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Antiparkinson potential of δ-opioid receptor agonists

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Abstract

δ-Opioid receptors, present in very high concentrations in striatum and overlying cortex, are thought to be involved in a number of processes, including analgesia, mood, reward, modulation of neuronal excitability, and alterations in neurotransmitter release. Given the localization of the receptors in motor circuits in brain, we thought it of interest to study the antiparkinson potential of δ-opioid receptor agonists. Rats were given unilateral 6-hydroxydopamine lesions of the nigrostriatal tract, and following recovery, were tested for rotational activity. Tonazocine mesylate is a nonpeptide, partial δ-opioid receptor agonist with μ-receptor antagonist properties. Tonazocine (0.1–10 mg/kg) evoked a dose-related, ipsilateral rotation, consistent with augmentation of dopaminergic function on the unlesioned side. The rotation evoked by tonazocine was blocked by the selective δ-opioid receptor antagonist naltrindole, suggesting that the effect was mediated by δ-opioid receptors. The full δ-opioid receptor agonist (+)-4-[9-α-*R*)-α-(2*S*,5*RO*-4-allyl-2,5-dimethyl-1-piperaziny l)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC-80) produced both contralateral and ipsilateral rotation. Tonazocine additionally augmented the effects of L-3,4 dihydroxyphenylalanine (L-DOPA) on reserpine-induced suppression of motor activity. Binding affinities and efficacies of tonazocine and SNC-80 against μ-, κ-, and δ-opioid receptors were also confirmed and compared to standards. These data suggest therapeutic potential of agents interacting with δ-opioid receptors, and indicate some differences in the activities of tonazocine and SNC-80.

Keywords: δ-Opioid receptor agonist; Tonazocine; SNC-80; Rotation; Parkinson's disease

1. Introduction

δ-Opioid receptors are G-protein coupled receptors with about 60% homology to the μ- and κ-opioid receptors (see Satoh and Minami, 1995; Knapp et al., 1995; Dhawan et al., 1996 for reviews). δ-Opioid receptors, and in most cases, associated endogenous ligand (enkephalins), are co-localized in numerous central nervous system (CNS) structures including hippocampus, septal region, accumbens, virtually all layers of cortex, and striatum, but are notably absent from or exist in very low numbers in thalamus, substantia nigra and hypothalamus (George et al., 1994; Le Moine et al., 1994; Goodman et al., 1980). Their localization, as well as those of other opioid receptor subtypes, appears to be primarily upon axons (Elde et al., 1995), suggesting presynaptic modulation. Cloned and expressed δ-opioid receptors have been shown to couple to both L type Ca^{2+} channels and to K^+ channels though G_i proteins (North, 1993). δ-opioid receptors are thought to be involved in a number of processes, including analgesia, mood, reward, and alterations in neurotransmitter release.

Ligands for the δ-opioid receptor include the peptide enkephalins, [D-Pen2,5]enkephalin (DPDPE), and non-peptide agents such as (+)-4-((alpha-*R*)-alpha-((2*S*, 5*R*)-4-allyl-2, 5-dimethyl-l-piperazinyl)-3-hydroxybenzyl)-*N*,*N*-diethylbenzamide (BW 373U86) and (+)-4-[9-alpha-*R*)-alpha-(2*S*,5*RO*-4-allyl-2,5-dimethyl-1-piperaziny l)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC-80). Tonazocine mesylate is a nonpeptide, partial δ-opioid agonist with μ antagonist properties and weak κ agonist activity (Michne et al., 1979; Ward et al., 1985), providing an additional probe for studying δ-opioid receptor function. Tonazocine has undergone phase II clinical trials for postoperative pain and appeared to possess reasonable efficacy (Lippmann et al., 1989).

Given the localization of the receptors in motor circuits in brain, we thought it of interest to study the antiparkin-

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son potential of δ-opioid receptor agonists. In the present study, the 6-hydroxydopamine rotational model (Ungerstedt, 1976) and the reserpine-induced motor depression (Andén et al., 1973) models were used to assess the therapeutic potential of this class of agents. At least one previous study has shown the potential efficacy of δ-opioid receptor agonists (Hille et al., 1998). The present study confirms and extends these findings, as well as points out differences between the activities of SNC-80 and tonazocine.

2. Materials and methods

2.1. Rotational behavior testing

2.1.1. Subjects

Individually housed male Long Evans rats weighing 400–500 g were used. Animals were given free access to food and water and were kept under a 12 h light/dark schedule.

