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Sgd 101/75: cardiovascular effects in various animal preparations; interactions with vascular postjunctional α_1- and α_2-adrenoceptors

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1 The effect of the imidazolidine Sgd 101/75 (2-[2-methylindazol-4-imino]-imidazolidine HCl) on blood pressure, as well as its α-adrenoceptor agonist activity and affinity for these receptors, were examined in various animal preparations.

2 After both intravenous administration to conscious spontaneously hypertensive rats and intravenous injection or infusion via the vertebral artery in chloralose-anaesthetized cats, Sgd 101/75 (1–10 mg kg^{-1}) elicited pressor responses. Intracisternal application of Sgd 101/75 (1 mg kg^{-1}) to chloralose-anaesthetized cats did not affect blood pressure.

3 In the pithed rat and pithed cat the vasopressor responses to i.v. Sgd 101/75 were effectively antagonized by prazosin (0.1–1.0 mg kg^{-1}, i.v.) but much less by yohimbine (1 mg kg^{-1}, i.v.).

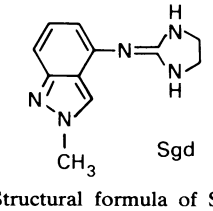
4 Sgd 101/75 proved a less potent and less selective displacing agent of [^{3}H]-clonidine- and [^{3}H]-prazosin-binding in rat brain membranes than clonidine.

5 The results suggest that Sgd 101/75 is a selective α_1-adrenoceptor agonist, devoid of any centrally or peripherally mediated hypotensive activity; this is probably caused by the low capacity of Sgd 101/75 for stimulating α_2-adrenoceptors.

Introduction

Sgd 101/75 (2- [2-methylindazol-4-imino] -imidazolidine HCl, Figure 1) is a clonidine-like derivative, which differs from its parent drug by not reducing arterial pressure upon intravenous administration in anaesthetized rats, cats and dogs (Ismail, Jahn & Weetman, 1981; unpublished results). In the rat isolated anococcygeus muscle, it has been proposed that Sgd 101/75 stimulates a class of α-adrenoceptors distinctly different from the classical α_1- and α_2-adrenoceptor subtypes (Coates *et al.*, 1982). The drug has been shown to act as a full α-adrenoceptor agonist on the rat isolated anococcygeus muscle, as a partial agonist for α_1-adrenoceptors in the guinea-pig isolated taenia caecum and as an α_2-adrenoceptor antagonist in the guinea-pig coaxially stimulated ileum (Ismail *et al.*, unpublished results 1981) and rat vas deferens (Jahn *et al.*, 1982).

On account of the differential interactions of Sgd 101/75 with different populations of α-adrenoceptors in various smooth muscle preparations, we have established the cardiovascular effects of Sgd 101/75 in various *in vivo* animal preparations. For this purpose, we have investigated the effects of Sgd 101/75 on blood pressure and heart rate after i.v. injection in conscious spontaneously hypertensive (SH) rats and after intracisternal (i.c.) application and infusion via the vertebral artery (a.v.) in chloralose-anaesthetized cats. Furthermore, the selectivity of Sgd 101/75 in activating vascular postjunctional α_1- and α_2-adrenoceptors in the intact circulatory system of pithed normotensive rats and cats was studied by means of selective α_1- or α_2-adrenoceptor blockade with prazosin and yohimbine,



Sgd 101/75

Figure 1 Structural formula of Sgd 101/75 (2- [2-methylindazol-4-imino] -imidazolidine HCl).

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respectively. Affinities for α_1- and α_2-adrenoceptors were estimated by means of the displacement of [^{3}H]-clonidine and [^{3}H]-prazosin specifically bound to rat brain membranes. In some experiments, clonidine was included for comparison.

