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Opposing roles for dopamine D_1 and D_2 receptors in the regulation of hypothalamic tuberoinfundibular dopamine neurons

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Abstract

The purpose of the present study was to characterize pharmacologically dopamine D_1 receptor-mediated inhibition of tuberoinfundibular dopamine neurons in males rats, and to determine if inhibitory dopamine D_1 receptors oppose stimulatory dopamine D_2 receptors and account for the inability of mixed dopamine receptor agonists to alter the activity of these neurons. Tuberoinfundibular dopamine neuronal activity was estimated by measuring the concentrations of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the median eminence, the region of the hypothalamus containing terminals of these neurons. Administration of the dopamine D_1 receptor agonist (±)-1 phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol (SKF38393) decreased median eminence DOPAC and increased plasma prolactin concentrations, whereas administration of the dopamine D_1 receptor antagonist ((−)-*trans*,6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5*H*-benzo[*d*]naphtho-[2,1*b*]azepine (SCH39166) increased median eminence DOPAC concentrations but had not effect on plasma prolactin. The inhibitory effect of SKF38393 on median eminence DOPAC concentrations was blocked by SCH39166. These results demonstrate that acute activation of dopamine D_1 receptors inhibits the activity of tuberoinfundibular dopamine neurons and thereby increases prolactin secretion, and that under basal conditions dopamine D_1 receptor-mediated inhibition of tuberoinfundibular dopamine neurons is tonically active. Administration of the dopamine D_2 receptor agonist (5a*R-trans*)-5,5a,6,7,8,9,9a,10-octahydro-6-propyl-pyridol[2,3-*g*]quinazolin-2-amine (quinelorane) increased median eminence DOPAC concentrations, and SKF38393 caused a dose-dependent reversal of this effect. Administration of the mixed dopamine D_1/D_2 receptor agonist *R*(−)-10,11-dihydroxy-apomorphine (apomorphine) had no effect per se, but blocked quinelorane-induced increases in DOPAC concentrations in the median eminence. These results reveal that concurrent activation of dopamine D_1 and D_2 receptors nullifies the actions of each of these receptors on tuberoinfundibular dopamine neurons, which likely accounts for the lack of an acute effect of mixed dopamine D_1/D_2 receptor agonists on these hypothalamic dopamine neurons.

Keywords: Dopamine D_1 receptor agonist; Dopamine D_2 agonist; SKF38393; Quinelorane; Apomorphine; Dopamine D_1 receptor antagonist; SCH39166; DOPAC (3,4-dihydroxyphenyl acetic acid); Median eminence

1. Introduction

Tuberoinfundibular dopamine neurons located in the hypothalamic arcuate nucleus project to the median eminence. Dopamine released from terminals of these neurons is transported in the hypophysial portal blood to the anterior pituitary where it inhibits prolactin secretion from lactotrophs (Moore and Lookingland, 1995). Tuberoinfundibular dopamine neurons lack dopamine autoreceptors, and are unresponsive to acute administration of non-selective dopamine agonists (e.g., apomorphine) which do not discriminate between D_1-like and D_2-like subtype families of the dopamine receptor (Demarest and Moore, 1979). Rather, tuberoinfundibular dopamine neurons are regulated by prolactin secreted by anterior pituitary lactotrophs, and increases or decreases in circulating prolactin produce corresponding changes in the activity of these neurons. By virtue of their ability to alter prolactin secretion via an

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action on dopamine D_2 receptors in the anterior pituitary, non-selective dopamine agonists and antagonists act indirectly to cause delayed alterations in the activity of tuberoinfundibular dopamine neurons (Moore and Lookingland, 1995).