2.1.2. Surgery

Medial forebrain bundle lesions were performed under isoflurane anesthesia. A 3-μl volume intracranial injection of 6-hydroxydopamine (3 μg/μl in 0.2% ascorbic acid in saline) was administered at the following coordinates: −3.5 mm anterior/posterior, −1.6 mm lateral/medial, and −8.8 mm dorsal/ventral from bregma with the incisor bar at −2 mm.

2.1.3. Behavioral testing

A 3-week recovery period was allowed each rat, following which rotational response to amphetamine (3 mg/kg s.c.) was determined, in order to select out poorly lesioned rats. Automated rotometers (Med Associates) were used to measure rotational behavior. Two-hour testing sessions were conducted on Tuesdays and Fridays.

2.1.4. Drug administration

Amphetamine and tonazocine were dissolved in saline. Naltrindole was dissolved in 3% lactic acid in citrate buffer, and SNC-80 was dissolved in 0.2 N HCl. Nal-

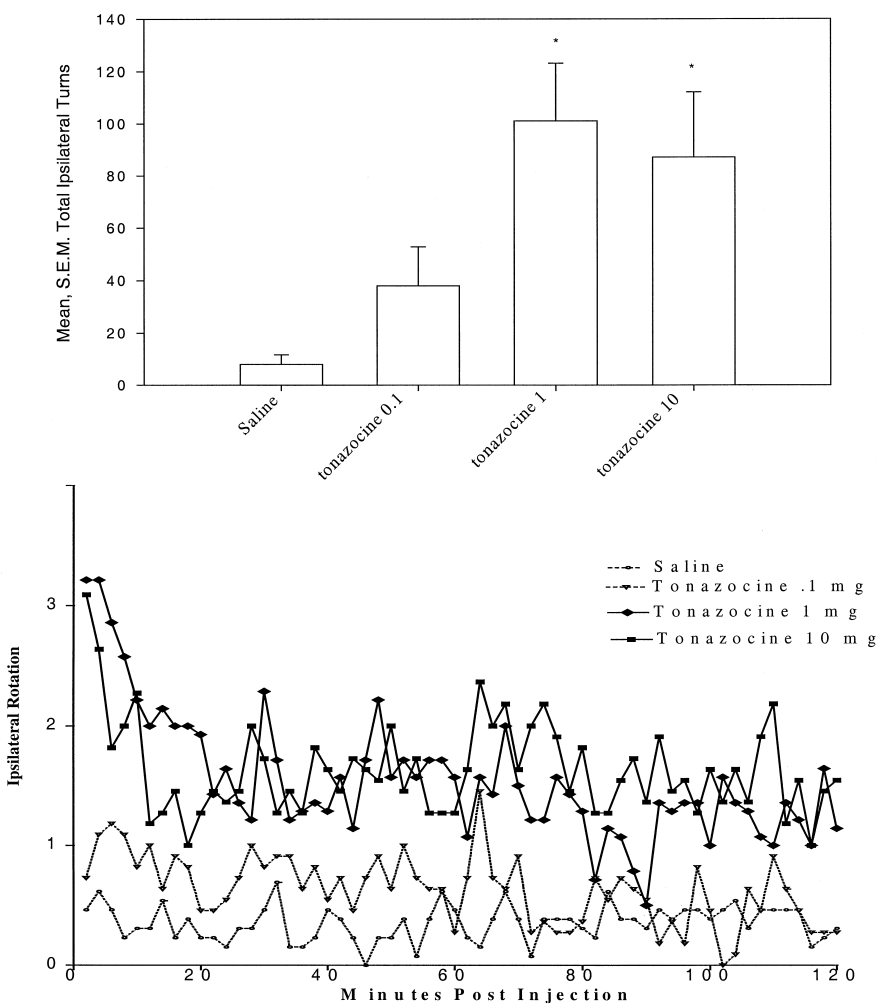

Fig. 1. Upper panel: Effects of tonazocine (0.1, 1 and 10 mg/kg; $N = 11$) on ipsilateral rotations over a 2-h observation period. Data shown are the mean and S.E.M. of total turns in the session. * Indicates significant difference from saline control (ANOVA, Dunnett's post-hoc analysis). Lower panel: data are shown in successive 2-min intervals in order to demonstrate drug onset and duration.

trindole was administered i.p.15 min prior to the testing session. All other compounds were given as an s.c. injection immediately prior to the testing session.