Methods

Animals

Male spontaneously hypertensive (SH) rats (CPB/NIH-strain, 300–330 g), male normotensive Wistar rats (Cpb/WU strain, 220–270 g) and male cats (Cpb/CaAu strain, 2.3–3.3 kg) were obtained from the Centraal Proefdieren Bedrijf TNO (Zeist, The Netherlands). All animals were housed at a constant temperature (21 ± 1°C) on a standardized light-dark cycle and kept on a standard diet (rats: Muracon; cats: Doko, Trouw Voeders, Putten, The Netherlands).

Conscious SH rats

Blood pressure and heart rate in conscious SH rats were measured via a permanently indwelling abdominal aortic catheter, implanted under hexobarbitone anaesthesia (150 mg kg^{-1}) according to the method of Still & Whitcomb (1956) and as modified by Weeks & Jones (1960). A PE-50 polyethylene catheter (Intramedic, Cyanamid) was introduced into the right jugular vein for the i.v. administration of drugs. The catheters were guided subcutaneously to a small skin incision in the neck between the ears, brought to the external surface, filled with heparinized saline (0.9% w/v NaCl solution) 100 iu ml^{-1}) fixed and closed with a metal stop. The animals were housed individually and allowed to recover from the operation for 24–48 h. The intra-aortic catheter was connected to a Statham P23 Db pressure transducer. Blood pressure and heart rate were continuously registered on Hellige HE 19 recording devices. One dose of Sgd 101/75 per animal per day was administered only. Catheters were flushed daily with 0.3–0.5 ml of heparinized saline.

Pithed rats and cats

Male normotensive Wistar rats were pithed under light ether anaesthesia by introducing a blunt steel rod into the vertebral canal via the orbit as described by Gillespie *et al.*, (1970). Immediately following pithing, the animals were subjected to forced respiration (40 × 5 ml per min) with room air via the cannulated trachea using a Braun-Melsungen positive pressure pump. The right jugular vein and carotid artery were cannulated for the i.v. injection of drugs and monitoring of intra-arterial pressure, respectively. Rectal temperature was kept constant at 37°C. Pressor responses to i.v. injections of Sgd 101/75 were generated in a cumulative manner, increasing the dose 3-fold immediately after the maximal effect of the previous dose had been reached (20–40 s after injection). The lower doses of Sgd 101/75 (up to 0.3 mg kg^{-1}) were administered after the response of the previous dose had disappeared. The cumulative part of the curve was generated within 5 min. Because the pressor effects of Sgd 101/75 in urethane-anaesthetized rats have been shown to be subject to tachyphylaxis a control dose-response curve in the pithed rat was constructed by administration of a single dose of Sgd 101/75 per animal in a number of animals. This latter curve did not differ significantly from the one constructed cumulatively.

In order to obtain pithed cat preparations, cats were anaesthetized with α-chloralose (60 mg kg^{-1}, i.p.) and placed on a thermostat-equipped table. The left femoral vein and artery were cannulated for i.v. injections and recording of arterial pressure, respectively. A tube was inserted into the trachea for artificial respiration with room air using a Braun-Melsungen positive pressure pump (12 × 20 ml kg^{-1} min^{-1}). After drilling a hole 5 mm wide in the skull, 1 cm above the right orbit, a steel rod (diameter 4 mm) was introduced via the brain into the vertebral canal and pushed caudally as far as possible. After an equilibrium period of approximately 30 min, dose-response curves were generated in a cumulative manner as described above. After the effect of the highest dose of Sgd 101/75 had disappeared, no further pressor responses could be elicited with Sgd 101/75, demonstrating tachyphylaxis. In some control experiments the pressor effect of a single dose of Sgd 101/75 could be obtained. These effects were generally the same as those produced after cumulative dosing.

Infusion via the vertebral artery in anaesthetized cats

Chloralose-anaesthetized (60 mg kg^{-1}, i.p.) cats were prepared for surgery as described above. After left-side thoracotomy the left subclavian artery was located and all the side branches, except the vertebral artery, were ligated close to the subclavian artery. After distal ligation of the left axillary artery a PE-50 polyethylene catheter was inserted and pushed caudally until its tip was situated just distal to the ostium of the vertebral artery. The method has been described previously in full detail (Van Zwieten, 1975). The left femoral vein and artery were cannulated for i.v. injection of drugs and measurement of blood pressure as described above. Sgd 101/75 was infused over 1 min either i.v. or via the vertebral artery in a volume of 150 μl.