More recently, utilization of second generation agonists which differentiate between the D_1-like and D_2-like subtype families of dopamine receptors (Jackson and Westlind-Danielsson, 1994) has revealed that tuberoinfundibular dopamine neurons are also regulated by a dopamine receptor-mediated mechanism which acts independently of prolactin (Eaton et al., 1993). Indeed, acute administration of dopamine agonists with preferential affinity for the dopamine D_2 family of dopamine receptors (i.e., quinpirole (Titus et al., 1983) and quinelorane (Bymaster et al., 1986; Foreman et al., 1989)) stimulates the activity of tuberoinfundibular dopamine neurons (Berry and Gudelsky, 1991; Eaton et al., 1993). This stimulatory action of dopamine D_2 receptor agonists appears to occur via an afferent neuronal mechanism involving, in part, disinhibition of tonically active dynorphinergic interneurons (Durham et al., 1996). The inability of dopamine D_2 receptor antagonists to alter the activity of tuberoinfundibular dopamine neurons per se suggests that there is little intrinsic endogenous dopamine agonism of the dopamine D_2 receptor under basal conditions (Eaton et al., 1993). Conversely, acute administration of dopamine D_1 receptor agonists inhibit 'activated' tuberoinfundibular dopamine neurons, but have little effect on the basal activity of these neurons (Berry and Gudelsky, 1990). The opposing actions of stimulatory dopamine D_2 and inhibitory dopamine D_1 receptors could account for the net lack of effect of mixed dopamine D_1/D_2 receptor agonists on tuberoinfundibular dopamine neurons.

The purpose of the present study was to characterize the regulation of tuberoinfundibular dopamine neurons by dopamine D_1 receptors, and to determine if activation of these receptors nullifies the stimulatory action of dopamine D_2 receptor agonists. To this end, the effects of the selective dopamine D_1 receptor agonist SKF38393 (Sibley et al., 1982) and dopamine D_1 receptor antagonist SCH39166 (Chipkin et al., 1988) were examined on the activity of tuberoinfundibular dopamine neurons as determined by measuring the concentrations of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the median eminence. Next, the ability of SKF38393 and apomorphine to reverse the stimulatory effect of the dopamine D_2 agonist quinelorane on tuberoinfundibular dopamine neurons was assessed. The results reveal that in the male rat tuberoinfundibular dopamine neurons are tonically regulated by inhibitory dopamine D_1 receptors, and suggest that the inability of mixed dopamine receptor agonists with affinity for both dopamine D_1 and dopamine D_2 receptors to affect these neurons may results from concurrent stimulation of these functionally antagonistic dopamine receptor subtypes.

2. Materials and methods

2.1. Animals

Male Long–Evans rats weighing 200–225 g were obtained from Harlan Laboratories (Indianapolis, IN, USA), housed in a temperature- (72 ± 2°F) and light- (lights on between 0500–1900 h) controlled room, and provided food (Wayne Lablox) and tap water ad libitum.

2.2. Drug preparation and administration

(−)-*Trans*-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5*H*-benzo[*d*]naphtho-[2, 1*b*]azepine (SCH39166; Dr. A. Barnett, Schering-Plough, Bloomfield, NJ) was dissolved in 50% ethanol. (±)-1-Phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol HCl (SKF38393; Research Biochemicals International, Natick, MA, USA) was dissolved in 0.1% ascorbic acid. (5a*R-trans*)-5,5a,6,7,8,9,9a,10-octahydro-6-propyl-pyridol[2,3-*g*]quinazolin-2-amine dihydrochloride (quinelorane; Dr. M.M. Foreman, Eli Lilly, Indianapolis, IN, USA) was dissolved in 0.9% saline, and *R*(−)-10,11-dihydroxyapomorphine HCl (apomorphine; Sigma, St. Louis, MO, USA) was dissolved in distilled water. Drugs were administered as indicated in the legends of the appropriate figures; except for SCH39166 doses of drugs were calculated as the respective salts.

2.3. Tissue dissection and biochemical determination of monoamines

Following drug treatments, rats were decapitated and brains were rapidly removed from the skull and frozen on aluminum foil placed over dry ice. Frontal brain sections (600 μm) beginning approximately at 9220 μm (König and Klippel, 1963) were prepared in a cryostat (−9°C), and the median eminence was dissected from appropriate sections according to a modification (Lookingland and Moore, 1984) of the method of Palkovits (1973). Median eminence tissue samples were placed in 65 μl of 0.1 M phosphate–citrate buffer (pH 2.5) containing 15% methanol and stored at −20°C until assayed.

On the day of the assay, tissue samples were thawed, sonicated for 3 s (Sonicator Cell Disruptor, Heat Systems-Ultrasonic, Plainview, NY, USA) and centrifuged for 30 s in a Beckman 152 Microfuge. Contents of DOPAC in supernatants were determined by high performance liquid chromatography coupled with electrochemical detection as described previously (Lindley et al., 1990). The amounts of these compounds in tissue samples were determined by comparing peak heights (as determined by a Hewlett Packard Integrator, Model 3395) with those obtained from external standards run on the same day. The lower limit of sensitivity of this assay for these compounds was approxi-

mately 1 pg per sample. Tissue pellets were dissolved in 1.0 M NaOH and assayed for protein (Lowry et al., 1951).

