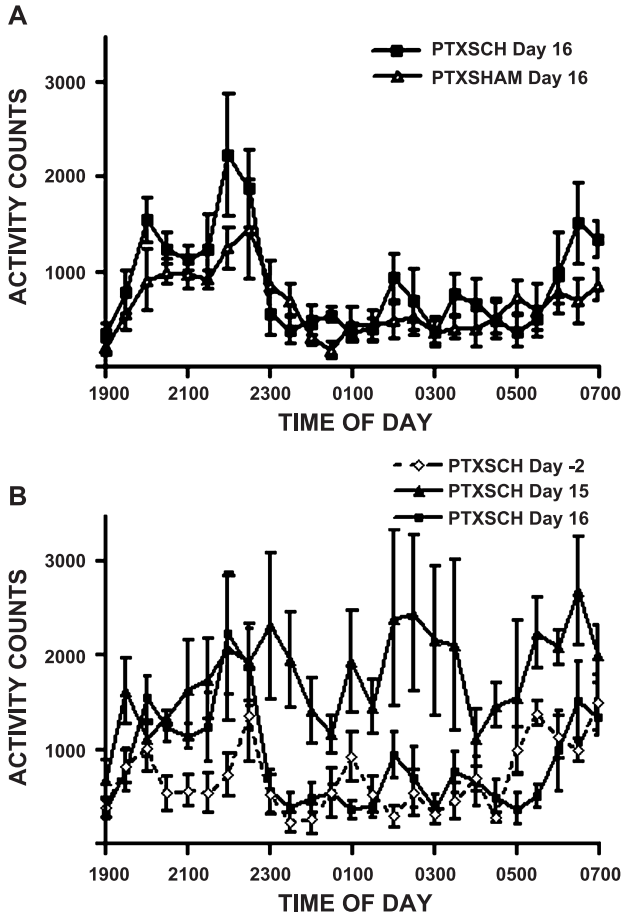

Fig. 4. (A) Comparison of the time course of the effects of SCH23390 (0.5 mg/kg) on Day 16 in PTX-injected versus sham-injected animals. D1 receptor antagonism by SCH23390 reduces PTX-induced hyperactivity to levels observed in sham-injected animals without producing a cataleptic effect. (B) Comparison of the activity of animals in the PTX-SCH0.5 group 2 days prior to PTX-injection, 15 days following PTX injection and 16 days following PTX-injection after receiving SCH23390 (0.5 mg/kg). SCH23390 reduces PTX-induced hyperactivity to levels observed prior to PTX-injection (baseline).

(pre-PTX), Day 15 (PTX) and Day 16 (PTX + SCH23390) is displayed in Fig. 4B. There was no significant difference between the activity of animals in the PTX-SCH0.5 group on Day −2 versus Day 16. However, activities on both Day −2 (baseline) and Day 16 (PTX + SCH23390) were significantly lower than that on Day 15 (PTX alone). These comparisons are provided to demonstrate that SCH23390 (0.5 mg/kg) did not have a cataleptic effect. SCH23390 administration reduced activity to baseline (Day −2) or to the level of sham-injected animals.

4. Conclusions

PTX-mediated ADP-ribosylation of inhibitory G-proteins in the rat nucleus accumbens produced a progressive and persistent locomotor hyperactivity. PTX-induced hyperactivity developed over the course of 2 weeks and peaked 15 days postinjection at 218% of preinjection activity. This effect was manifest by monitoring activity over the course of 12 h during the active part of the rats' light/dark cycle. Intra-accumbens PTX injection produced a prolonged effect on activity as evidenced by the observation that the activity of PTX-injected animals remained elevated 28 days post-PTX injection. This gradual and persistent effect supports previous studies which have demonstrated that PTX steadily and continually ADP-ribosylates inhibitory G-proteins (Gilman, 1987; Ui and Katada, 1990), and by studies examining the behavioral effects of intracranial PTX injection which show a gradual development of PTX's behavioral effects (Steketee et al., 1990, 1992; Self et al., 1994; Hummel and Unterwald, 2003). Thus, it appears that the slow appearance and long-lasting effect of PTX on activity is dependent upon the degree of G-protein inactivation and suggests that signal transducers, particularly $G_{i/o}$ proteins, play an important role in the expression of accumbens-mediated locomotion. This study adds to a growing body of evidence suggesting that disruption of signal transduction mechanisms has profound effects on dopamine-related behavior (Miller and Kelly, 1975; Steketee et al., 1990; Steketee et al., 1991; Steketee et al., 1992; Cunningham and Kelley, 1993; Self et al., 1994; Hummel and Unterwald, 2003; Culm et al., 2003).