Intracisternal application in anaesthetized cats

Chloralose-anaesthetized (60 mg kg^{-1}, i.p.) cats were prepared for surgery as described above. The skin overlying the dorsal base of the skull and the cervical vertebrae was incised. The dura mater overlying the cisterna cerebellomedullaris was exposed. A needle (outside diameter 0.30 mm), connected to a PE-10 polyethylene catheter and a microsyringe was introduced into the cisterna through the dura mater and left in position. The injection volume containing Sgd 101/75 did not exceed 50 μl kg^{-1} body weight.

Affinity for α_1- and α_2-adrenoceptors

Cerebral membranes from male normotensive Wistar rats were prepared as described by Greenberg *et al.*, (1976) and U'Prichard *et al.*, (1977). For this purpose, the animals were decapitated and their brains (minus cerebella) were homogenized in 20 vol (w/v) of ice-cold 10 mM Tris-HCl buffer (pH = 7.7 at 25°C). After centrifugation at 50,000 *g* for 10 min at 4°C the pellet was rehomogenized in fresh cold buffer and the procedure was repeated. The final tissue pellet was suspended in Tris-HCl buffer. The protein concentration, as determined according to the method of Lowry *et al.* (1951), was 1 mg ml^{-1} for the [^{3}H]-prazosin and 4 mg ml^{-1} for the [^{3}H]-clonidine binding assays. Aliquots of 500 μl were incubated at 25°C for 60 min with [^{3}H]-clonidine (specific activity: 26.7 Ci mmol^{-1}; 0.4 nM) or [^{3}H]-prazosin (specific activity 33 Ci mmol^{-1}; 0.2 nM). The specific binding of [^{3}H]-clonidine was determined as the excess over blanks containing 10 μM of (−)-noradrenaline. Similarly, 2 μM of phentolamine was used to define the specific binding of [^{3}H]-prazosin. In the displacement studies, the inhibition of the specific binding of [^{3}H]-clonidine and [^{3}H]-prazosin was examined in the presence of various concentrations of Sgd 101/75 and clonidine. Incubations (total volume 1 ml) were determined by rapid vacuum filtration through Whatman GF/B filters. Filters were washed by three 5 ml portions of ice-cold Tris-HCl buffer, left to solubilize in 10 ml of Instagel and counted for radioactivity at 35–40 % efficiency. The concentrations of the compounds inhibiting 50% of the specific binding of each radioligand, IC_{50} were obtained by log probit analysis of the binding data.

Drugs and chemicals

Clonidine HCl and [^{3}H]-clonidine HCl (Boehringer Sohn), α-chloralose (Merck); heparin (Novo Industri A/S), hexobarbitone sodium (OPG), Instagel (Packard-Becker), (−)-noradrenaline (Sigma), phentolamine HCl (Ciba-Geigy), prazosin HCl and [^{3}H]-prazosin HCl (Pfizer), reserpine (Ciba-Geigy), Sgd 101/75 (Siegfried), yohimbine HCl (Sigma). Drugs were dissolved in saline except reserpine, which was dissolved in 5% (w/v) citric acid.