2.4. Neurochemical estimation of tuberoinfundibular dopamine neuronal activity

The activity of tuberoinfundibular dopamine neurons was estimated by determining concentrations of the dopamine metabolite DOPAC in the median eminence (Lookingland et al., 1987). Due to the tight coupling between the release and metabolism of dopamine and its replenishment by de novo synthesis, tissue concentrations of DOPAC have been shown to reflect the activity of tuberoinfundibular dopamine neurons (Lookingland et al., 1987).

2.5. Radioimmunoassay for plasma prolactin

Trunk blood collected following decapitation was centrifuged for 20 min at 4°C. The plasma was drawn off and stored at −20°C for later determination of prolactin concentrations by double-antibody radioimmunoassay. Prolactin was measured using the reagents and procedures of the NIDDK assay with rat prolactin (Reference Preparation 3) as the standard (generously provided by Drs. A.F. Parlow and S. Raiti, NIDDK National Hormone and Pituitary Program). Using a 100-ml aliquot of plasma, the lower limit of sensitivity for prolactin was 120 pg/tube. The intra-assay coefficient of variation for prolactin was approximately 6%.

2.6. Statistical analyses

Statistical analyses were conducted using either one-way (Figs. 1, 2 and 4) or two-way (Figs. 3 and 5) analysis of variance (ANOVA) followed by Bonferroni's *t*-test for multiple comparisons. Differences were considered significant if the probability of error was less than 5%.

3. Results

The effects of incremental doses of the dopamine D_1 receptor agonist SKF38393 on concentrations of DOPAC in the median eminence and prolactin in plasma are depicted in Fig. 1. SKF38393 was administered in this experiment using doses previously shown to be effective in inhibiting 'activated' tuberoinfundibular dopamine neurons (Berry and Gudelsky, 1990). SKF38393 (5, 10 and 20 mg/kg; 1 h; i.p.) decreased median eminence DOPAC concentrations (Fig. 1A), and this was accompanied by corresponding increases in plasma prolactin concentrations (Fig. 1B). The lowest dose of SKF38393 (5 mg/kg) was effective in producing maximal effects on median eminence DOPAC and plasma prolactin in this experiment. The dose response and time course effects of the dopamine D_1 receptor antagonist SCH39166 on DOPAC concentrations in the median eminence are shown in Fig. 2. Blockade of dopamine D_1 receptors with SCH39166 caused dose-related increases in median eminence DOPAC concentrations that were significant at doses of 1 and 3 mg/kg (2 h; s.c.; Fig. 2A). SCH39166 (3 mg/kg; s.c.) significantly elevated median eminence DOPAC concentrations by 1 h, and this effect lasted at least an additional 7 h. By 16 h post injection, values in SCH39166-treated rats were not different from those determined in vehicle-injected zero time controls (Fig. 2B). In contrast, SCH39166 had no effect on plasma prolactin concentrations at any of the doses or times examined in these experiments (data not shown). As shown in Fig. 3, the inhibitory effect of

