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The σ receptor ligand rimcazole alters secretion of prolactin and α-melanocyte stimulating hormone by dopaminergic and non-dopaminergic mechanisms

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Abstract

The role of tuberoinfundibular and periventricular-hypophysial dopaminergic neurons in mediating rimcazole-induced decreases in plasma concentrations of prolactin and α-melanocyte stimulating hormone was assessed. Dopaminergic neuronal activity was estimated by measuring concentrations of 3,4-dihydroxyphenylacetic acid (DOPAC) in the median eminence and intermediate lobe of the pituitary which contain terminals of tuberoinfundibular and periventricular-hypophysial dopaminergic neurons, respectively. Rimcazole decreased plasma concentrations of both prolactin and α-melanocyte stimulating hormone, increased the concentration of DOPAC in median eminence, but did not alter DOPAC concentrations in the intermediate lobe of the pituitary. Pretreatment with a 'putative' σ receptor agonist, pentazocine, prevented the rimcazole-induced increase of the concentration of DOPAC in the median eminence, but did not block the ability of rimcazole to decrease plasma concentrations of prolactin. The results of this study reveal that the ability of rimcazole to decrease α-melanocyte stimulating hormone secretion is not mediated by a dopaminergic mechanism, whereas the ability of rimcazole to decrease prolactin secretion appears to be mediated by both dopaminergic and non-dopaminergic mechanisms.

Keywords: Median eminence; Intermediate lobe; Pentazocine; Haloperidol; Raclopride; Prolactin secretion; α-MSH (α-melanocyte stimulating hormone) secretion

1. Introduction

The existence of σ receptors was first proposed by Martin et al. (1976) and these receptors have been subsequently associated with the psychotomimetic effects of many benzomorphans such as SKF 10,047 (for review, see Walker et al., 1990). Two classes of σ receptors have been categorized pharmacologically and have been designated as σ_1 and σ_2 (Quirion et al., 1992), but the endogenous ligand for these receptors is unknown. This lack of a known endogenous ligand makes it difficult to establish the physiological functions of σ receptors; however, there is some evidence which indicates that these receptors may regulate secretion of prolactin and α-melanocyte stimulating hormone. For example, σ binding sites have been identified in the hypothalamus and in the anterior and intermediate lobes of the pituitary (Gundlach et al., 1986; Largent et al., 1986; Wolfe et al., 1989; Jansen et al., 1991). Furthermore, it has been demonstrated that σ receptor ligands alter secretion of prolactin in rat (Gudelsky and Nash, 1992; Karbon et al., 1993), although interpretation of these studies is confounded by the fact that the σ receptor ligands employed in these studies have high affinity for other receptor types, such as dopamine, 5-HT and phencyclidine (PCP) receptors; all of these receptors regulate prolactin secretion (Ben-Jonathan, 1985; Clemens et al., 1978; Lozovsky et al., 1983). Rimcazole is a relatively selective σ receptor ligand which has little or no affinity for dopamine, adreno-, histamine, neurotensin, acetylcholine or 5-HT receptors and is 100 times more selective for σ than for PCP receptors in the brain (Ferris et al., 1986). This selectivity makes rimcazole a useful compound to investigate the role of σ receptor ligands in the regulation of prolactin and α-melanocyte stimulating hormone secretion.

Tuberoinfundibular dopaminergic neurons which have cell bodies in the arcuate nucleus and terminals in the

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median eminence regulate circulating levels of prolactin. Dopamine released from these neurons is transported through the portal vessels to the anterior lobe of the pituitary where it activates D_2 receptors on lactotrophs thereby inhibiting secretion of prolactin (MacLeod, 1986). Periventricular-hypophysial dopaminergic neurons have cell bodies in the caudal portion of the periventricular nucleus of the hypothalamus and terminals in the intermediate lobe of the pituitary (Goudreau et al., 1992). Dopamine released from these neurons activates dopamine D_2 receptors on melanotrophs in the intermediate lobe of the pituitary thereby inhibiting secretion of α-melanocyte stimulating hormone (Millington and Chronwall, 1988).