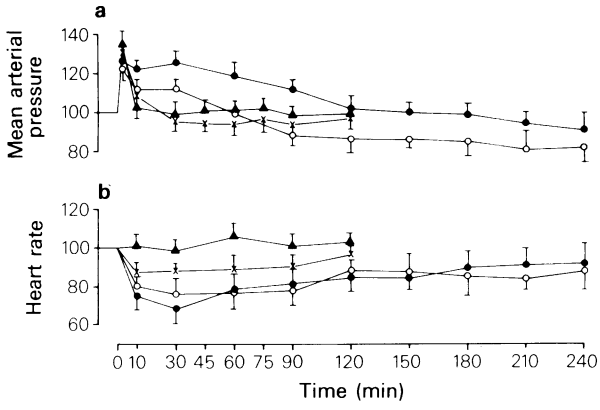

Figure 2 The effects of i.v. administrations of Sgd 101/75, (▲) 0.3, (X) 1, (○) 3 and (●) 10 mg kg^{-1}, on (a) mean arterial pressure and (b) cardiac frequency in conscious, unrestrained SH rats. Values are expressed as a % of the control level (time = 0) and presented as mean values ± s.e. mean (n = 6–8).

Statistics

All values presented are means ± s.e.mean. Statistical significance was ascertained by means of analysis of variance and a Student's *t* test (Wallenstein *et al.*, 1980).

Results

Effect of Sgd 101/75 on arterial pressure and heart rate in conscious SH rats

The initial value of the mean arterial pressure (diastolic pressure + pulse pressure) in the conscious SH rats varied between 139 ± 7.2 and 151 ± 8.9 (n = 6–8) on the different days of the experiment. The initial heart rate varied between 326 ± 21 and 356 ± 27 beats min^{-1} (n = 6–8). Administration of Sgd 101/75 (0.3–10 mg kg^{-1}, i.v.) was followed by a pressor response after which the blood pressure returned to the base-line level. No significant or dose-dependent reduction of arterial pressure was observed (Figure 2). The duration of the hypertensive response was directly related to the dose of Sgd 101/75. The heart rate was reduced significantly and dose-dependently (Figure 2). Following an injection of 3 or 10 mg kg^{-1} the animals displayed piloerection.

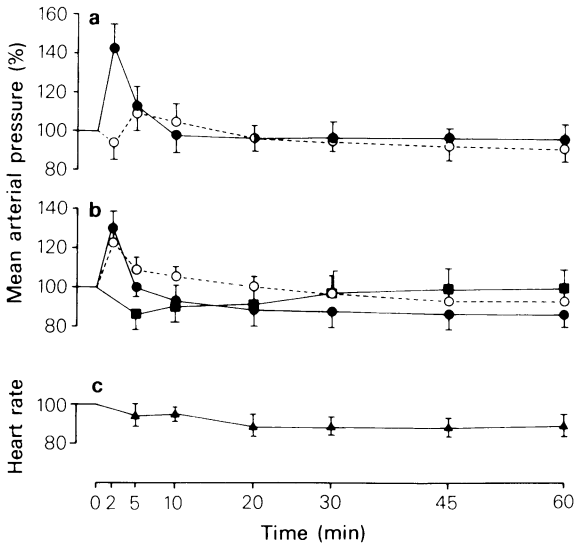

Figure 3 The effects of Sgd 101/75, (●) 1 mg kg^{-1} and (○) 3 mg kg^{-1}, on mean arterial pressure after i.v. injection (a), after infusion via the vertebral artery (b) and after intracisternal (i.c.) application 1 mg kg^{-1} (■) (b), in chloralose-anaesthetized cats. The lower curve (c) shows the effect of Sgd 101/75 (1 mg kg^{-1} i.c.) on heart rate. Values are expressed as a % of the baseline level (time = 0) and presented as mean values ± s.e.mean (n = 4–5).

Infusion of Sgd 101/75 via the left vertebral artery and intracisternal injection in anaesthetized cats

Infusion of Sgd 101/75 (1 and 3 mg kg^{-1}) into the left vertebral artery of the chloralose-anaesthetized cat resulted in a pressor response. No subsequent hypotensive effect was observed (Figure 3). Intravenous injection of Sgd 101/75 (1 and 3 mg kg^{-1}) also caused a short-lasting increase in blood pressure (Figure 3). After i.c. application of 1 mg kg^{-1} of Sgd 101/75 no pressor response was observed. In fact, blood pressure was not affected significantly. After Sgd 101/75 (1 mg kg^{-1} i.c.) heart rate was slightly reduced. Infusion via the vertebral artery and i.v. injection of Sgd 101/75 elicited inconsistent changes in heart rate which were generally cardiodepressive but not dose-dependent (results not shown).