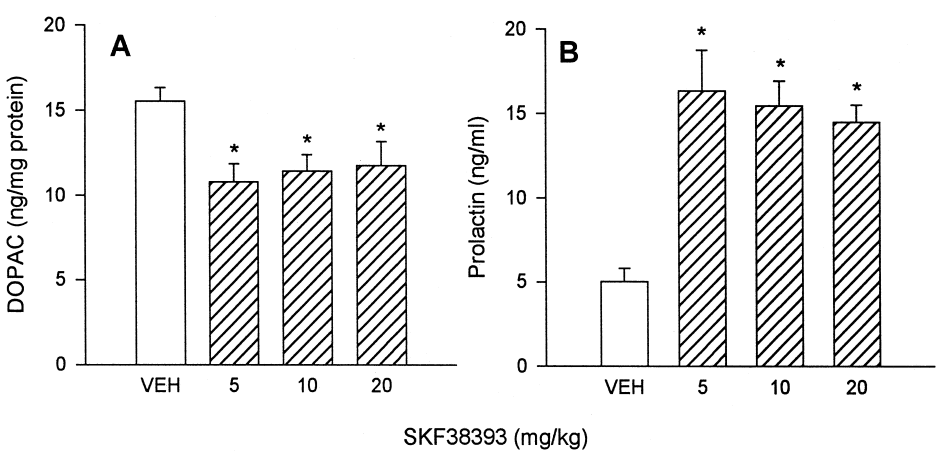

Fig. 1. Effects of SKF38393 on DOPAC concentrations in the median eminence (Panel A) and prolactin concentrations in the plasma (Panel B). Rats were injected i.p. with either SKF38393 (5, 10 or 20 mg/kg) or its 0.1% ascorbic acid vehicle (1 ml/kg) and killed by decapitation 1 h later. Columns represent means and vertical lines 1 S.E.M. of concentrations of DOPAC (Panel A) and prolactin (Panel B) sampled from 7–8 rats. ∗Values for SKF38393-treated rats (hatched columns) that are significantly different ($P < 0.05$) from vehicle-treated controls (VEH; open columns).

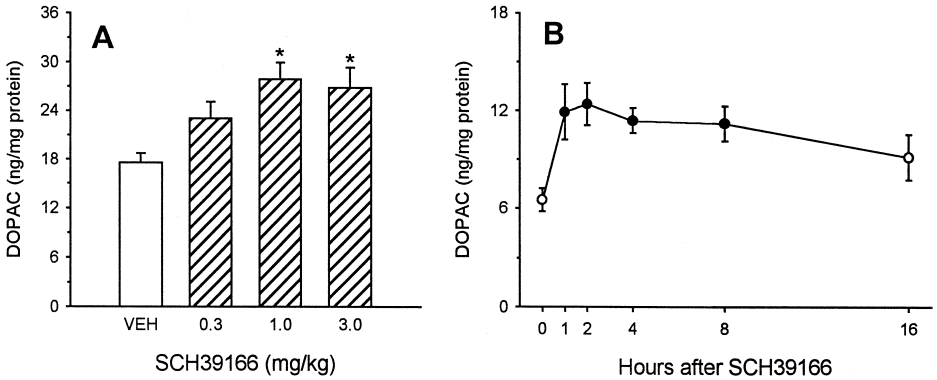

Fig. 2. Dose response (A) and time-course (B) effects of SCH39166 on median eminence DOPAC concentrations. (A) Rats were injected s.c. with either SCH39166 (0.3, 1 or 3 mg/kg) or its 50% ethanol vehicle (1 ml/kg) and killed by decapitation 2 h later. Columns represent means and vertical lines 1 S.E.M. of DOPAC concentrations in the median eminence sampled from 7–9 rats. ∗Values for SCH39166-treated rats (hatched columns) that are significantly different ($P < 0.05$) from vehicle-treated controls (VEH; open column). (B) Rats were injected with SCH39166 (3 mg/kg; s.c.) and decapitated either 1, 2, 4, 8 or 16 h later. Zero time controls were injected with vehicle (50% ethanol; 1 ml/kg; s.c.) 1 h prior to decapitation. Symbols represent means and vertical lines 1 S.E.M. of DOPAC concentrations in the median eminence sampled from 7–9 male rats. Solid symbols represent those values that are significantly different ($P < 0.05$) from zero time controls.

SKF38393 (20 mg/kg; 1 h) on median eminence DOPAC concentrations was blocked by pre-treatment with SCH39166 (3 mg/kg; s.c.; 2 h), i.e., there was no difference in median eminence DOPAC concentrations between vehicle- and SKF38393 + SCH39166-treated rats, whereas values for SKF38393-treated rats were lower than those obtained in either of these groups. Consistent with results shown in Fig. 1, administration of SCH39166 in the absence of SKF38393 increased median eminence DOPAC concentrations (Fig. 3). There was no significant interaction between SKF38393 and SCH39166 on median eminence DOPAC concentrations in this study ($P = 0.395$; two way ANOVA). Taken together, these results reveal that acute pharmacological activation of dopamine D_1 receptors inhibits the activity of tuberoinfundibular dopamine neurons, and that under basal conditions dopamine D_1 receptor-mediated inhibition of these neurons is tonically active.

