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Short communication

BW373U86, a δ-opioid receptor agonist, reverses bradykinin-induced thermal allodynia in rhesus monkeys

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Abstract

The synthetic δ-opioid receptor agonist BW373U86 (0.18–0.56 mg/kg s.c.) was studied in rhesus monkeys with a warm-water, tail-withdrawal assay, designed to detect bradykinin (0.1 μg) and prostaglandin E_2 (5–15.8 μg)-induced thermal allodynia. BW373U86 dose-dependently reversed bradykinin allodynia, but was ineffective against prostaglandin E_2 allodynia. The BW373U86 dose-effect curve was shifted to the right by the δ-opioid receptor-selective antagonist naltrindole (1.0 mg/kg) but not by the μ-opioid receptor-selective antagonist quadazocine (0.1 mg/kg). The present findings add to the conditions in which δ-opioid receptor-mediated behavioral effects have been detected in primates, and suggest that δ-opioid agonists may be of therapeutic interest in the treatment of some types of hyperalgesic conditions.

Keywords: BW373U86; δ-Opioid receptor agonist; Allodynia; Hyperalgesia; Rhesus monkey

1. Introduction

The synthetic amine (±)-4-((α-*R**)-α-((2*S**,5*R**)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-*N*,*N*-diethylbenzamide dihydrochloride (BW373U86) has recently been described as a selective δ-opioid receptor agonist in vitro and in vivo in rodents and pigeons (e.g., Chang et al., 1993; Comer et al., 1993). BW373U86 also produced δ-opioid receptor-mediated modulation of μ-opioid agonist effects in a shock titration assay in squirrel monkeys (Dykstra et al., 1993), but it was found to be largely devoid of antinociceptive effect by itself. In rhesus monkeys, BW373U86 was also inactive in a test of thermal antinociception (the warm water tail withdrawal assay; Negus et al., 1994), but produced δ-opioid receptor-mediated suppression of food-reinforced responding. In the present studies, we characterized the effects of s.c. BW373U86 on bradykinin- and prostaglandin E_2-induced thermal allodynia/hyperalgesia in a modified version of the warm water tail withdrawal assay in rhesus monkeys (see Negus et al., 1993b).

2. Materials and methods

2.1. Subjects

Male and female adult rhesus monkeys (macaca mulatta) were individually caged, with free access to water. They were fed approximately 30 Purina monkey chows daily and fresh fruit twice per week. The monkeys were extensively habituated to sit in standard restraint chairs; they were maintained in accordance with procedures approved by the University Committee on Care and Use of Animals, University of Michigan, and guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council (Dept. of Health, Education and Welfare, Publication No. (NIH) 85-23, revised 1983).

2.2. Procedure

The procedure has been described in detail previously (Negus et al., 1993b). Briefly, the terminal 10 cm

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of a rhesus monkey's tail ($n = 3$) is immersed in water maintained at 38° C, 42° C or 50° C, and tail withdrawal latencies are manually recorded (maximum allowed [cutoff] latency = 20 s). Under normal conditions, 38° C and 42° C water is non-noxious (yielding cutoff latencies), whereas 50° C water is noxious (latencies in the range of 1–2 s). Bradykinin (0.1 μg) or prostaglandin E_2 (5 or 15.8 μg) were injected s.c. into the terminal 1 cm of the tail, and withdrawal latencies were measured at 15–30 min intervals up to 120 min.

2.3. Design

Single BW373U86 doses (0.18–0.56 mg/kg) were administered 15 min prior to bradykinin or prostaglandin E_2. In antagonism experiments, naltrindole (1.0 mg/kg) or quadazocine (0.1 mg/kg) were administered in the back, 30 min before BW373U86.

2.4. Drugs

BW373U86 (Burroughs Wellcome Co., Research Triangle Park, NC, USA), naltrindole HCl (NIH-NIDDK, Bethesda, MD, USA) and quadazocine methanesulfonate (Sterling Winthrop, Rensselaer, NY, USA) were dissolved in sterile water and injected s.c. in the back, typically at a volume of 0.1 ml/kg. Bradykinin and prostaglandin E_2 were dissolved in saline, and injected s.c. into the terminal 1 cm of the tail, at a constant volume of 0.1 ml.

3. Results

Bradykinin (0.1 μg) caused a transient decrease in withdrawal latencies in 42° C, starting within 15 min after injection. This effect had completely subsided by 90 min (Fig. 1); a similar profile was observed after prostaglandin E_2 (5 or 15.8 μg; see Negus et al., 1993b). Latencies in 38° C were not affected by bradykinin or prostaglandin E_2 administration, and remained at cutoff levels throughout (not shown). BW373U86 (0.18–0.56 mg/kg) completely and dose-dependently prevented the effects of bradykinin (see Fig. 1, for time-course data). At the same dose range, BW373U86 did not elevate 42° C latencies in the presence of prostaglandin E_2 (5 or 15.8 μg), or 50° C latencies in the absence or the presence of bradykinin (not shown). Higher BW373U86 doses could not be evaluated, due to the presence of brief convulsions after bolus doses larger than 0.56 mg/kg. A BW373U86 dose-effect curve was constructed from data obtained 15 min after bradykinin administration (Fig. 2). The BW373U86 dose required to obtain a 10 s latency in the presence of bradykinin (ED10″) was 0.30 mg/kg, as determined by linear regression from the mean