2.1.5. Statistical analysis

Treatment groups were comprised of 6–11 animals. Data were summed across the 2-h observation period for individual subjects, and means derived from these sums were compared by analysis of variance (ANOVA). If the omnibus ANOVA was significant, then post-hoc comparisons were made using Dunnett's method between saline control and drug-treated groups. When single drugs were administered (e.g., tonazocine and SNC-80 alone), data were also plotted in successive 2-min intervals during the session in order to assess drug onset time and duration of action.

2.2. Reserpine induced motor activity depression

2.2.1. Subjects

Group housed male Long Evans rats weighing 120–160 g were used. Animals were given free access to food and water and were kept under 12-h light/dark schedule.

2.2.2. Behavioral testing

Following a reserpine injection only rats with a severe level of motor activity depression were used; those rats that were active or unresponsive to handling were excluded from the study. Automated motor activity chambers (Columbus Instruments) were used to measure activity levels in terms of distance traveled. Baseline normal (without pre-treatment) and motor activity depression was measured for 10 min prior to the 1 h of activity testing session. Test compounds were given immediately prior to the beginning of the 1 h of activity testing session.

2.2.3. Drug administration

Reserpine was dissolved in.5 ml of glacial acetic acid then 9.5 ml of water was added; injections were given at 3% body weight of each rat. Compounds were prepared as follows: Carbidopa and L-3,4 dihydroxyphenylalanine (L-DOPA) were dissolved in 0.1N HCl. Reserpine (3.5 mg/kg i.p.) was administered 24 h prior to activity testing. Carbidopa (25 mg/kg i.p.) was given 30 min prior to the 1 h activity testing session. L-DOPA and tonazocine were given just prior to the 1 h testing session.

2.2.4. Statistical analysis

Treatment groups were comprised of 6–12 animals. Comparisons were made through one way analysis of variance on the total distance traveled in the 2-h activity testing session. Any significant differences were then compared by the Dunnett's method against the associated control group (the group given reserpine alone).

2.3. Receptor binding and functional assays

2.3.1. Cell culture and membrane preparation

Human embryonic kidney (HEK)-293S cells expressing cloned human μ, δ, and κ receptors were obtained from H.K. Vu, M. Valiquette, and P. Walker of AstraZeneca Research Center, Montreal, Molecular Biology Department. Cells were grown in suspension culture, harvested, and P2 membrane preparations were produced.

2.3.2. Receptor binding assays

Membranes were combined with test compounds and approximately 0.07 nM of the appropriate radioligand [^{125}I][D-Ala^2]deltorphin II ($K_d = 0.933$ nM at δ), [^{125}I]-FK33824 ($K_d = 1.14$ nM at μ), and [^{125}I]D-Pro^{10}-Dynorphin A-(1-11) ($K_d = 0.156$ nM at κ) in 50 mM Tris, 3 mM $MgCl_2$, 1 mg/ml bovine serum albumin, pH 7.4. The amounts of bound radioactivity were determined at equilibrium by filtration. The nonspecific (NS) binding was defined in the presence of 10-μM naloxone.

2.3.3. GTP[γ]^{35}S binding assays

Membranes were combined with test compounds and approximately 0.2 nM [^{35}S]GTPγS in 50 mM Hepes, 20 mM NaOH, pH 7.4, 5 mM $MgCl_2$, 100 mM NaCl, 1 mM ethylenediaminetetraacetic acid, 1 mM dithiothreitol, 0.1%