Previous studies have demonstrated that acute pharmacological activation of dopamine D_2 receptors stimulates tuberoinfundibular dopamine neurons (Berry and Gudelsky, 1991; Eaton et al., 1993; Durham et al., 1996, 1997). This and the results depicted in Figs. 1–3 suggest that concurrent activation of dopamine D_1 and dopamine D_2 receptors have opposing actions on tuberoinfundibular dopamine neurons, which could account for the inability of mixed dopamine D_1/D_2 receptor agonists to affect these

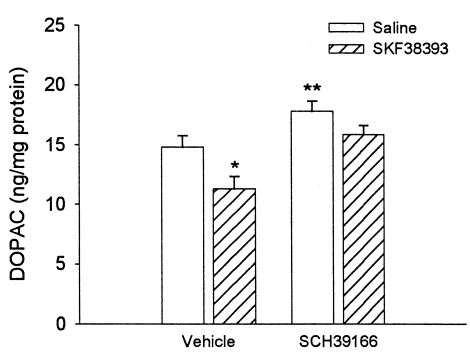

Fig. 3. Effects of SKF38393 on median eminence DOPAC concentrations in vehicle- and SCH39166-treated rats. Rats were injected with either SCH 39166 (3 mg/kg; s.c.) or its 50% ethanol vehicle (1 ml/kg; s.c.) 2 h prior to decapitation and with either SKF38393 (20 mg/kg) or its 0.1% ascorbic acid vehicle (1 ml/kg; i.p.) 1 h prior to decapitation. Columns represent means and vertical lines 1 S.E.M. of median eminence DOPAC concentrations sampled from 7–8 rats. ∗Values for SKF38393-treated rats (hatched columns) that are significantly different ($P < 0.05$) from vehicle-treated controls (open columns). ∗∗Values for SCH39166-treated rats that are significantly different ($P < 0.05$) from saline-treated controls.

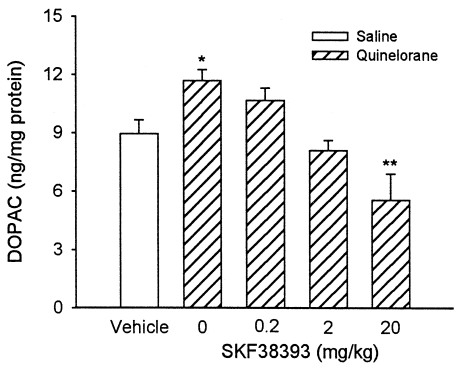

Fig. 4. Dose–response effects of SKF38393 on DOPAC concentrations in the median eminence of quinelorane-treated rats. Rats were injected with either quinelorane (100 μg/kg; i.p.) or its 0.9% saline vehicle (1 ml/kg; i.p.) 60 min prior to decapitation and with either SKF38393 (0.2, 2 or 20 mg/kg; i.p.) or its 0.1% ascorbic acid vehicle (1 ml/kg; i.p.) 60 min prior to decapitation. Columns represent means and vertical lines 1 S.E.M. of median eminence DOPAC concentrations sampled from 6–8 rats. ∗Values for quinelorane-treated rats (hatched columns) that are significantly different ($P < 0.05$) from vehicle-treated controls (open columns). ∗∗Values for SKF38393-treated rats that are significantly different ($P < 0.05$) from saline-treated controls.

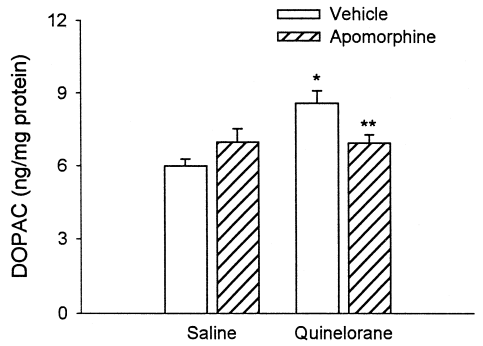

Fig. 5. Effects of apomorphine on median eminence DOPAC concentrations in vehicle- and quinelorane-treated rats. Rats were injected with either quinelorane (100 μg/kg; i.p.) or its 0.9% saline vehicle (1 ml/kg; i.p.) 60 min prior to decapitation and with either apomorphine (2 mg/kg; s.c.) or its 0.9% saline vehicle (1 ml/kg; s.c.) 30 min prior to decapitation. Columns represent means and vertical lines 1 S.E.M. of median eminence DOPAC concentrations sampled from 6–8 rats. ∗Values for quinelorane-treated rats that are significantly different ($P < 0.05$) from saline-treated controls. ∗∗Values for apomorphine-treated rats (hatched columns) that are significantly different ($P < 0.05$) from quinelorane-treated rats (open columns).