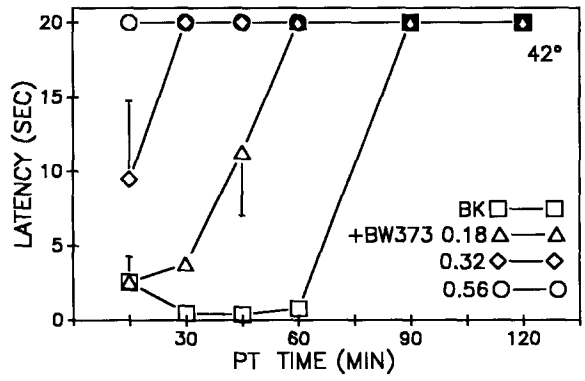

Fig. 1. Time course of the effects of tail injection of bradykinin (0.1 μg, $n = 3$, data points are mean ± S.E.M.) alone or after pretreatment with BW373U86 (s.c., midscapular region of the back). Ordinate: withdrawal latency; abscissa: time after bradykinin injection. Latencies in 42° C in the absence of bradykinin were at cutoff (not shown).

dose-effect curve. The δ-opioid-selective antagonist naltrindole (1.0 mg/kg) was administered 30 min prior to BW373U86 in the presence of bradykinin; this pretreatment caused a parallel rightward shift in the BW373U86 dose-effect curve (Fig. 2). The ED10″ value in the presence of naltrindole was 0.96 mg/kg, indicating approximately a 1/2 log unit shift relative to baseline. Pretreatment with a small dose of the μ-opioid receptor-selective antagonist quadazocine (0.1 mg/kg) did not shift the BW373U86 dose-effect curve (Fig. 2).

4. Discussion

Bradykinin (0.1 μg/kg) caused transient thermal allodynia in 42° C in this model, similar to previously reported treatment with prostaglandin E_2 (5–15.8 μg; Negus et al., 1993b). BW373U86 dose-dependently

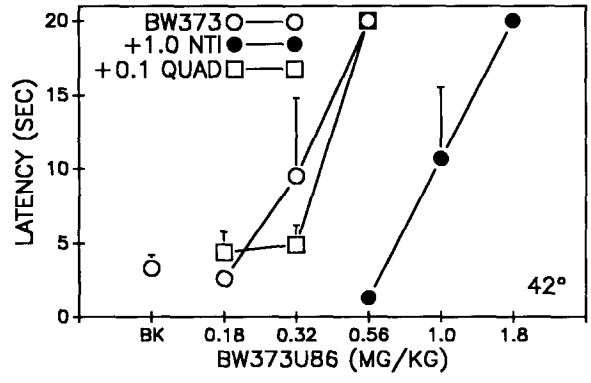

Fig. 2. Effects of BW373U86 on thermal hyperalgesia, measured 15 min after tail injection of bradykinin in 42° C water. BW373U86 dose-effect curve was redetermined 30 min after pretreatment with naltrindole (NTI, 1.0 mg/kg) or quadazocine (0.1 mg/kg). Point above 'BK' represents latencies after bradykinin alone. Abscissa: BW373U86 dose; other details as in Fig. 1.

prevented bradykinin-induced allodynia, but was ineffective against a thermal stimulus that is noxious in the absence of any treatment (i.e., 50° C water; see also Negus et al., 1994). The effect of BW373U86 was surmountably antagonized by naltrindole (1.0 mg/kg) pretreatment. The magnitude of the naltrindole shift is commensurate with a δ-opioid receptor-mediated effect of BW373U86 in this assay (Negus et al., 1994). Since sufficiently high naltrindole doses can also block μ-opioid receptor-mediated effects (France et al., 1990; Negus et al., 1994), we tested whether a μ-opioid receptor-selective dose of quadazocine (i.e., 0.1 mg/kg, see Negus et al., 1993a) would block the effect of BW373U86; the lack of antagonism observed after this quadazocine dose eliminates the possibility that BW373U86 produced its present effect by a μ-receptor mechanism. Up to the highest dose that could be tested, BW373U86 was ineffective against prostaglandin E_2-induced allodynia; for comparison, morphine was effective against both bradykinin- and prostaglandin E_2-induced allodynia (Negus et al., 1993b; submitted). A similar selectivity profile in the effects of a δ-opioid receptor agonist was reported in rats, with local administration of the δ-selective peptide [D-Pen^{2,5}]enkephalin (DPDPE) and bradykinin or prostaglandin E_2 (Taiwo and Levine, 1991). Taiwo and Levine (1991) concluded that this selectivity was accounted for by colocalization of bradykinin and δ-opioid receptors in post-ganglionic sympathetic fibers, whereas prostaglandin E_2 receptors were presumed to be located on primary afferent neurons. In these studies, BW373U86 was administered s.c. in the back, at doses that decrease food-reinforced operant responding (Negus et al., 1993a), therefore it cannot be concluded at present that BW373U86 decreased bradykinin-induced hyperalgesia by a local mechanism. These findings add to the set of conditions under which δ-opioid receptor-mediated behavioral effects have been observed in primates (e.g., Negus et al., 1993a, 1994; Dykstra et al., 1993), and strengthen suggestions that δ-receptor agonists possess therapeutic potential in the treatment of at least some types of allodynia or hyperalgesia.

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