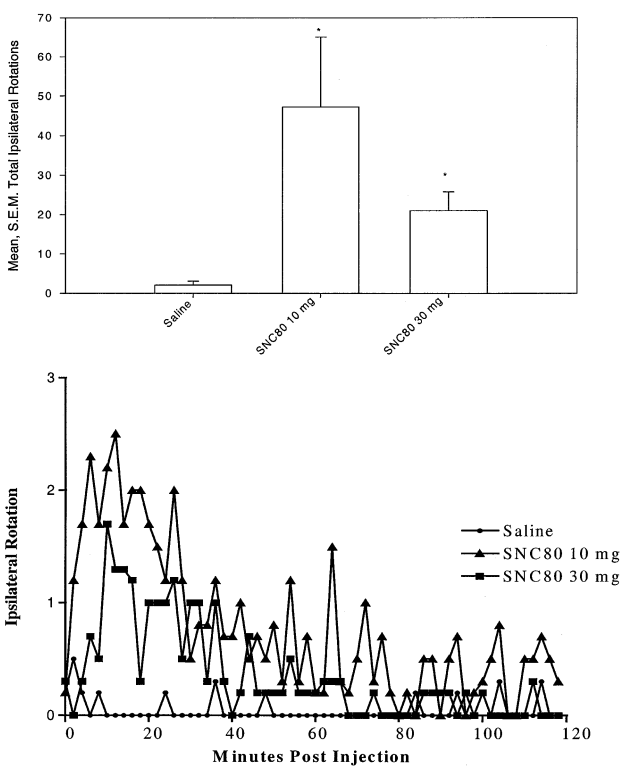

Fig. 2. Effects of SNC-80 (10 and 30 mg/kg; $N = 6$) on ipsilateral rotations over a 2-h observation period. Other details are as described in the legend for Fig. 1. * Indicates significant difference from saline control (ANOVA, Dunnett's post-hoc analysis).

bovine serum albumin, 15 μM GDP. After 1 h, the bound radioactivity was determined by filtration. Control and stimulated binding were determined in the absence and presence of reference agonists: 3 μM SNC-80 for δ-opioid receptors, 30 μM [D-Ala(2), *N*-MePhe(4), Gly-ol(5)]enkephalin (DAMGO) for μ-opioid receptors, and 3 [(+)-(5alpha,7alpha, 8beta)-*N*-methyl-*N*-(7-(1-pyrrolidinyl)-1-oxaspiro(4,5)dec-8-yl)-benzeneacetamide] μM (U69593) for κ-opioid receptors.

3. Results

3.1. Effects of delta opioid on rotational activity

Tonazocine induced ipsilateral rotation (Fig. 1, upper panel; $F(3,39) = 5.2$, $P < 0.01$), without causing significant contralateral rotation (data not shown), suggesting activity on the unlesioned side. Post-hoc analysis showed that the 1 and 10 mg/kg doses of tonazocine significantly evoked rotation relative to saline. Turning was highest during the first 20-min following drug administration (Fig. 1, lower panel), decreased by about 50% thereafter, but remained sustained at that level for the remainder of the 2-h test session. The 10-mg/kg dose was not more effective than the 1-mg/kg dose, suggesting a ceiling on efficacy.

SNC-80 (10 and 30 mg/kg) also induced significant ipsilateral rotation (Fig. 2, upper panel; $F(2,15) = 4.5$, $P < 0.05$) that diminished after 40 min (Fig. 2, lower panel). The higher dose of SNC-80 (30 mg/kg) caused contralateral rotation as well (Fig. 3, upper panel; $F(2,15) = 4.8$, $P < 0.05$) which was evident between 20 and 80 min post injection (Fig. 3, lower panel). The level of efficacy of SNC-80 on ipsilateral rotation (early after drug administration) was somewhat lower than that of tonazocine, and its duration of action either in inducing ipsilateral or contralateral rotation was shorter than that of tonazocine (Figs. 2 and 3, lower panels).

The ipsilateral rotation induced by tonazocine at 10 mg/kg was blocked by the selective δ-opioid receptor antagonist naltrindole (Fig. 4). While the lower naltrindole dose (0.1 mg/kg) was unable to block the effects of tonazocine, 3 mg/kg naltrindole reduced the number of