A single intraperitoneal injection of the D1 receptor antagonist SCH23390 (0.5 mg/kg) attenuated PTX-induced hyperactivity 16 or 23 days after PTX injection. We chose to evaluate the effect of D1 receptor antagonism on these days because the peak effect of PTX was evidenced on Day 15. Following SCH23390 administration on Day 16, animals displayed a slight "rebound" in activity on Day 17 (Fig. 2); therefore, Day 23 (1 week later) was chosen for subsequent SCH23390 administration to insure that any residue effects of previous SCH23390 administration were minimized. In a preliminary study conducted on two animals, the D2 receptor antagonist eticlopride failed to attenuate PTX-induced hyperactivity 16 days post-PTX injection (Fig 3A). These findings suggest that ADP-ribosylation of G_i proteins by intra-accumbens PTX administration reduces D2 while enhancing D1 receptor signaling resulting in a D1 receptor-mediated hyperactivity.

Evidence suggests that a balance between D1- and D2-receptor-mediated signaling in the nucleus accumbens is critical for dopamine-related behaviors (Braun and Chase, 1986; Walters et al., 1987). ADP-ribosylation and inactivation of inhibitory G-proteins coupled to D2 receptors presumably alters the balance of accumbens dopamine signaling in favor of the D1 receptor signaling pathway. In an earlier report from this laboratory, intra-accumbens PTX injection did not alter D1 receptor number in the striatum 21 days following PTX injection (Hummel and Unterwald, 2003). Taken together, our studies suggest that the hyperactivity resulting from intra-accumbens PTX administration is mediated by the relative increase in D1 receptor-mediated signaling in the nucleus accumbens rather than the level of D1 receptor expression. PTX not

only attenuates dopamine-mediated D2 receptor inhibition of adenylyl cyclase cAMP production, but has the added effect of enhancing D1 receptor stimulation of adenylyl cyclase in the rat striatum (Olianas and Onali, 1987). It can be hypothesized that the downstream effects of dopamine receptor activation (i.e., adenylyl cyclase activation and production of cAMP, as well as phospholipase C generation of inositol phosphate and diacylglycerol) are the crucial factors governing motor and/or dopamine-related behavior. Recently, we have demonstrated that intracranial forskolin enhances the locomotor-activating effects of cocaine (Schroeder et al., 2004). Forskolin directly activates adenylyl cyclase independent of receptor activation. In addition, it has been demonstrated that deletion of the gene for adenylyl cyclase V, the major form of adenylyl cyclase in the striatum, results in mice with severe parkinsonian-like motor dysfunctions (Iwamoto et al., 2003), suggesting that adenylyl cyclase V and hence cAMP are important contributors to motor activity.

It is possible that PTX inactivation of $G_{i/o}$ proteins associated with receptors other than D2 receptors contributes to the effects observed in this study. Such an influence may involve metabotropic glutamate, serotonin and or opioid receptors, all of which couple to inhibitory G-proteins. This possibility is worthy of additional investigation. The specific findings of this study illustrate the importance of dopamine receptor signal transducers and downstream effectors as mediators of motor activity, and in conjunction with other reports, support the hypothesis that increased D1 receptor signaling and or excess adenylyl cyclase activation and cAMP production are associated with locomotor hyperactivity, whereas interference with the D1 receptor signaling pathway results in motor deficits.

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