Pressor responses in pithed rats and cats

The initial diastolic pressure of the pithed rats amounted to 38 ± 1.4 mmHg (n = 46). Figure 4 shows the dose-response curve of the increase in diastolic pressure by Sgd 101/75 in pithed rats. It was noted, that the log dose-pressor response relationship of Sgd 101/75 was rather shallow, as observed previously for selective α_2-adrenoceptor agonists (Timmermans & Van Zwieten, 1980; Van Meel *et al.*, 1981). Pretreatment with prazosin (0.1 mg kg^{-1}, i.v., − 15 min) resulted in an approximately 10-fold parallel shift to the right of the dose-response curve. On the other hand, pretreatment of the pithed rats with yohimbine (1 mg kg^{-1}, i.v., − 15 min) did not significantly alter the shape or position of the dose-response curve to Sgd 101/75. Moreover, combined pretreatment with prazosin and yohimbine (0.1 and 1 mg kg^{-1} i.v. respectively) did not result in a greater shift to the right of the dose-response curve than that caused by pretreatment with prazosin alone (Figure 4).

Pretreatment of the rats with reserpine (5 mg kg^{-1} day, i.p. for 2 days) resulted in a slight potentiation of the pressor response to Sgd 101/75, evaluated in pithed rat preparations (Figure 5). The vehicle of reserpine (5% w/v citric acid) did not influence the log dose-vasopressor response curve to Sgd 101/75 (Figure 5).

Figure 6 shows the dose-response curves of the increase in diastolic pressure caused by Sgd 101/75 in pithed cats. Pretreatment with yohimbine (1 mg kg^{-1}, i.v., − 15 min) resulted in a moderate (about 5-fold) parallel shift to the right of the dose-response curve, whereas prazosin (1 mg kg^{-1}, i.v., − 15 min) caused a much stronger inhibition. For comparison, the dose-pressor effect relationship of clonidine and the shifts by prazosin and yohimbine in pithed cats are shown in Figure 7. Prazosin affected the pressor responses to clonidine to a small extent, especially those to the higher doses of this agonist, whereas yohimbine caused an approximately 20-fold rightward shift of the dose-response curve (Figure 7).

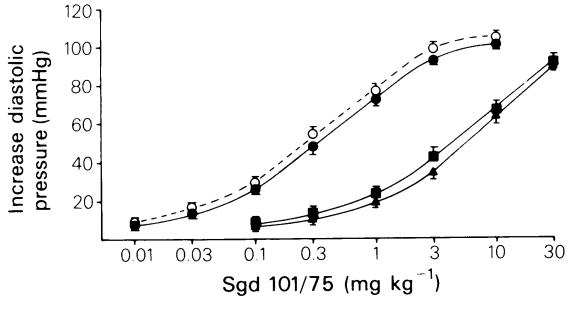

Figure 4 Log dose-response curves of the increase in diastolic pressure caused by Sgd 101/75 applied i.v. in pithed normotensive rats after pretreatment (− 15 min) with saline (1 ml kg^{-1}, i.v.) (○---○), yohimbine (1 mg kg^{-1}, i.v.) (●—●), prazosin (0.1 mg kg^{-1}, i.v.) (■—■) or a combination of yohimbine (1 mg kg^{-1}) and prazosin (0.1 mg kg^{-1}, i.v.) (▲—▲). Symbols represent mean values ± s.e. mean (n = 6–7).

