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Discriminative stimulus properties of the selective and highly potent α_2-adrenoceptor agonist, S18616, in rats: Mediation by the α_{2A} subtype, and blockade by the atypical antidepressants, mirtazapine and mianserin

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Abstract

The novel spiroimidazoline, S18616, a potent and efficacious agonist at α_2-adrenoceptors (ARs), shows >100-fold selectivity *versus* α_1-ARs, imidazoline receptors and all other sites examined. Herein, we characterized its discriminative stimulus (DS) properties in rats trained to recognise S18616 (0.01 mg/kg, s.c.) from saline. S18616 dose-dependently (0.0063–0.01) and "fully" (≥80% "S18616" lever selection) substituted for itself. Full substitution was also acquired for the agonist, UK14,304 (0.04–0.16), while the partial agonist, clonidine (0.01–0.08), yielded submaximal substitution (67%). Guanfacine (0.16–1.25) and guanabenz (0.00063–0.04), preferential agonists at α_{2A}-ARs, revealed full substitution for S18616. In contrast, the α_1-AR agonists, cirazoline and ST587 (both 0.04–0.63), did not substitute. The α_2-AR antagonists, RX821,002, atipamezole (both 0.0025–0.04) and idazoxan (0.04–0.63) blocked the S18616 DS, whereas the α_1-AR antagonists, prazosin (0.16–0.63) and WB4101 (0.04–0.63), were inactive. Prazosin is also a preferential antagonist at $\alpha_{2B/2C}$- *versus* α_{2A}-ARs and a further preferential $\alpha_{2B/2C}$-AR antagonist, BRL41,992 (0.63–2.5), was likewise ineffective. In contrast, the α_{2A}-AR antagonist, BRL44,408 (0.04–0.16), dose-dependently abolished the S18616 DS. Finally, the "atypical" antidepressants, mirtazapine (0.16–10.0) and mianserin (0.63–10.0), which behave as antagonists at α_{2A}-ARs, dose-dependently blocked the S18616 DS. In conclusion, S18616 elicits a robust DS in rats that principally reflects engagement of α_{2A}-ARs. This novel procedure should prove useful in the characterisation of psychoactive drugs which interact with α_2-ARs.
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1. Introduction

Drug discrimination procedures have been widely used to assess the interoceptive properties of a variety of centrally-active agents such as antidepressants, antipsychotics and analgesics (Dekeyne and Millan, 2003; Dykstra et al., 1997; Goudie et al., 2004). They have also proven useful in the characterisation of drugs that interact with various classes of monoaminergic receptor (Dekeyne and Millan, 2003; Dykstra et al., 1997; Goudie et al., 2004). As concerns multiple subtypes of α- and β-adrenoceptor (AR), it has been shown that a specific discriminative stimulus (DS) can be generated in rats by selective agonists at α_1-ARs (Arnt, 1992; Schechter, 1991). Further, agonists at β_1- and β_2-ARs elicit robust DS that have been related to the role of β-ARs in the control of mood and the aetiology of depressive states (Crissman et al., 2001; Crissman and O'Donnell, 2002). Data are, however, less extensive for α_2-ARs of which three functionally-relevant subtypes have been cloned: α_{2A} (also known as the α_{2D} homologue in rats), α_{2B} and α_{2C} (Hieble et al., 1995; Kable et al., 2000; Millan, 2002). Successful attempts to produce an interoceptive cue have been reported with the subtype non-selective

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antagonists, yohimbine, ethoxy-idazoxan (RX811,059) and idazoxan, but the role of α_2-ARs as compared to imidazoline and 5-HT_{1A} receptors in their actions has been questioned (Jordan et al., 1996; Millan et al., 2000f; Sanger, 1989; Winter and Rabin, 1993). Moreover, curiously few studies have been devoted to agonists, with the exception of one investigation of xylazine (Colpaert and Janssen, 1985), and several reports on the partial agonist, clonidine (Bennett and Lal, 1982; Cunningham et al., 1985; Jordan et al., 1993; Lal and Yaden, 1985). In addition, these studies present several important limitations.

First, in the study of the full agonist, xylazine (Colpaert and Janssen, 1985), no pharmacological characterisation of its DS properties was undertaken with other agonists at α_2-ARs. *Second*, though substitution studies with agonists have been undertaken with a clonidine DS (Bennett and Lal, 1982; Jordan et al., 1993; Lal and Yaden, 1985), this ligand is a *partial* agonist at all subtypes of α_2-AR (Buccafusco, 1992; Hieble et al., 1995; Millan et al., 2000a,b) complicating interpretation of substitution studies. *Third*, the implication of α_2-AR subtypes in the DS properties of clonidine, xylazine and other α_2-AR agonists has never been examined. *Fourth*, clonidine and xylazine show only modest selectivity for α_2-ARs *versus* α_1-ARs, and they are both potent ligands at imidazoline (I_1 and I_2) receptors which mediate DS in rodents (Jordan et al., 1996; MacInnes and Handley, 2003; Millan et al., 1994, 2000b). *Finally*, despite the potential significance of α_2-ARs in the interoceptive actions of antidepressants and other classes of psychotropic agent (Invernizzi and Garattini, 2004; Millan, 2003, 2006; Nutt, 1994; Nutt and Pinder, 1996; Svensson, 2003), no DS studies with α_2-AR agonists have, as yet, been undertaken.