The present study was undertaken to assess the role of σ receptors in regulation of prolactin and α-melanocyte stimulating hormone by determining if σ receptor ligands alter secretion of these hormones from the pituitary. Secondly, the mechanism by which σ receptor ligands alter secretion of prolactin and α-melanocyte stimulating hormone was examined to determine if dopaminergic or non-dopaminergic mechanisms are involved, i.e. do σ receptor ligands alter the activity of tuberoinfundibular and periventricular-hypophysial dopaminergic neurons?

2. Materials and methods

2.1. Animals

Long-Evans male rats weighing between 175 and 225 g were purchased from Harlan Laboratories (Indianapolis, IN, USA) and were maintained in a temperature (21 ± 1°C) and light (illumination 05:00–19:00 h) -controlled environment. Rats were housed in small groups (three per cage) and had free access to food (Teklad-Harlan Laboratory Diets-Rodent Food) and tap water.

2.2. Drug preparation and administration

Rimcazole dihydrochloride (*cis*-9-[3-(3,5-dimethyl-1-piperazinyl)propyl]-9*H*-carbazole dihydrochloride; Research Biochemicals, Natick, MA, USA) was dissolved in either water or 0.9% saline. Haloperidol (4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone; Sigma Chemical Co., St. Louis, MO, USA) and (±)-pentazocine (1,2,3,4,5,6-hexahydro-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol; Sterling-Winthrop) were dissolved in 0.3% tartaric acid. Raclopride tartrate (*S*-(−)-3,5-dichloro-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-6-methoxybenzamide (+)-tartrate) was provided by S.-O. Ögren (Astra Laboratory, Södertälje, Sweden) and was dissolved in 0.9% saline. Doses of rimcazole and raclopride refer to their respective salts. Drugs were administered as indicated in the legends of the appropriate figures.

2.3. Tissue dissection and biochemical determination of monoamines

Following systemic injections of various σ receptor ligands, animals were decapitated. Brains and pituitaries were quickly removed and frozen on aluminum foil placed directly over dry ice. Frontal brain sections (600 μm thick) beginning at approximately 9820 μm (König and Klippel, 1963) were obtained using a cryostat (−9°C). The median eminence, nucleus accumbens and striatum were dissected according to the method of Palkovits (1973). The intermediate lobe of the pituitary was dissected from the frozen pituitaries as described previously (Lookingland et al., 1985). Tissue samples were placed in 65 or 100 μl of 0.1 M phosphate-citrate buffer (pH 2.5) containing 15% methanol and stored at −20°C. On the day of the assay, tissue samples were thawed, sonicated for 3 s (Sonicator Cell Disrupter, Heat Systems-Ultrasonics, Plainview, NY, USA) and centrifuged for 30 s in a Beckman Microfuge B. The pellets were dissolved in 1 N NaOH and assayed for protein as described by Lowry et al. (1951). Concentrations of dopamine and DOPAC in supernatants were determined by high performance liquid chromatography coupled with electrochemical detection as described previously (Chapin et al., 1986).

2.4. Radioimmunoassay of prolactin and α-melanocyte stimulating hormone

Trunk blood obtained following decapitation was centrifuged at 2250 rpm for 20 min at 4°C. The plasma was drawn off and kept frozen (−20°C) until prolactin and α-melanocyte stimulating hormone concentrations were determined by double-antibody radioimmunoassay. Prolactin was measured utilizing the reagents and procedures of the NIDDK assay with rat prolactin (RP-3) as the standard (generously provided by Drs. A.F. Parlow and S. Raiti, NIDDK National Hormone and Pituitary Program). Using a 150 μl aliquot of plasma, the lower limit of sensitivity for prolactin was 1.0 ng/ml. The concentrations of α-melanocyte stimulating hormone in plasma were determined using a double-antibody radioimmunoassay modified from a procedure originally described by Penny and Thody (1978). Antiserum to α-melanocyte stimulating hormone was generously supplied by Dr. G. Mueller, Uniformed Services University for the Health Sciences (Bethesda, MD, USA). Using a 200 μl aliquot of plasma, the lower limit of sensitivity for α-melanocyte stimulating hormone was 20.0 pg/ml. The interassay coefficients of variation for prolactin and α-melanocyte stimulating hormone were approximately 6.0% and 8.6%, respectively, whereas the intraassay coefficients of variation were approximately 5.5% and 7.9% for prolactin and α-melanocyte stimulating hormone, respectively.