neurons (for review see Moore, 1987). To determine if this is the case, the effects of the dopamine D_1 receptor agonist SKF38393 and the mixed dopamine D_1/D_2 agonist apomorphine were examined on tuberoinfundibular dopamine neurons in rats pre-treated with the dopamine D_2 agonist quinelorane. As shown in Fig. 4, quinelorane (100 μg/kg; i.p.; 1 h) increased median eminence DOPAC concentrations as compared with saline-treated controls. SKF38393 (administered in lower doses than that employed in the experiment depicted in Fig. 1) caused a dose-dependent decrease in median eminence DOPAC concentrations in quinelorane-treated rats; i.e., administration of 2 mg/kg SKF38393 completely reversed the quinelorane-induced increase in median eminence DOPAC concentrations, and 20 mg/kg SKF38393 significantly suppressed median eminence DOPAC concentrations below values determined in saline-treated controls. As shown in Fig. 5, apomorphine had no effect per se, but blocked the ability of quinelorane to increase DOPAC concentrations in the median eminence. There was a significant interaction between quinelorane and apomorphine on median eminence DOPAC concentrations in this study ($P = 0.005$; two-way ANOVA).

4. Discussion

Central dopamine receptors were originally divided into two pharmacologically distinct subtypes on the basis of their biochemical effects on adenylyl cyclase activity (Kebabian and Calne, 1979). Dopamine D_1 receptors are stimulatory and linked to the activation of adenylyl cyclase; whereas dopamine D_2 receptors are inhibitory and suppress adenylyl cyclase. More recent binding and molecular cloning studies have established multiple variants of these receptors which form two separate families, the D_1-like and D_2-like dopamine receptors (Civelli et al., 1993). The dopamine D_1-like family is composed of two subtypes (D_1 and D_5) which are predominantly distributed as postsynaptic receptors (Richtand et al., 1995), whereas the dopamine D_2-like family consists of three subtypes (D_2, D_3 and D_4) which function both as pre- and postsynaptic receptors (Richtand et al., 1995). The discovery of multiple subtypes of the dopamine receptor led to the development of second generation agonists and antagonists selective for D_1- and D_2-like dopamine receptors with utility for studying the role of these receptors in the regulation of central dopamine neurons and their neurological functions. These include the substituted benzazepines SKF38393 (Sibley et al., 1982) and SCH39166 (Chipkin et al., 1988) with D_1-like dopamine receptor affinity, and the ergoline-derived compounds quinpirole (Titus et al., 1983) and quinelorane (Bymaster et al., 1986) with affinity for D_2-like dopamine receptors.

Using these selective pharmacological agents, the results of the present study are consistent with a previous report demonstrating an inhibitory role for dopamine D_1 receptors in the regulation of tuberoinfundibular dopamine neurons in the male rat (Berry and Gudelsky, 1990). Indeed, activation of dopamine D_1 receptors with SKF38393 inhibits, whereas blockade of dopamine D_1 receptors with SCH39166 stimulates the activity of tuberoinfundibular dopamine neurons. This latter finding indicates that in the male rat under basal conditions inhibitory dopamine D_1 receptors are tonically activated by endogenous dopamine, and in this respect, these receptors resemble inhibitory dopamine D_2 autoreceptors which regulate the activity of mesotelencephalic and incertohypothalamic dopamine neuronal systems (Demarest and Moore, 1979; Lookingland and Moore, 1984; Elsworth and Roth, 1997). It is unlikely, however, that dopamine D_1 inhibition of tuberoinfundibular dopamine neurons is mediated by autoreceptors since dopamine D_1 receptors have direct stimulatory effects on intracellular activity of target cells (Kebabian and Calne, 1979), and neither dopamine D_1 receptor protein (Huang et al., 1992; Mansour et al., 1992) nor dopamine D_1 receptor mRNA (Fremeau et al., 1991; Mansour et al., 1992) have been detected in appreciable amounts within regions of the mediobasal hypothalamus containing tuberoinfundibular dopamine neurons. Rather, dopamine D_1 receptors likely function in the afferent neuronal regulation of these neurons by stimulating the release of an inhibitory neurotransmitter such as dynorphin which has been shown to inhibit the basal activity of tuberoinfundibular dopamine neurons in male rats via an action on tonically active κ-opioid receptors (Manzanares et al., 1992a,b).