Recently, we described the pre-clinical profile of a chemically novel and exceptionally potent agonist at all three subtypes of α_2-ARs, the spiroimidazoline derivative, S18616. This agent displays striking (>100-fold) selectivity *versus* α_1- and β-ARs, imidazoline (I_1 and I_2) receptors, and all other (>50) classes of binding site evaluated (Millan et al., 2000b). Reflecting actions at segmental α_2-ARs involved in the modulation of nociception (Hayashi and Maze, 1993; Millan, 2002), S18616 displays potent antinociceptive properties in both behavioural and electrophysiological paradigms (Millan et al., 2000b; Suzuki et al., 2002). Further, in line with its actions at α_2-autoreceptors inhibitory to "overactive" monoaminergic pathways participating in anxious states (Millan, 2003; Schramm et al., 2001), S18616 displayed potent anxiolytic properties in several rodent procedures (Millan et al., 2000e). These observations suggest the utility of S18616 in the treatment of anxious and, *via* systemic or spinal administration, painful states. In addition, S18616 shares the sedative and hypnotic properties of other α_2-AR agonists (Millan et al., 2000e), so it is of potential therapeutic use as an anesthetic agent, and in the handling of large animals in the veterinarian domain (Cormack et al., 2005; Eisenach et al., 1996; Hall et al., 2000; Hayashi and Maze, 1993; Moens et al., 2003).

In light of the above observations, the present study evaluated whether S18616 can elicit a specific and stable DS in rats. We also characterized the role of α_2-ARs as compared to α_1-ARs and imidazoline sites in the mediation of its potential DS properties. Moreover, we determined whether α_{2A}-, α_{2B}- and/or α_{2C}-ARs are implicated in the interoceptive effects of S18616. A final aspect of the present work was to examine whether the antidepressant agents, mirtazapine and mianserin, interfere with the DS properties of S18616. These "atypical" agents, which do *not* modify serotonin reuptake, possess antagonist properties at α_2-ARs, blockade of which has been implicated in their beneficial influence upon mood (Invernizzi and Garattini, 2004; Millan, 2006; Nutt and Pinder, 1996) and their preservation of sexual function in depression (Benelli et al., 2004; Gelenberg et al., 2000; Millan, 2006).

2. Material and methods

2.1. Animals

Male Wistar rats (180–200 g body weight upon arrival; Iffa-Credo, l'Arbresle, France) were housed individually in sawdust-lined standard polycarbonate cages with free access to water and, with restricted access to chow (10–11 g per day) in order to maintain their weight at 80% of free-feeding values. They were kept under a 12 h/12 h light–dark cycle with lights on at 07:00. Laboratory temperature was 21 ± 1.0 °C and humidity, 60 ± 5%. All animal use procedures conformed to international European ethical standards (86/609-CEE) and the French National Committee (décret 87/848) for the care and use of laboratory animals.

2.2. Drug discrimination procedure

As described previously (Dekeyne et al., 1999; Dekeyne and Millan, 2003), rats were trained to discriminate S18616 (0.01 mg/kg, s.c.) from saline in operant conditioning chambers equipped with two levers. They were reinforced with food according to a fixed ratio 10 schedule of reinforcement. Each 15-min daily session (5 days/week) started 15 min after injection. During "S18616" sessions, responses on only one lever were reinforced while, during "saline" sessions, responses on the other lever were reinforced. Drug (D) or saline (S) sessions alternated as follows: DSSDS-SDDSS-SDSDD-DSDSD-, etc. Correct responding was defined as no more than 13 presses on both levers to obtain the first reinforcement. The discrimination criterion was 10 consecutive sessions with correct responding, and animals failing to reach the criterion after 100 sessions were not used further. Thereafter, substitution or antagonism tests were conducted every Wednesday and Friday, whereas training sessions continued on the other days. Rats were tested only if they showed correct responding on the two preceding training sessions. Test drugs were administered instead of S18616, 15 min before the test session (substitution studies), or 30 min prior to the training dose of S18616 (antagonism studies).

Substitution/blockade testing was performed at several doses for each compound. The highest dose tested corresponded to that for which either "full" substitution or blockade (defined as ≥80% "S18616" or "saline" lever selection, respectively) was obtained, or a marked decrease in response rates. Test sessions began with individual verification of appropriate lever selection as a function of the dose of the training drug.

2.3. Data analysis

Data recorded during a test session were as follows: (1) lever selection, that is, the lever on which 10 (not necessarily consecutive) presses were recorded first and (2) response rates that is the total number of presses on both levers. Lever selection data were expressed as the percentage of rats selecting the drug lever and were compared by Fisher Exact Probability Tests to control values (0% in substitution studies, 100% in antagonist studies). Inhibitory $dose_{50}$s (ID_{50}s) plus 95% confidence limits (95% CL) were calculated to estimate drug potency in antagonism studies. Response rates in the presence of drug were compared by paired *t*-tests to response rates obtained during the preceding "saline" (or "S18616" in antagonist studies) training sessions.

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