2.5. Neurochemical estimation of neuronal activity

Dopaminergic neuronal activity was estimated by determining the concentrations of dopamine and DOPAC, a metabolite of this amine, in regions of the brain containing terminals of tuberoinfundibular (median eminence), periventricular-hypophysial (intermediate lobe of the pituitary), nigrostriatal (striatum), and mesolimbic (nucleus accumbens) dopaminergic neurons. Procedures that increase or decrease the activities of these neurons produce corresponding changes in the concentrations of DOPAC in median eminence (Lookingland et al., 1987b), intermediate lobe of the pituitary (Lookingland et al., 1985), striatum and nucleus accumbens (Roth et al., 1976).

2.6. Statistical analyses

Data were analyzed statistically using one-way analysis of variance followed by the least-significant difference test (Steel and Torrie, 1960). Differences were considered significant if the probability of error was less than 5%.

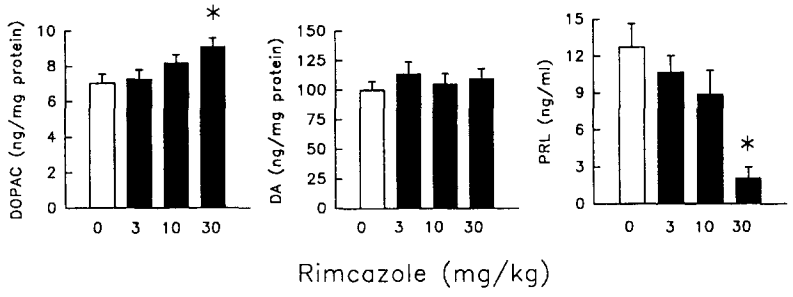

Fig. 1. Dose-response effects of rimcazole on concentrations of DOPAC and dopamine (DA) in the median eminence and on concentrations of prolactin (PRL) in plasma. Rats were injected with either rimcazole (3.0, 10.0 or 30.0 mg/kg i.p.) or its 0.9% saline vehicle (2 ml/kg i.p.) 35 min prior to decapitation. Columns represent the means and vertical lines 1 S.E.M. of 7–9 determinations in either vehicle- (open) or rimcazole-treated (solid) rats. * Values that are significantly different ($P < 0.05$) from vehicle-treated controls.

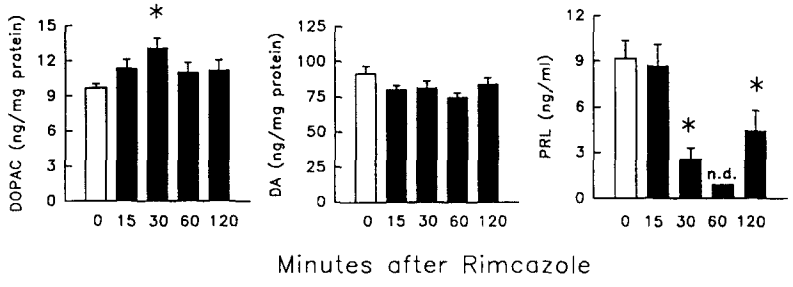

Fig. 2. Time-course effects of rimcazole on concentrations of DOPAC and dopamine (DA) in the median eminence and on concentrations of prolactin (PRL) in plasma. Rats were injected with rimcazole (30.0 mg/kg i.p.) and killed at various times thereafter by decapitation. Animals injected with distilled water (1 ml/kg i.p.) were killed 15 min later and used as zero time controls. Columns represent the means and vertical lines 1 S.E.M. of 6–9 determinations in either vehicle- (open) or rimcazole-treated (solid) rats. * Values that are significantly different ($P < 0.05$) from vehicle-treated controls. n.d. indicates non-detectable levels of PRL (n.d. < 1.0 ng/ml).

