Modulation of the hypothermic and hyperglycaemic effects of 8-OH-DPAT by α_2 -adrenoceptor antagonists

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1 The effects of pretreatment with two novel and relatively specific α_2 -adrenoceptor antagonists on the hypothermic and hyperglycaemic responses induced by the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) were investigated in mice. The α_2 -adrenoceptor antagonists used were, atipamezole, which occupies both central and peripheral receptors, and L 659,066, which poorly penetrates the blood brain barrier.

2 Atipamezole (1 and 3 mg kg⁻¹) alone had no effect on body temperature but significantly attenuated the 8-OH-DPAT-induced hypothermic response. The hyperglycaemic effect of 8-OH-DPAT was also attenuated by pretreatment with atipamezole; however, 3 mg kg⁻¹ atipamezole did cause some hypoglycaemia when administered alone.

3 Pretreatment with L 659,066 (3–30 mg kg⁻¹) failed to alter the hypothermic effects of 8-OH-DPAT. All doses of L 659,066 tested attenuated 8-OH-DPAT-induced hyperglycaemia, but the highest dose (30 mg kg⁻¹) produced hypoglycaemia when administered alone.

4 The results suggest that the attenuation of 8-OH-DPAT-induced hypothermia by α_2 -adrenoceptor antagonists may be centrally mediated whereas the blockade of 8-OH-DPAT-induced hyperglycaemia may involve peripheral mechanisms.

Introduction

8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) is a relatively selective centrally acting 5-hydroxytryptamine (5-HT) agonist (Hjorth *et al.*, 1982), which has been shown to have a high affinity for the 5-HT_{1A} receptor subtype (Middlemiss & Fozard, 1983). In rodents, 8-OH-DPAT produces both hypothermia and hyperglycaemia (Hjorth, 1985; Goodwin *et al.*, 1985; Middlemiss *et al.*, 1985; Gudelsky *et al.*, 1986; Chaouloff & Jeanrenaud, 1987; Wozniak *et al.*, 1988), although the precise mechanism of action of 8-OH-DPAT on body temperature and blood glucose levels is, at present, not fully understood. In addition to its 5-HT agonist properties, 8-OH-DPAT is reported to have α_2 -adrenoceptor antagonist properties (Crist & Suprenant, 1987) and it can generalize to the α_2 -adrenoceptor antagonist yohimbine in a drug discrimination task (Winter, 1988). Additionally, 8-OH-DPAT has reported activity at dopamine D₂ receptors (Smith & Cutts, 1989; Bull *et al.*, 1990). The relatively selective α_2 -adrenoceptor antagonist, idazoxan, can however, block the decrease in extracellular 5-hydroxy-indoleacetic acid (5-HIAA) produced by 8-OH-DPAT and also reverse 8-OH-DPAT-induced hyperglycaemia (Chaouloff & Jeanrenaud, 1987). In this study the effects of pretreatment with the novel and relatively specific α_2 -adrenoceptor antagonists atipamezole (Scheinin *et al.*, 1988) and L 659,066 (Clineschmidt *et al.*, 1988) on 8-OH-DPAT-induced responses were investigated in mice. Atipamezole occupies both central and peripheral receptors, whereas L 659,066 poorly penetrates the blood/brain barrier. Therefore, these compounds enabled differentiating central from peripheral effects of α_2 -adrenoceptor antagonism on 8-OH-DPAT-induced phenomena.

Methods

Naïve NIH Swiss male mice housed in groups of 5 on a 12 h light:12 h dark cycle with food and water available *ad libitum* were used in all experiments. The mice weighed between 21 and 25 g at the time of testing.

Temperature recording

Core body temperatures were measured with a rectal probe and a digital thermometer (Sensortek Inc.). The probe was inserted 2.5 cm into the rectum of each mouse.

Blood glucose determinations

Blood glucose determinations were made from blood drawn from the tail tip and the measurements made with a Glucometer II reflectance photometer (Ames Division, Miles Laboratories, Inc., Yellow Springs, OH, U.S.A.).

Drug administration

The drugs used in these experiments were 8-OH-DPAT (Research Biochemicals Inc, Natic, MA, U.S.A.), atipamezole (Farnos Group Ltd., Turku, Finland), and L 659,066 ((2R-trans)-N-(2-(1,3,4,6,7,12b-hexahydro-2'-oxospiro(2H-benzofuro(2,3-a)quinolizine-2,3-imidazolin)-3'-yl)ethyl)methane-sulphonamide monohydrochloride, MK 912) (Merck, Sharp and Dohme, West Point, PA, U.S.A.).