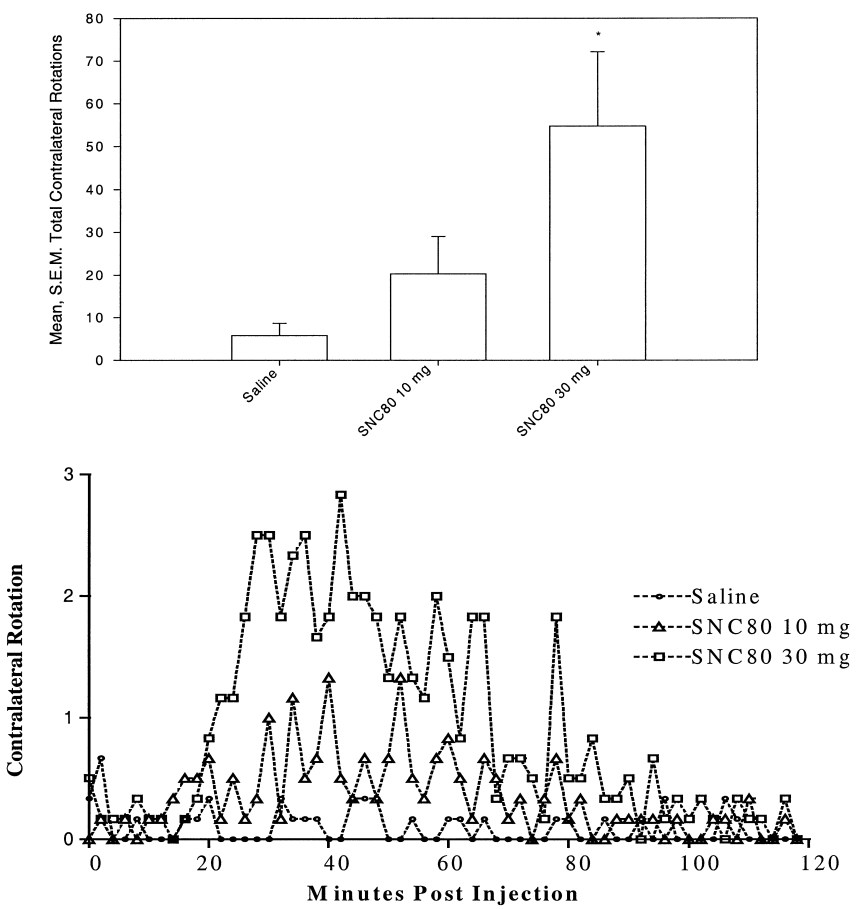

Fig. 3. Effects of SNC-80 (10 and 30 mg/kg; $N = 6$) on contralateral rotations over a 2-h observation period. Other details are as described in the legend for Fig. 1. * Indicates significant difference from saline control (ANOVA, Dunnett's post-hoc analysis).

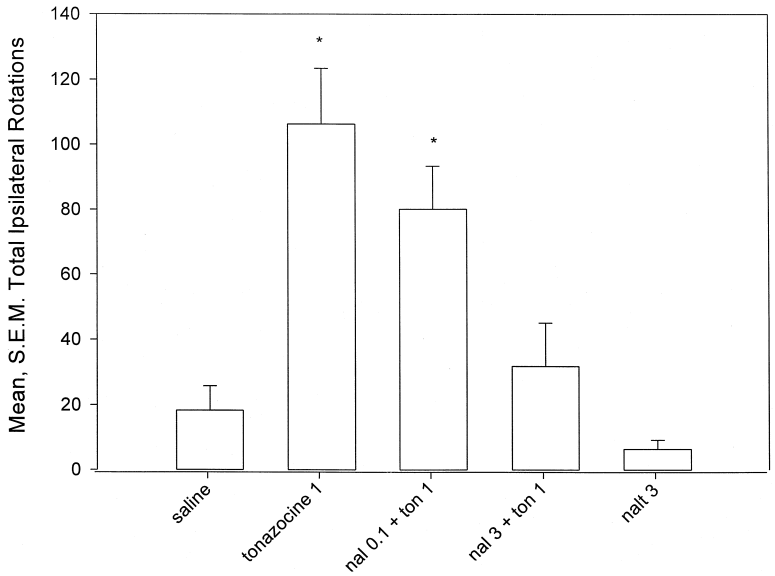

Fig. 4. Effects of naltrindole (0.1 and 3 mg/kg; nal) on tonazocine (1 mg/kg; ton)-induced turning behavior. Saline-treated group ($N = 8$), tonazocine alone or with naltrindole ($N = 8$–10). Data shown are group mean, S.E.M. of total ipsilateral turns in the observation period. * Indicates significant difference from saline control alone (ANOVA, Dunnett's post-hoc analysis).

turns to that of the saline control. 3 mg/kg naltrindole when administered alone, was without effect on turns. These data indicate that the rotation induced by tonazocine was likely mediated by δ receptors.

3.2. Effects of tonazocine on reserpine-induced depression of motor activity

On its own tonazocine (10 and 30 mg/kg) did not reverse the motor activity depression induced by reserpine (data not shown). However, in combination with another-wise ineffective dose of L-DOPA (Fig. 5) there was a reversal of motor activity depression (ANOVA, $F(4,36) = 5.7$, $P < 0.001$); restoring levels of activity to that of the naïve group.