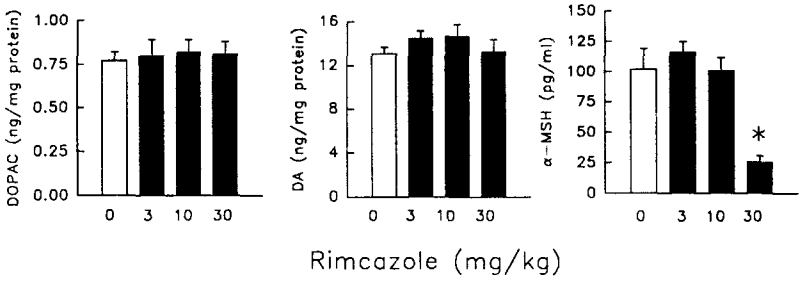

Fig. 3. Dose-response effects of rimcazole on concentrations of DOPAC and dopamine (DA) in the intermediate lobe of the pituitary and on concentrations of α-melanocyte stimulating hormone (α-MSH) in plasma. Rats were injected with either rimcazole (3.0, 10.0 or 30.0 mg/kg i.p.) or its 0.9% saline vehicle (2 ml/kg i.p.) 35 min prior to decapitation. Columns represent the means and vertical lines 1 S.E.M. of 7–9 determinations in either vehicle- (open) or rimcazole-treated (solid) rats. * Values that are significantly different ($P < 0.05$) from vehicle-treated controls.

3. Results

Thirty-five minutes after intraperitoneal (i.p.) administration of rimcazole to male rats, this σ receptor ligand increased the concentration of DOPAC, but not dopamine in the median eminence and produced a corresponding decrease in the concentration of prolactin in plasma (Fig. 1). The time course of the effects of rimcazole on DOPAC and dopamine concentrations in the median eminence and on plasma concentrations of prolactin is shown in Fig. 2. Rimcazole (30 mg/kg i.p.) increased the concentration of DOPAC within 30 min and this increase was accompanied by reductions for up to 120 min in plasma concentrations of prolactin.

The dose-response and time-course effects of rimcazole on DOPAC and dopamine concentrations in the intermediate lobe of the pituitary and on plasma concentrations of α-melanocyte stimulating hormone were also assessed. Although rimcazole did not alter DOPAC or dopamine concentrations in the intermediate lobe of the pituitary (Figs. 3 and 4), this drug decreased plasma concentrations of α-melanocyte stimulating hormone at doses and times at which prolactin concentrations were reduced (Figs. 1 and 2).

Table 1
Lack of effect of various doses of rimcazole on DOPAC concentrations in nucleus accumbens and striatum

	Nucleus accumbens	Striatum
0 mg/kg	28.68 ± 1.08	31.52 ± 1.12
3.0 mg/kg	28.75 ± 0.97	30.34 ± 1.40
10.0 mg/kg	27.55 ± 1.14	30.84 ± 2.70
30.0 mg/kg	26.51 ± 1.02	25.71 ± 0.47

Concentrations of DOPAC in nucleus accumbens and striatum of rats following injections of either rimcazole (3.0, 10.0 or 30.0 mg/kg i.p.) or its 0.9% saline vehicle (2 ml/kg i.p.) 35 min prior to decapitation. Values represent the means and 1 S.E.M. of 7–9 determinations in either vehicle- or rimcazole-treated rats.

The dose-response and time-course effects of rimcazole on DOPAC concentrations in nucleus accumbens and striatum are summarized in Tables 1 and 2. Unlike the tuberoinfundibular dopaminergic neurons terminating in the median eminence and similar to the periventricular-hypophysial dopaminergic neurons terminating in the intermediate lobe of the pituitary, rimcazole did not alter DOPAC concentrations in striatum and nucleus accumbens, which contain terminals of nigrostriatal and mesolimbic dopaminergic neurons, respectively.

