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Short communication

Evidence for a 5-HT_{1D} receptor-mediated hypothermic effect of the α_1-adrenoceptor agonist, SDZ NVI-085, in guinea-pigs

Hans O. Kalkman *, Vroni Neumann

Preclinical Research, Sandoz Pharma Ltd, Building 360–405, CH-4002 Basel, Switzerland

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Abstract

The α_1-adrenoceptor agonist, SDZ NVI-085 ((−)-(4*aR*,10*aR*)-3,4,4*a*,5,10,10*a*-hexahydro-6-methoxy-4-methyl-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine · HCl; 1 mg/kg i.p.), decreased body temperature of guinea-pigs. Two 5-HT_{1D} receptor antagonists, GR127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3yl)[1,1-biphenyl]-4-carboxamide) and PAPP (*p*-aminophenylethyl-*m*-trifluoromethylphenyl piperazine; both compounds at 1 mg/kg i.p., −30 min) blocked this response, whilst the α_1-adrenoceptor blocker prazosin (1 mg/kg i.p.) and the 5-HT_{1A} receptor antagonist, SDZ 216-525 (methyl 4-{-[4-(1,1,3-trioxo-2*H*-1,2-benzoisothiazol-2-yl)butyl]-1-piperazinyl}1*H*-indole-2-carboxylate; 1 mg/kg i.p.) were inactive. Another α_1-adrenoceptor agonist, St 587 (2-(2-chloro-5-trifluoromethylphenylimino)-imidazoline; 1 mg/kg i.p.) did not alter body temperature. SDZ NVI-085-induced hypothermia in guinea-pigs is probably mediated by 5-HT_{1D} receptors.

Keywords: α_1-Adrenoceptor agonist; 5-HT_{1D} receptor agonist; Hypothermia

1. Introduction

While testing centrally acting α_1-adrenoceptor agonists, a discrepancy was noted in the results with St 587 (2-(2-chloro-5-trifluoromethylphenylimino)-imidazoline; De Jonge et al., 1981) and SDZ NVI-085 ((−)-(4*aR*,10*aR*)-3,4,4*a*,5,10,10*a*-hexahydro-6-methoxy-4-methyl-9-(methylthio)-2*H*-naphth[2,3-*b*]-1,4-oxazine · HCl; Nozulak et al., 1992). Whereas the latter compound reduced body temperature of conscious unrestrained guinea-pigs, the former compound was inactive at otherwise pharmacologically active doses. The hypothermic effect of SDZ NVI-085 was further investigated, using the α_1-adrenoceptor antagonist prazosin (Cambridge et al., 1977), the 5-HT_{1A} receptor antagonist SDZ 216-525 (methyl 4-{-[4-(1,1,3-trioxo-2*H*-1,2-benzoisothiazol-2-yl)butyl]-1-piperazinyl}1*H*-indole-2-carboxylate; Schoeffter et al., 1993), the 5-HT_{1D} receptor antagonists GR127935 (*N*-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3yl)[1,1-biphenyl]-4-carboxamide; Skingle et al., 1994) and the low efficacy 5-HT_{1D} receptor agonist PAPP (*p*-aminophenylethyl-*m*-trifluoromethylphenyl piperazine; Schoeffter and Hoyer, 1989).

2. Materials and methods

Twenty male GOHI guinea-pigs (BRL Füllinsdorf, Switzerland) weighing between 300 and 500 g were used. When the animals weighed 300 g, they were implanted with a transmitter for telemetric measurement of body temperature. To this end, the animals were anaesthetized with fentanyl/fluanison (Hypnorm, Janssen Pharmaceutica, Beerse, Belgium; 1 ml/kg i.p.) and diazepam (Valium, Hoffmann-la Roche, Basel, Switzerland; 5 mg/kg i.p.). The abdomen was opened, the transmitter device (type TA10TA-F40; Data Sciences, St Paul, MN, USA; size approximately 20 × 10 × 5 mm) introduced into the abdominal cavity and the skin closed with an internal and external suture. Thereafter, the guinea-pigs were placed underneath a heating lamp for 2–6 h in order to regain normal body temperature as quickly as possible.