3.3. Receptor binding and in vitro functional activity

In cell lines transfected with human μ, δ and κ receptors, tonazocine demonstrated high (nM) affinity for each of the opioid receptor types, although agonist activity was appreciable only at the δ-opioid receptor, where it showed

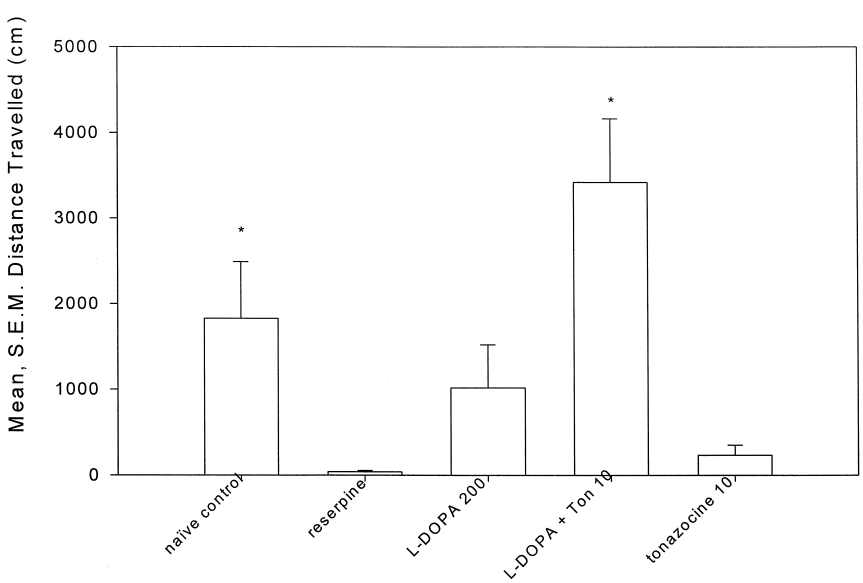

Fig. 5. Effects of combination of L-DOPA (200 mg/kg) with tonazocine (10 mg/kg) on reserpine-induced suppression of motor activity. Naive controls ($N = 12$), reserpine ($N = 8$), L-DOPA alone ($N = 8$), L-DOPA with tonazocine ($N = 7$), tonazocine alone ($N = 6$). Data shown are mean, S.E.M. cm travelled in the observation period. * Indicates significant difference from the group treated with reserpine alone (ANOVA, Dunnett's post hoc).

Table 1
Receptor binding data are expressed as K_i values for inhibition of radioligand binding. Radioligands used were [^{125}I]-FK33824, [^{125}I]-[D-Ala^2]-deltorphin II and [^{125}I]-D-Pro^{10}-Dynorphin A[1-11] for labelling μ, δ, and κ receptors, respectively. Receptor activation data are expressed as EC_{50} and E_{max} in stimulating [^{35}S]GTPγS binding. Values shown are means of at least three independent determinations as described in Section 2.

Ligand	Receptor binding			Receptor activation					
	μ	δ	κ	μ		δ		κ	
	K_i (nM)	K_i (nM)	K_i (nM)	EC_{50} (nM)	% E_{max}	EC_{50} (nM)	% E_{max}	EC_{50} (nM)	% E_{max}
DAMGO	0.466	429	396	223	100.00	–	–	–	–
SNC-80	309	1.05	1661	303	12.41	2.14	100.00	11232	22.60
SNC-86	1.97	0.212	13.5	458	64.04	0.050	96.88	–	–
U-69593	216	> 3700	0.895	–	–	–	–	23.6	100.00
Tonazocine	0.097	1.39	0.317	Antagonist		9.38	40.01	7.28	7.56

partial agonism (40% maximal effect), unlike SNC-80, which had full agonist efficacy (Table 1). Confirming sensitivity of the efficacy assay, DAMGO, SNC-80 and U-69593 produced full agonist efficacy at μ, δ, and κ receptors, respectively. The metabolite of SNC-80, SNC-86, while having full agonist efficacy at δ receptors, also had partial agonist efficacy at μ receptors.