Prolactin secretion is inhibited by endogenous dopamine acting on dopamine D_2 receptors located on anterior pitu-

itary lactotrophs (Ben-Jonathan, 1985). Dopamine D_2 receptor antagonists increase, whereas dopamine D_2 receptor agonists decrease prolactin release via a direct action on these dopamine D_2 receptors (Moore, 1987), and this accounts for some of the unwanted prolactin-mediated side effects of dopamine therapeutic agents currently employed in the treatment of neurological disorders such as Parkinson's disease and schizophrenia. The results of the present study reveal that selective activation of dopamine D_1 receptors also increases prolactin secretion, albeit via an indirect action on tuberoinfundibular dopamine neurons. Indeed, administration of SKF38393 increases plasma concentrations of prolactin and this is associated with decreases in median eminence DOPAC. Although these data are coincidental, they do suggest that dopamine D_1 receptor-mediated activation of prolactin secretion occurs secondary to suppression of dopamine release from tuberoinfundibular dopamine neurons. The absence of dopamine D_1 receptors in the anterior pituitary (Cocchi et al., 1987; Albert et al., 1997) supports the conclusion that dopamine D_1 receptor-mediated regulation of prolactin secretion occurs via a central action. It is interesting to note that in sheep, central administration of SKF38393 increases prolactin secretion (Curlewis et al., 1994), possibly via an action in the hypothalamic ventromedial nucleus (Curlewis et al., 1995a). It has been postulated that dopamine D_1 receptors located in this region mediate photoperiod-induced changes in prolactin secretion in this species (Curlewis et al., 1995b). Thus, alterations in prolactin secretion are potential side effects that should be considered in the development of novel therapeutic centrally-acting dopamine D_1 receptor agonists and antagonists.

The results of the present study are consistent with a stimulatory role for dopamine D_2-like receptors on the activity of tuberoinfundibular dopamine neurons (Berry and Gudelsky, 1991; Eaton et al., 1993; Durham et al., 1996, 1997), i.e., acute administration of quinelorane increases median eminence DOPAC concentrations. Although quinelorane does not discriminate between D_2 and D_3 receptor subtypes of the dopamine receptor (Gackenheimer et al., 1995), this effect is likely mediated via activation of dopamine D_2 receptors since the stimulatory effect of quinelorane is mimicked by the dopamine D_2 receptor agonist PNU 98666, but not the dopamine D_3 receptors agonist PD 128907 (Durham et al., 1997). Results of the present study reveal that inhibitory dopamine D_1 receptors oppose the stimulatory actions of dopamine D_2 receptors on tuberoinfundibular dopamine neurons. Indeed, activation of dopamine D_1 receptors with SKF38393 reverses the effect of quinelorane on DOPAC concentrations in the median eminence. Accordingly, the inability of the mixed agonist apomorphine to have any effect on the activity of tuberoinfundibular dopamine neurons probably results from concurrent activation of both inhibitory and stimulatory dopamine receptor-mediated mechanisms. On the other hand, apomorphine decreased median eminence DOPAC in quinelorane-treated rats, likely through its ability to activate dopamine D_1 receptors. Accordingly, the relative balance of dopamine D_1/D_2 receptor occupancy may determine the level of activity of tuberoinfundibular dopamine neurons. That blockade of dopamine D_1 receptors (but not dopamine D_2 receptors; Eaton et al., 1993) increases DOPAC concentrations in the median eminence suggests that dopamine D_1 receptors are more important in control of basal activity of tuberoinfundibular dopamine neurons in male rats.

In conclusion, the results of the present study reveal that tuberoinfundibular dopamine neurons in the male rat are inhibited following activation of dopamine D_1 receptors, and that under basal condition these neurons are tonically regulated by inhibitory dopamine D_1 receptors. Furthermore, these results suggest that concurrent activation of dopamine D_1 and dopamine D_2 receptors nullifies their respective actions on tuberoinfundibular dopamine neurons, which likely accounts for the inability of mixed dopamine D_1/D_2 receptor agonists to have an acute effect on these hypothalamic dopamine neurons.

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