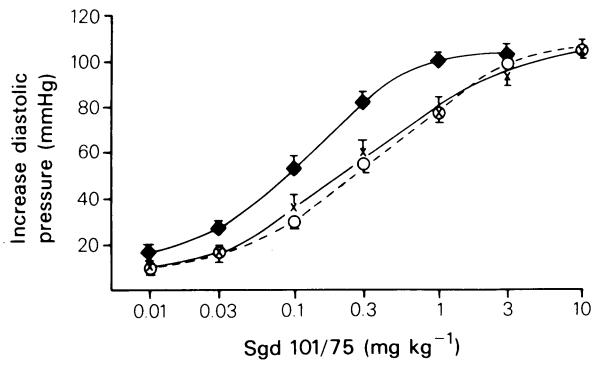

Figure 5 Log dose- response curves of the increase in diastolic pressure elicited by Sgd 101/75, administered i.v. to pithed normotensive rats after pretreatment with reserpine (5 mg kg^{-1} per day, i.v. for 2 days) (◆—◆), the vehicle (2 ml kg^{-1} per day, i.v. for 2 days) (X—X) or saline (1 ml kg^{-1} per day, i.v. for two days) (O---O). Symbols represent mean values ± s.e. mean ($n = 6-7$).

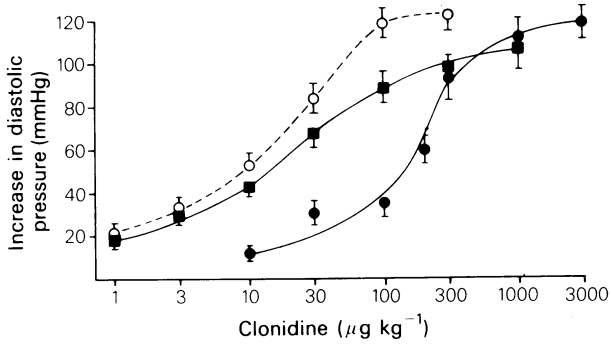

Figure 7 Log dose-response curves of the increase in diastolic pressure caused by clonidine, applied i.v. in pithed normotensive cats after pretreatment (− 15 min) with saline (0.1 ml kg^{-1}, i.v.) (O---O), yohimbine (1 mg kg^{-1}, i.v.) (●—●) or prazosin (1 mg kg^{-1}, i.v.) (■—■). Symbols represent mean values ± s.e. mean ($n = 4-5$).

Affinity of Sgd 101/75 and clonidine for α_1- and α_2-adrenoceptors

The displacement by Sgd 101/75 and clonidine of [^{3}H]-prazosin (0.2 nM) and [^{3}H]-clonidine (0.4 mM) from their specific binding sites in rat brain membranes is illustrated by Figure 8. Sgd 101/75 proved a less potent and less selective displacing agent than clonidine. The IC_{50} values for inhibiting [^{3}H]-prazosin and [^{3}H]-clonidine amounted to 65,000 and 1,000 nM for Sgd 101/75 and 1,300 and 4.3 nM for clonidine, respectively. The ratio of the IC_{50}s for inhibiting [^{3}H]-prazosin and [^{3}H]-clonidine binding was 65 for Sgd 101/75 and 300 for clonidine.

Discussion

The observations that Sgd 101/75 does not reduce the arterial pressure either upon intravenous injection in conscious rats, or upon infusion via the left vertebral artery or after i.c. injection in chloralose-

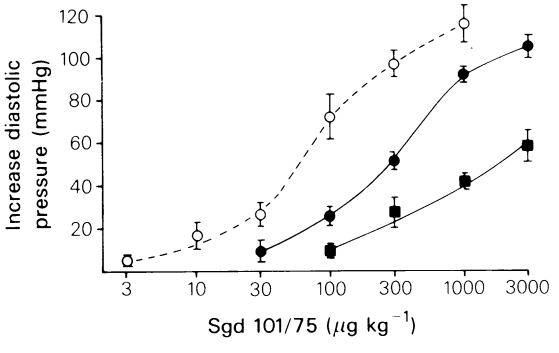

Figure 6 Log dose-response curves of the increase in diastolic pressure provoked by Sgd 101/75, applied i.v. in pithed normotensive cats after pretreatment (− 15 min) with saline (0.1 ml kg^{-1}, i.v.) (O---O), yohimbine (1 mg kg^{-1}, i.v.) (●—●) or prazosin (1 mg kg^{-1}, i.v.) (■—■). Symbols represent mean values ± s.e. mean ($n = 4-5$).