In Experiment 1 groups of mice ($n = 12$ – 14) were given either 1 or 3 mg kg⁻¹ atipamezole dissolved in distilled water vehicle (i.p.) or vehicle alone immediately following baseline temperature and blood glucose determination. Twenty minutes later body temperature and blood glucose levels were again measured and subsequently followed by the administration of 0.25 mg kg⁻¹ 8-OH-DPAT or saline vehicle (s.c.). Three additional body temperature and blood glucose measurements were performed at 20 min intervals. All injections were administered at a volume of 10 ml kg⁻¹.

In Experiment 2 groups of mice ($n = 8$ – 11) were administered 3, 10 or 30 mg kg⁻¹ L 659,066 dissolved in distilled water vehicle (i.p.) or vehicle alone immediately following the measurement of a baseline temperature and blood glucose. Twenty minutes later body temperature and blood glucose level were again measured and subsequently followed by the administration of 0.25 mg kg⁻¹ 8-OH-DPAT or saline vehicle (s.c.). An additional group of animals received pretreatment with 3 mg kg⁻¹ atipamezole (i.p.) followed 20 min later by 0.25 mg kg⁻¹ 8-OH-DPAT (s.c.) for the purposes of comparison. Three further body temperature and blood glucose mea-

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Figure 1 Mean body temperatures of groups of animals pretreated with 1–3 mg kg⁻¹ atipamezole 20 min before 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) or vehicle treatment. (□) Vehicle + vehicle; (■) vehicle + 8-OH-DPAT; (○) 1 mg kg⁻¹ atipamezole + vehicle; (●) 1 mg kg⁻¹ atipamezole + 8-OH-DPAT; (△) 3 mg kg⁻¹ atipamezole + vehicle; (▲) 3 mg kg⁻¹ atipamezole + 8-OH-DPAT. All s.e.means < 0.3°C. ** $P < 0.01$ vs. vehicle-only treated animals at the same time point; †† $P < 0.01$ vs. vehicle + 8-OH-DPAT treated animals at the same time point.

measurements were performed at 20 min intervals. All injections were administered at a volume of 10 ml kg⁻¹.

Statistics

The data were analyzed by a repeated measures analysis of variance with difference between means compared by *post hoc* Tukey tests.

Results

In Experiment 1, 8-OH-DPAT caused a significant reduction in body temperature ($P < 0.01$) when administered alone, whereas atipamezole alone had no effect on body temperature (Figure 1). The 8-OH-DPAT temperature reduction was

Figure 2 Mean change in blood glucose levels from initial baseline levels of animals pretreated with 1–3 mg kg⁻¹ atipamezole before treatment with either vehicle or 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT); data points shown are for 40 min post 8-OH-DPAT administration (a similar pattern of results is seen at both 20 and 60 min post 8-OH-DPAT, data not shown). Open columns, pretreatment + vehicle; solid columns, pretreatment + 8-OH-DPAT. * $P < 0.05$ vs. vehicle only treated animals; †† $P < 0.01$ vs. vehicle + 8-OH-DPAT-treated animals.

Figure 3 Mean body temperatures of groups of animals pretreated with 3–30 mg kg⁻¹ L 659,066 before 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) or vehicle treatment. To enhance clarity the pretreatments with 3 mg kg⁻¹ L 659,066 and atipamezole are shown in (a) the pretreatments with 10 and 30 mg kg⁻¹ L 659,066 are shown in (b); the vehicle only and vehicle + 8-OH-DPAT groups are the same in both graphs. All s.e.means < 0.3°C. (□) Vehicle + vehicle; (■) vehicle + 8-OH-DPAT; (○) 3 mg kg⁻¹ L 659,066 + vehicle; (●) 3 mg kg⁻¹ L 659,066 + 8-OH-DPAT; (△) 10 mg kg⁻¹ L 659,066 + vehicle; (▲) 10 mg kg⁻¹ L 659,066 + 8-OH-DPAT; (▨) 30 mg kg⁻¹ L 659,066 + vehicle; (▩) 30 mg kg⁻¹ L 659,066 + 8-OH-DPAT. * $P < 0.05$; ** $P < 0.01$ vs. vehicle only treated animals at the same time point.

maximal at 20 min after its administration, decreasing thereafter. This 8-OH-DPAT-induced hypothermia was significantly ($P < 0.01$) attenuated by both doses of atipamezole at each time point post 8-OH-DPAT administration.