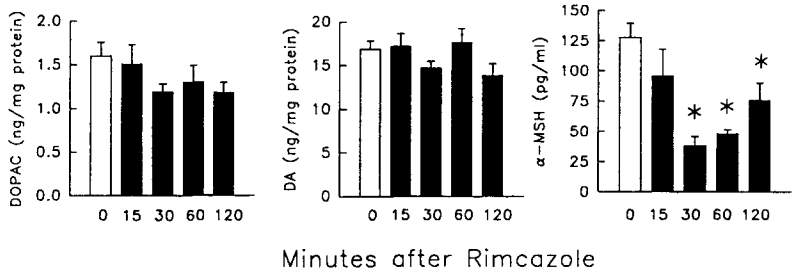

Fig. 4. Time-course effects of rimcazole on concentrations of DOPAC and dopamine (DA) in the intermediate lobe of the pituitary and on concentrations of α-melanocyte stimulating hormone (α-MSH) in plasma. Rats were injected with rimcazole (30.0 mg/kg i.p.) and killed at various times thereafter by decapitation. Animals injected with distilled water (1 ml/kg i.p.) were killed 15 min later and used as zero time controls. Columns represent the means and vertical lines 1 S.E.M. of 6–9 determinations in either vehicle- (open) or rimcazole-treated (solid) rats. * Values that are significantly different ($P < 0.05$) from vehicle-treated controls.

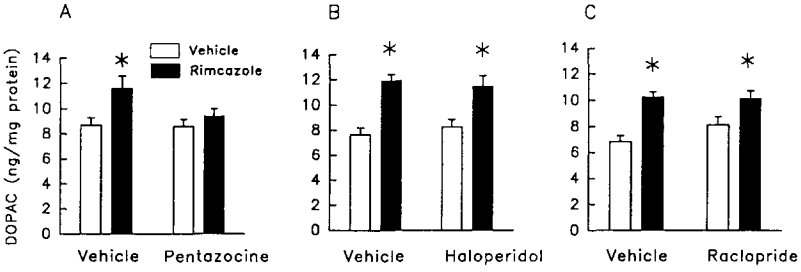

Fig. 5. Effects of rimcazole, pentazocine, haloperidol and raclopride on concentrations of DOPAC in the median eminence. (A) Rats were injected with either pentazocine (10.0 mg/kg i.p.) or its 0.3% tartaric acid vehicle (1 ml/kg i.p.) 60 min prior to decapitation, and with either rimcazole (30.0 mg/kg i.p.) or its distilled water vehicle (1 ml/kg i.p.) 30 min prior to decapitation. (B) Rats were injected with either haloperidol (0.1 mg/kg s.c.) or its 0.3% tartaric acid vehicle (1 ml/kg i.p.) 60 min prior to decapitation, and with either rimcazole (30.0 mg/kg i.p.) or its distilled water vehicle (1 ml/kg i.p.) 30 min prior to decapitation. (C) Rats were injected with either raclopride (3.0 mg/kg i.p.) or its 0.9% saline vehicle (1 ml/kg i.p.) 60 min prior to decapitation, and with either rimcazole (30.0 mg/kg i.p.) or its distilled water vehicle (1 ml/kg i.p.) 30 min prior to decapitation. Columns represent the means and vertical lines 1 S.E.M. of 7–9 determinations in either water vehicle- (open) or rimcazole-treated (solid) rats. * Values for rimcazole-treated rats that are significantly different ($P < 0.05$) from their corresponding vehicle-treated controls.

Table 2
Lack of effect of rimcazole over time on DOPAC concentrations in nucleus accumbens and striatum

	Nucleus accumbens	Striatum
0 min	41.75 ± 1.41	28.35 ± 0.73
15 min	42.17 ± 2.11	31.15 ± 0.83
30 min	42.62 ± 1.81	29.38 ± 1.31
60 min	39.57 ± 1.43	26.73 ± 0.82
120 min	38.25 ± 1.25	26.37 ± 1.42

Concentrations of DOPAC in nucleus accumbens and striatum of rats injected with rimcazole (30.0 mg/kg i.p.) and killed at various times thereafter by decapitation. Animals injected with distilled water (1 ml/kg i.p.) were killed 15 min later and used as zero time controls. Values represent the means and 1 S.E.M. of 6–9 determinations in either vehicle- or rimcazole-treated rats.