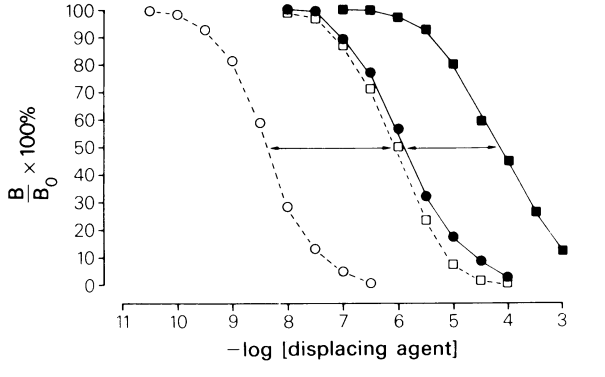

Figure 8 Displacement of [^{3}H]-clonidine (----) and [^{3}H]-prazosin (——) from their specific binding sites in rat brain membrane preparation by Sgd 101/75 (□/■) and clonidine (○/●). The mean values of four separate determinations performed in duplicate are shown (s.e. mean 10% of the mean values).

anaesthetized cats, demonstrate that the drug does not possess any centrally or peripherally mediated hypotensive activity. In this respect, Sgd 101/75 differs greatly from its congener clonidine. The latter drug is well known to reduce blood pressure at low doses in the aforementioned animal models (Van Zwieten, 1975; Schmitt, 1977; Timmermans & Van Zwieten, 1977; Kobinger, 1978). Although Sgd 101/75 may be a relatively hydrophilic drug, its inability to reduce blood pressure via a central mechanism cannot be solely attributed to a poor penetration of the blood brain barrier after systemic injection, since i.c. application of a rather high dose was still ineffective. The bradycardia observed after i.v. injection of Sgd 101/75 in conscious SH rats is likely to be caused by baroreceptor reflex activation.

The pressor responses to Sgd 101/75 in the pithed rat were not diminished by catecholamine depletion with reserpine. The increase in blood pressure should therefore be considered a direct effect. The observation that sympathectomy with reserpine resulted in a potentiation of the pressor response to Sgd 101/75 in pithed rats is intriguing. Several authors have described changes in sensitivity of postjunctional α-adrenoceptors after sympathectomy in animals. Treatment with 6-hydroxydopamine (Baker & Drew, 1981), or reserpine (Hicks & Waldron, 1982) gave rise to a selective supersensitivity of vascular postjunctional α_2-adrenoceptors in pithed rats. Van Meel *et al.* (1981), however, did not observe significant changes after reserpine treatment in pithed rats. In conscious rabbits, pretreated with 6-hydroxydopamine, the α_1-adrenoceptor mediated vasopressor responses were potentiated significantly, in contrast to the vasoconstriction caused by α_2-adrenoceptor stimulation (Hamilton & Reid, 1982). It appears that the selectivity of the observed supersensitivity is in part determined by the experimental conditions. The implications of the observed potentiation of the effects of Sgd 101/75 after reserpine-treatment are therefore not clear.