4. Discussion

Tonazocine caused ipsilateral rotation whereas SNC-80 caused ipsilateral rotation early in the observation period, and contralateral rotation later in the period. Tonazocine augmented the efficacy of L-DOPA in the reserpine model. These data, while confirming the therapeutic potential of δ-opioid receptor agonists in Parkinson's, also demonstrate some differences among the activities of the compounds tested. This may be due in part to partial verses the full agonist properties of tonazocine and SNC-80, respectively. It is also possible that SNC-80, or a metabolite, possesses other properties unrelated to δ-opioid receptor activity, and thereby responsible for the late, contralateral rotation. There is evidence (Schetz et al., 1996) suggesting that, following systemic administration, SNC-80 may be converted to SNC-86, an analog that has only 9-fold selectivity for binding to δ vs. μ receptors (Table 1). Tonazocine additionally possesses μ antagonist and slight κ agonist activity, whereas SNC-80 lacks affinity for these receptors. While partial μ agonist activity was detected for SNC-86 in the present study, this activity is unlikely to have contributed to the ipsilateral rotation engendered by SNC-80, since the prototypic μ agonist, morphine, produces modest ipsilateral, not contralateral rotation in unilaterally-lesioned rats (Kimmel et al., 1995; Ehsan and Akerman, 1997).

Although not quantified in the present study, following high doses, SNC-80 appeared to have behavioral stimulant activity, which has also been reported in other laboratories (Spina et al., 1998). Following administration of higher doses of tonazocine, however, sedation was apparent (decreased motor activity). Whereas some δ-opioid receptor agonists appear to have proconvulsant activity (Comer et al., 1993), tonazocine was effective in our hands in blocking seizure induced by maximal electrical stimulation (MES test), with an ED_{50} value of 4 mg/kg (Hudzik, unpublished observations). This suggested to us that perhaps tonazocine may have additional biochemical properties, one of which might have been NMDA receptor antagonist activity. However, tonazocine lacks any potency in displacing [^{3}H]MK-801 (R. Ray and T. Hudzik, unpublished observations), indicating that it is not an NMDA open channel blocker. The sedative-like effects of tonazocine noted after administration of the high dose could possibly have been due to it's partial agonist efficacy at κ receptors, although the low level of efficacy measured in the present study (< 10%) would indicate that this is an unlikely.

The mechanism whereby δ-opioid receptor agonists may induce turning behavior remains to be clarified. One possibility is that δ-opioid receptor agonists directly induce release of dopamine on the unlesioned side, thereby inducing ipsilateral rotation. There is evidence for dopamine agonist-like or CNS stimulatory activity of δ-opioid receptor agonists. For example, Negus et al. (1998) have shown that in rhesus monkeys trained to discriminate cocaine from saline, SNC-80 produces cocaine-like discriminative stimulus effects which are blocked by naltrindole, the selective δ-opioid receptor antagonist. Interestingly, the dopamine D_2 receptor antagonist flupenthixol was unable to block the cocaine-like discriminative stimulus effects of SNC-80, suggesting that these δ-opioid receptor mediated effects may be independent of dopaminergic transmission, ''downstream'' from dopamine D_2 receptors, or mediated by another dopamine receptor subtype. SNC-80 was not self-administered by rhesus monkeys in this study, suggesting that although SNC-80 may share some cocaine-like effects, under these conditions, it does not share its abuse liability. Other stimulant like effects of δ-opioid receptor agonists have been shown by Spina et al. (1998) which include stereotyped behaviors and enhanced locomotion, reversible by naltrindole but

only partially by dopamine receptor agonists. The peptidergic δ-opioid receptor agonist DPDPE has also been shown to enhance the motor stimulatory effects of cocaine (Waddell and Holtzman, 1998). However, despite the stimulant like profile of some δ-opioid receptor agonists, SNC-80 and BW373U86 do not evoke dopamine release in striatum, but after high doses, may actually decrease dopamine release in striatum (Longoni et al., 1998).

The circuitry underlying motor control and its disruption by dopaminergic denervation is fairly complex, (reviewed by Schwarting and Huston, 1996). Within striatum, cholinergic interneurons provide net inhibition of motor outflow, thus partially explaining the efficacy of anticholinergics in treatment of the disorder. Given that δ-opioid receptors appear to be localized on these striatal cholinergic neurons (Le Moine et al., 1994), it is possible that a net indirect anticholinergic effect underlies the effects of δ-opioid receptor agonists. At the present time, this explanation of activity cannot be ruled out. In cortex, reciprocal circuitry to striatum and thalamus, or to substantia nigra, may also provide another potential site of activity. However, this speculation awaits anatomical localization of δ-opioid receptors upon glutamatergic, gabaergic or dopaminergic neurons in these pathways.

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