The basal blood glucose levels in mice before any treatment were in the range 160–180 mg 100 ml⁻¹. 8-OH-DPAT induced a significant ($P < 0.01$) increase in blood glucose level, although blood glucose levels in the vehicle-treated controls were also moderately elevated; in consequence, the change in glucose level from the initial baseline was analyzed (Figure 2). Pretreatment with atipamezole alone tended to reduce or reverse the increase in blood glucose seen in vehicle-treated controls, with the 3 mg kg⁻¹ dose causing significant ($P < 0.01$) hypoglycaemia. Both doses of atipamezole significantly ($P < 0.01$) blocked the 8-OH-DPAT-induced increases in blood glucose levels at each time point.

In Experiment 2, L 659,066 (3 and 10 mg kg⁻¹) had no intrinsic effect on body temperature; however, the highest dose tested (30 mg kg⁻¹) did significantly ($P < 0.05$) reduce core temperature compared to vehicle-treated control values at all time points (Figure 3). The hypothermic effect of 8-OH-DPAT was not significantly affected by pretreatment with any dose of L 659,066, although pretreatment with 3 mg kg⁻¹ atipamezole

Figure 4 Mean change in blood glucose levels over time from initial baseline levels of animals treated with 3–30 mg kg⁻¹ L 659,066 prior to treatment with either vehicle or 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT), data points shown are for 40 min post 8-OH-DPAT administration (a similar pattern of results is seen at both 20 and 60 min post 8-OH-DPAT, data not shown). Open columns, pretreatment + vehicle; solid columns, pretreatment + 8-OH-DPAT. **P* < 0.05; ***P* < 0.01 vs. vehicle only treated animals at the same time point; †*P* < 0.05; ††*P* < 0.01 vs. vehicle + 8-OH-DPAT-treated animals at the same time point.

pamezole once again significantly (*P* < 0.05) attenuated the hypothermia at both 20 and 40 min after the administration of 8-OH-DPAT. In this experiment the hypothermic effects of 8-OH-DPAT were no longer significant at the 60 min time point.

L 659,066, 30 mg kg⁻¹, caused a significant (*P* < 0.05) fall in blood glucose levels relative to the vehicle-treated control group, 40 to 80 min after administration, although, once again, an increase in blood glucose level was also seen in the vehicle-treated control group (Figure 4). Significant (*P* < 0.01) 8-OH-DPAT-induced increases in blood glucose levels were detected 40 and 60 min after 8-OH-DPAT administration. This 8-OH-DPAT-induced rise in blood glucose level was significantly (*P* < 0.01) blocked both by 3 mg kg⁻¹ of atipamezole and by 3 to 30 mg kg⁻¹ of L 659,066.

Discussion

The observed hypothermic and hyperglycaemic effects of 8-OH-DPAT are similar to those described previously (Chaouloff & Jeanrenaud, 1987; Wozniak *et al.*, 1988). The lack of any intrinsic effects of atipamezole on body temperature has also been noted previously (Durcan *et al.*, 1989). The lower doses (3 and 10 mg kg⁻¹) of the mainly peripherally-acting α_2 -adrenoceptor antagonist, L 659,066 had no effects on body temperature, although, the highest dose tested (30 mg kg⁻¹) did induce hypothermia. The mechanism of this effect is not clear at the present time.

Although 8-OH-DPAT is reported to have α_2 -adrenoceptor antagonist activity (Crist & Surprenant, 1987), its hypothermic effect is thought to be mediated by central 5-hydroxytryptaminergic mechanisms, because it can be blocked by the centrally active 5-HT_{1A} antagonists, methiothepin, spiperone, pizotifen and pindolol (Middlemiss *et al.*, 1985; Gudelsky *et al.*, 1986; Wozniak *et al.*, 1988) whereas xylamide, which is only active peripherally, is without effect (Gudelsky *et al.*, 1986). Further evidence derives from selective lesions of central 5-hydroxytryptaminergic neurones produced by the neurotoxin 5,7 dihydroxytryptamine, which abolish the hypothermic effects of 8-OH-DPAT, implicating presynaptic 5-HT receptors (presumably 5-HT_{1A}). Additionally, depletion of 5-HT with *p*-chlorophenylalanine also abolishes the hypo-

thermic effects of 8-OH-DPAT (Goodwin *et al.*, 1985) and centrally active α_2 -adrenoceptor antagonists, unlike 8-OH-DPAT, do not affect body temperature (Durcan *et al.*, 1989; the present study). Furthermore, the blockade of the hypothermic effect of 8-OH-DPAT by α_2 -adrenoceptor antagonists appears to be centrally mediated since this effect was not seen following pretreatment with L 659,066 which poorly penetrates into the brain.