* Corresponding author. Tel.: +41 61 324 4304; fax: +41 61 324 4866.

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The animals were studied at weekly intervals. For each experiment, the animals were habituated to individual cages (Macrolon 60 × 34 × 20 cm) overnight. Room temperature was maintained at 22°C. The next day, animals were injected twice. For the testing of agonists, the first injection was always saline, followed 30 min later by the drug. During antagonism tests, the putative antagonist was given 30 min prior to the agonist, whilst the effect of antagonists alone was tested by administration of the antagonist followed 30 min later by injection of saline. For a given agonist, the saline/agonist, antagonist/agonist and antagonist/saline experiment was randomized and performed within one month. Absolute body temperature values were measured at 10 min intervals for 5.5 h, transmitted to two interconnected receivers (type RLA 100; Data Sciences) which were placed underneath the cage, and the signal fed into a computer (Hewlett-Packard Vectra). Data handling was performed under OS/2 (IBM, version 1.3), using the software package Dataquest IV (version 2.2; Data Sciences, St Paul, MN, USA). The maximal hypothermic effect was compared with the control values at the same time point using the Student t-test.

All compounds were synthetised at Sandoz, except prazosin and PAPP, which were purchased from RBI. Drugs were dissolved in physiological saline or glucose solution (prazosin) and injected intraperitoneally.

3. Results

The mean ± S.E.M. abdominal body temperature measured by the implanted transmitter was 39.0 ± 0.1°C in the non-drug-treated state. As shown in Fig. 1, i.p. administration of St 587, at a high dose (1 mg/kg; De

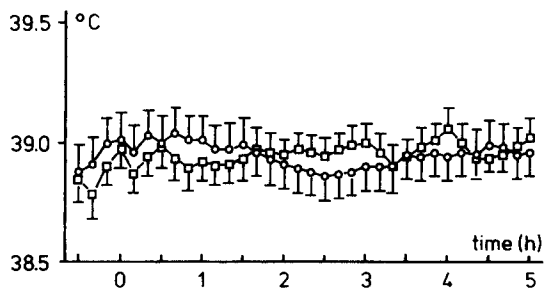

Fig. 1. Effect of St 587 (1 mg/kg i.p.) on body temperature of conscious unrestrained guinea-pigs. Body temperature (in °C) was measured in the abdomen using an implanted telemetrical device. Animals ($n = 20$) were injected physiological saline at $t = -30$ min, and at $t = 0$ h either St 587 or solvent. The experiment was randomized in that half of the animals were first treated with agonist and one week later with the solvent, the other half had the reversed order. Key: Circles represent data for solvent-treated animals, squares are for St 587-treated animals. Data are means ± S.E.M.

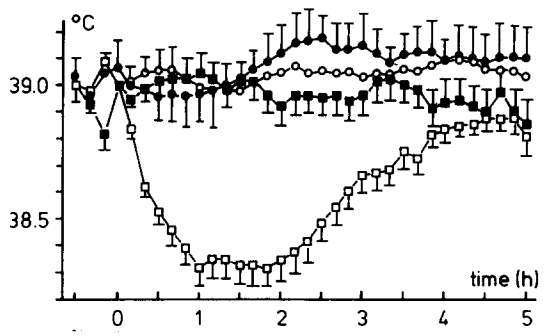

Fig. 2. Effect of SDZ NVI-085 (1 mg/kg i.p. at $t = 0$) on body temperature of guinea-pigs. The hypothermic effect of SDZ NVI-085 ($n = 20$; open squares) was abolished by PAPP (closed squares; $n = 20$) and by GR127935 ($n = 16$, closed circles). As in Fig. 1, open circles represent the temperature data of saline/saline-treated controls. The antagonists, in the doses used (1 mg/kg i.p. at $t = -30$ min) did not influence body temperature (not shown). Data are means ± S.E.M. A comparison (Student's t-test) between agonist- and saline-treated groups at $t = 1$ h gave a P value of less than 0.001.