The ability of σ and dopamine receptor ligands to block the action of rimcazole in the median eminence was assessed. As shown in Fig. 5, the putative σ receptor agonist pentazocine had no effect on DOPAC concentrations in the median eminence, per se, but blocked the rimcazole-induced increase in the concentration of DOPAC in the median eminence. In contrast, the σ/dopamine receptor antagonist haloperidol and the dopamine receptor antagonist raclopride failed to antagonize the stimulatory effects of rimcazole.

Fig. 6 shows the effects of rimcazole, pentazocine, haloperidol and raclopride on plasma concentrations of prolactin. Rimcazole decreased, whereas pentazocine, haloperidol and raclopride increased plasma concentrations of prolactin. Furthermore, rimcazole markedly reduced (64.6%) the stimulatory effect of the σ receptor agonist pentazocine on plasma prolactin concentrations, whereas it marginally reduced (23.4%) the stimulatory effect of the σ/dopamine receptor ligand haloperidol. Rimcazole failed to alter the stimulatory effect of the dopamine D_2 receptor antagonist raclopride on plasma concentrations of prolactin.

4. Discussion

The results of the present study reveal that rimcazole activates tuberoinfundibular dopaminergic neurons, but fails to alter the activity of periventricular-hypophysial, nigrostriatal or mesolimbic dopaminergic neurons. The lack of effect of rimcazole on nigrostriatal and mesolimbic dopaminergic neurons is consistent with the reports of others (Steinfels et al., 1989; Ferris et al., 1982; Ceci et al., 1988) which have shown that acute administration of rimcazole has no reliable effect on the activity of nigrostriatal or mesolimbic dopaminergic neurons terminating in striatum and nucleus accumbens, respectively. Furthermore, the present results show that the putative σ receptor antagonist rimcazole decreases plasma concentrations of both prolactin and α-melanocyte stimulating hormone. The ability of rimcazole to suppress prolactin secretion is consistent with the findings of Karbon et al. (1993) who reported that NCP 16377 (another σ receptor ligand) decreases plasma concentrations of prolactin.

In the present study, changes in plasma concentrations of α-melanocyte stimulating hormone are not associated with changes in periventricular-hypophysial dopaminergic neuronal activity, therefore suggesting that this effect is not mediated by a dopaminergic mechanism. In contrast, doses of rimcazole which increase tuberoinfundibular dopaminergic neuronal activity produce corresponding decreases in plasma concentrations of prolactin. Previous studies using electrical stimulation of the arcuate nucleus (Lookingland et al., 1987a) and various pharmacological (Moore and Lookingland, 1995) and physiological (Lookingland et al., 1990) manipulations have shown that plasma concentrations of prolactin are decreased when tuberoinfundibular dopaminergic neuronal activity is increased. Taken together, these findings suggest that rimcazole decreases prolactin secretion, in part, by activating tuberoinfundibular dopaminergic neurons.