The mechanism of the observed attenuation of 8-OH-DPAT-induced hypothermia by atipamezole is unclear. The extent of any direct activity of atipamezole or L 659,066 at 5-HT_{1A} sites is not well established; however, other α_2 -adrenoceptor antagonists such as yohimbine, WY 26392 and idazoxan do show significant affinity for 5-HT_{1A} receptor sites (Fozard *et al.*, 1987) and thus direct actions of atipamezole or L 659,066 at 5-HT_{1A} receptor sites cannot be ruled out. α_2 -Adrenoceptors have been found on 5-hydroxytryptaminergic neurones (Göthert & Huth, 1980; Frankhuysen & Mulder, 1980; Göthert *et al.*, 1981), including those in the hypothalamus (Galzin *et al.*, 1982), a brain region associated with thermoregulation (Perkins *et al.*, 1981; Rothwell *et al.*, 1985; Addae *et al.*, 1986). These α_2 -adrenoceptors have been reported to modulate 5-HT release (Göthert & Huth, 1980; Ellison & Campbell, 1986), although their precise physiological function remains to be established (Galzin *et al.*, 1984; Blier *et al.*, 1989). Interestingly, the α_2 -adrenoceptor antagonists, atipamezole and idazoxan, also attenuate ethanol-induced hypothermia (Durcan *et al.*, 1989), for which central 5-hydroxytryptaminergic mechanisms have been implicated (Ritzmann & Tabakoff, 1976; Tabakoff *et al.*, 1978).

The hyperglycaemic effect of 8-OH-DPAT is thought to be, at least in part, centrally mediated, since it can be produced by central (intracerebroventricular) administration (Chaouloff & Jeanrenaud, 1987). The failure of 8-OH-DPAT to cause an increase in blood glucose in animals pretreated with either atipamezole or L 659,066 indicates that the α_2 -adrenoceptor antagonism can influence hyperglycaemia in mice; the α_2 -adrenoceptor antagonist, idazoxan, also attenuates 8-OH-DPAT-induced hyperglycaemia in rats (Chaouloff & Jeanrenaud, 1987). The present results are consistent with a recent report demonstrating that L 659,066 prevents the rise in plasma glucose levels seen following administration of the α_2 -adrenoceptor agonists clonidine and 3,4-dihydroxyphenylimino-2-imidazoline and also improves glucose tolerance in saline pretreated animals (Goldman *et al.*, 1989). The fact that both L 659,066, which poorly penetrates into the brain, as well as the centrally and peripherally active antagonist, atipamezole, have similar effects implicate peripheral mechanisms in the attenuation of hyperglycaemic effects of 8-OH-DPAT. A number of both *in vivo* (Nakadate *et al.*, 1980a,b) and *in vitro* (Nakaki *et al.*, 1980, 1981; Hillaire-Buys *et al.*, 1985) studies have demonstrated α_2 -adrenoceptor involvement in the regulation of insulin secretion. The α_2 -adrenoceptor antagonist yohimbine has been shown to increase insulin secretion (Hsu *et al.*, 1987; Ribes *et al.*, 1989). Conversely, the α_2 -adrenoceptor agonist clonidine has been shown to decrease insulin levels (Senft *et al.*, 1968; Ismail *et al.*, 1983) and increase blood glucose levels (Rehbinder & Deckers, 1968). 8-OH-DPAT has been reported to cause increases in plasma catecholamines, especially adrenaline and noradrenaline (Bagdy *et al.*, 1989). These may increase blood glucose levels since noradrenaline reduces glucose-induced insulin release from the islets of Langerhans (Morgan & Montague, 1985). The adrenaline enhancing properties of 8-OH-DPAT have been linked to its hyperglycaemic effects and can be blocked by (–)-pindolol, which antagonizes 5-HT_{1A} receptor sites as well as β -adrenoceptors (Chaouloff *et al.*, 1990). 8-OH-DPAT-induced increases in catecholamines may therefore result in the observed increases in blood glucose; an effect which may be attenuated by α_2 -adrenoceptor antagonists acting peripherally. A rise in blood glucose is also evident following treatment with vehicle only (possibly as a result of a mild stress resulting from the procedure inducing increased

plasma catecholamine levels), although this is a lesser effect than that seen following 8-OH-DPAT treatment: this effect is also reversed by α_2 -adrenoceptor pretreatment.

In summary, 8-OH-DPAT-induced hypothermia is attenuated by a centrally active α_2 -adrenoceptor antagonist (atipamezole), whereas it is unaffected by pretreatment with an α_2 -adrenoceptor antagonist which poorly penetrates the blood brain barrier (L 659,066). Both antagonists attenuated the hyperglycaemia induced by 8-OH-DPAT. These results

suggest that the attenuation of the 8-OH-DPAT-induced hypothermia by atipamezole may be centrally mediated whereas the blockade of hyperglycaemia, evident with both antagonists, may involve peripheral mechanisms.

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