Jonge et al., 1981) did not change temperature. In contrast, SDZ NVI-085 at 1 mg/kg i.p. produced an 0.8°C fall at $t = 1$ h ($P < 0.001$). This hypothermic effect was totally abolished by GR 127935 and PAPP (each at 1 mg/kg i.p.; see Fig. 2), but remained unaffected by prazosin or SDZ 216-525 (both at 1 mg/kg): for instance at $t = 90$ min, SDZ NVI-085 in animals pretreated with prazosin's solvent caused a fall in temperature of 0.59 ± 0.07°C, in animals receiving prazosin/SDZ NVI-085 this was 0.67 ± 0.07°C (means ± S.E.M., $P > 0.05$). The data in the experiment with SDZ 216-525 were: solvent/SDZ NVI-085 0.55 ± 0.08°C, SDZ 216-525/SDZ NVI-085 0.58 ± 0.08°C, $P > 0.05$). None of the antagonists produced significant temperature effects by themselves, except prazosin which after 1 h slightly increased body temperature. This effect did, however, not influence the hypothermia to SDZ NVI-085.

4. Discussion

SDZ NVI-085 displays α_1-adrenoceptor agonist properties in rats (Nozulak et al., 1992) and dogs (Renaud et al., 1991) at doses of 1 mg/kg and higher. In the pithed rat SDZ NVI-085 was slightly less potent than St 587 with respect to α_1-adrenoceptor-mediated hypertension (ED_{50} values 70 μg/kg and 20 μg/kg, respectively; Nozulak et al., 1992; De Jonge et al., 1981). St 587 (0.125–8 mg/kg i.v.) caused dose-dependent EEG changes in conscious rabbits and this effect was blocked by prazosin (1 mg/kg i.v.; Stumpf and Pichler, 1988). This summary shows that SDZ NVI-085 and St 587 are centrally acting α_1-adrenoceptor agonists at 1 mg/kg, with possibly St 587 being slightly

more potent than SDZ NVI-085. However, in the present experiment only SDZ NVI-085 diminished body temperature in the guinea-pig.

SDZ NVI-085 has significant affinity for serotonin 5-HT_{1D} (pK_D 8.1) and 5-HT_{1A} (pK_D 7.4) receptors (Hoyer, unpublished). These findings have guided the choice of antagonists in the present study.

PAPP, a drug with partial agonist effects at 5-HT_{1A} and 5-HT_{1D} receptors (Schoeffter and Hoyer, 1989), blocked the hypothermic response to SDZ NVI-085 in guinea-pigs (Fig. 2). In contrast, the selective 5-HT_{1A} receptor antagonist, SDZ 216-525 (1 mg/kg i.p.) did not affect the hypothermia in guinea-pigs, whilst the same dose abolished the hyperlocomotor response to the selective 5-HT_{1A} receptor agonist, 8-OH-DPAT, in this species (not shown). *In rats*, SDZ 216-525 (1 mg/kg s.c.) abolished 8-OH-DPAT-induced hypothermia and strongly inhibited two other 5-HT_{1A}-mediated behaviours, flat body posture and forepaw treading (Schoeffter et al., 1993). These results indicate that 5-HT_{1A} receptors are not involved in the hypothermic response to SDZ NVI-085. Skingle et al. (1994) reported that the selective 5-HT_{1D} receptor antagonist, GR127935, dose-dependently (0.1–1.0 mg/kg p.o.) inhibited the hypothermic effect of the 5-HT receptor agonist, GR46611, in guinea-pigs. In the present experiments, GR127935 (1 mg/kg i.p.) blocked SDZ NVI-085-induced hypothermia (Fig. 2), thus providing evidence for the involvement of 5-HT_{1D} receptors.

Thus in conclusion, the results indicate that SDZ NVI-085 induces hypothermia in guinea-pigs by activation of 5-HT_{1D} receptors, whereas α_1-adrenoceptors and 5-HT_{1A} receptors seem not to be involved.

Acknowledgements

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