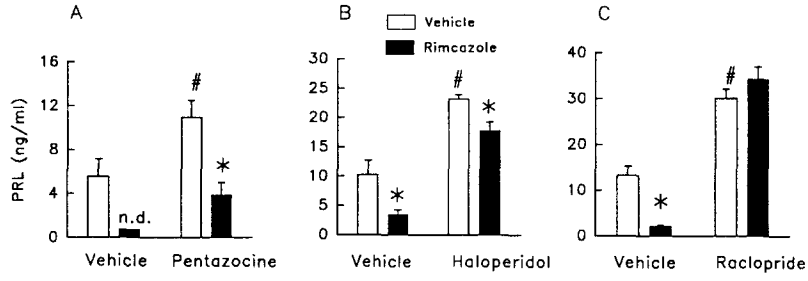

Fig. 6. Effects of rimcazole, pentazocine, haloperidol and raclopride on plasma concentrations of prolactin (PRL). (A) Rats were injected with either pentazocine (10.0 mg/kg i.p.) or its 0.3% tartaric acid vehicle (1 ml/kg i.p.) 60 min prior to decapitation, and with either rimcazole (30.0 mg/kg i.p.) or its distilled water vehicle (1 ml/kg i.p.) 30 min prior to decapitation. (B) Rats were injected with either haloperidol (0.1 mg/kg s.c.) or its 0.3% tartaric acid vehicle (1 ml/kg i.p.) 60 min prior to decapitation, and with either rimcazole (30.0 mg/kg i.p.) or its distilled water vehicle (1 ml/kg i.p.) 30 min prior to decapitation. (C) Rats were injected with either raclopride (3.0 mg/kg i.p.) or its 0.9% saline vehicle (1 ml/kg i.p.) 60 min prior to decapitation, and with either rimcazole (30.0 mg/kg i.p.) or its distilled water vehicle (1 ml/kg i.p.) 30 min prior to decapitation. Columns represent the means and vertical lines 1 S.E.M. of 7–9 determinations in either water vehicle- (open) or rimcazole-treated (solid) rats. * Values for rimcazole-treated rats that are significantly different ($P < 0.05$) from their corresponding vehicle-treated controls. # Values for pentazocine-, haloperidol- or raclopride-treated animals that are significantly different from their corresponding vehicle/vehicle-treated controls. n.d. indicates non-detectable levels of PRL (n.d. < 1.0 ng/ml).

There is also evidence to suggest that rimcazole decreases plasma concentrations of prolactin by a non-dopaminergic mechanism. The putative σ receptor agonist pentazocine blocks rimcazole-induced changes in tuberoinfundibular dopaminergic activity, but fails to alter the ability of rimcazole to decrease circulating levels of prolactin. If decreases in prolactin were solely due to changes in tuberoinfundibular dopaminergic activity, then pentazocine would block this action of rimcazole. Since this is not the case, it is likely that σ receptors regulate circulating levels of prolactin by non-dopaminergic mechanisms such as direct effects at the level of the pituitary or by activating prolactin-releasing factors.

The idea that σ receptors can mediate changes in circulating levels of prolactin by a dopaminergic-independent mechanism is supported not only by the localization of σ receptors in the pituitary (Wolfe et al., 1989; Jansen et al., 1991), but also by the lack of correlation between the time course of action of rimcazole on plasma concentrations of prolactin and on tuberoinfundibular dopaminergic neuronal activity. The present study demonstrates that prolactin concentrations are decreased long after tuberoinfundibular dopaminergic neuronal activity has returned to baseline.

Earlier reports have established that the σ receptor ligand pentazocine increases plasma concentrations of prolactin (Pende et al., 1986; Manner et al., 1987). The present study extends these findings by demonstrating that pentazocine-stimulated prolactin secretion is not mediated by decreased activity of tuberoinfundibular dopaminergic neurons. The ability of rimcazole to block the stimulatory effect of pentazocine on prolactin supports the idea that elevations in prolactin are mediated by σ receptors. The dopamine receptor antagonist raclopride, which has no effect on tuberoinfundibular dopaminergic activity (Eaton et al., 1993) and does not bind to σ receptors, also increases plasma concentrations of prolactin presumably by direct blockade of dopamine D_2 receptors on lactotrophs in the anterior lobe of the pituitary (Kebabian and Calne, 1979). Rimcazole fails to alter the ability of raclopride to stimulate secretion of prolactin. Haloperidol, which is a σ receptor ligand as well as a dopamine receptor antagonist, increases plasma concentrations of prolactin. This effect is partially reversed by administration of the putative σ receptor ligand rimcazole suggesting that there is a σ component to the stimulatory effect of haloperidol on prolactin secretion. Taken together, these results reveal that the ability of rimcazole to block pentazocine-stimulated prolactin secretion is specific in that rimcazole does not reverse indiscriminately elevations in prolactin produced by blockade of dopamine D_2 receptors by either raclopride or haloperidol.

In summary, the results of this study reveal that rimcazole decreases plasma concentrations of prolactin and α-melanocyte stimulating hormone. The ability of rimcazole to decrease α-melanocyte stimulating hormone secretion is not mediated by a dopaminergic mechanism, whereas the ability of rimcazole to decrease prolactin secretion appears to be mediated by both dopaminergic and non-dopaminergic mechanisms. Rimcazole has a differential effect on dopaminergic neuronal activity in that this drug activates tuberoinfundibular dopaminergic activity without altering the activity of periventricular-hypophysial, nigrostriatal and mesolimbic dopaminergic neurons.

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