The pressor effects of Sgd 101/75 in pithed rats were little affected by pretreatment with the selective α_2-adrenoceptor antagonist yohimbine (Borowski *et al.*, 1977; Doxey *et al.*, 1977; Timmermans, Van Meel & Van Zwieten, 1980), but strongly and competitively antagonized by the α_1-adrenoceptor blocking agent prazosin (Cambridge *et al.*, 1977; Doxey *et al.*, 1977; Timmermans *et al.*, 1980). Thus, in the circulatory system of the pithed rat, Sgd 101/75 behaves as a selective α_1-adrenoceptor agonist, in contrast to clonidine, which is known to stimulate both α_1- and α_2-adrenoceptors in this animal model (Timmermans & Van Zwieten, 1980). Upon comparing the rightward shifts of the dose-response curves to clonidine and Sgd 101/75 by prazosin and yohimbine in the pithed cat, Sgd 101/75 also shows a more selective α_1-adrenoceptor agonism than clonidine. The finding that yohimbine causes a somewhat greater shift of the dose-response curve to Sgd 101/75 in pithed cats as compared to pithed rats can be explained by the extreme sensitivity of the pithed cat preparation to α_2-adrenoceptor stimulating drugs (Van Zwieten *et al.*, 1982; Timmermans *et al.*, 1983). In both the pithed rat and cat, the dose-response curve to Sgd 101/75 is rather shallow, like those to selective α_2-adrenoceptor stimulants (Van Meel *et al.*, 1981). In this respect, Sgd 101/75 appears to differ from other selective α_1-adrenoceptor agonists, such as cirazoline, methoxamine or phenylephrine, of which the dose-response curves in pithed rats are markedly steeper (Timmermans & Van Zwieten, 1980; Van Meel *et al.*, 1981). An explanation for this characteristic of Sgd 101/75 cannot be given on the basis of the results obtained so far.

The question now arises as to whether Sgd 101/75 stimulates an α_{1s}-adrenoceptor in the circulatory system of rats and cats, as it has been shown to do in the rat isolated anococcygeus muscle (Coates *et al.*, 1982). The characteristics of the dose-vasopressor response curve in pithed rats and the potentiation by reserpine pretreatment differ from the pressor effects brought about by the common α_1-adrenoceptor agonists (Van Meel et al., 1981; Baker & Drew 1981; Hicks & Waldron, 1982). In the rat isolated anococcygeus muscle, the α_{1s}-adrenoceptor is susceptible to blockade by prazosin (Coates & Weetman, unpublished observations). In our animal assay a possible interaction of Sgd 101/75 with α_{1s}-adrenoceptors cannot be distinguished on the basis of the antagonism by prazosin and yohimbine. However, prazosin ($0.1\ mg\ kg^{-1}$) caused an approximately 10-fold parallel shift to the right of the log dose-vasopressor response curve to Sgd 101/75 in pithed rats. This value is similar to those observed at our department with the dose-response curves to cirazoline and methoxamine (Van Meel *et al.*, 1981). It is therefore not likely that the vasoconstriction caused by Sgd 101/75 in pithed rats is due to stimulation of α_{1s}-adrenoceptors, as identified in the rat isolated anococcygeus muscle (Coates *et al.*, 1982).

The displacement curves of [^{3}H]-clonidine and [^{3}H]-prazosin binding in rat brain membranes by Sgd 101/75 and clonidine reveal a greater difference in affinities of clonidine and Sgd 101/75 for α_2- and α_1-adrenoceptors. Therefore, at doses that stimulate α_1-adrenoceptors Sgd 101/75 may act as an α_2-adrenoceptor antagonist. In fact, Ismail *et al.*, (1981) have shown that Sgd 101/75 possesses presynaptic α-adrenoceptor blocking properties in the isolated, electrically stimulated guinea-pig ileum.

In conclusion, the results described in the present paper confirm and extend the previous study showing that Sgd 101/75 is unable to reduce blood pressure in

animal models (Ismail, Jahn & Weetman, unpublished results, 1981). Sgd 101/75 is characterized as a selective α_1-adrenoceptor agonist in the circulatory system of pithed rats and cats. It has previously been shown that centrally located α_1 adrenoceptors do not play an important role in the regulation of the circulation (Berthelsen & Pettinger, 1977; De Jonge *et al.* 1981; Kobinger & Pichler, 1982; Timmermans *et al.*, 1981). The absence of any central hypotensive activity elicited by Sgd 101/75 must be attributed to its low ability to stimulate α_2-adrenoceptors.

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