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The antimigraine agent alniditan selectively constricts porcine carotid arteriovenous anastomoses via 5-$HT_{1B/1D}$ receptors

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Abstract

In previous studies, we have shown that several 5-$HT_{1B/1D}$ receptor agonists, including sumatriptan, potently constrict porcine carotid arteriovenous anastomoses. This effect seems to be of high predictive value for antimigraine activity. In the present experiments, we studied the effects of a new non-indole 5-$HT_{1B/1D}$ receptor agonist, alniditan, on systemic and carotid haemodynamics in anaesthetised pigs. In control animals, no significant changes in either systemic or carotid haemodynamics were observed after four consecutive i.v. injections of physiological saline (0.5 ml each, every 20 min; $n = 4$). On the other hand, i.v. doses of alniditan (3, 10, 30 and 100 μg kg^{-1} in 0.5 ml saline, every 20 min; $n = 6$) dose-dependently decreased total carotid conductance (maximum change: $-31 \pm 6\%$) by a selective vasoconstrictor action on arteriovenous anastomoses (maximum change: $-72 \pm 5\%$); the nutrient vascular bed dilated in response to alniditan (maximum change: $+103 \pm 39\%$). The dose of alniditan that decreased arteriovenous anastomotic conductance by 50% was 24 ± 8 μg kg^{-1} (64 ± 20 nmol kg^{-1}). Alniditan produced a slight bradycardia (maximum change: $-4 \pm 1\%$) and a more pronounced hypotensive effect (maximum change: $-23 \pm 5\%$). In six animals pre-treated with the potent and selective 5-$HT_{1B/1D}$ receptor antagonist, GR127935, the alniditan-induced changes in carotid haemodynamics were clearly antagonised, whereas the bradycardia and hypotension remained unaffected. These results suggest that alniditan selectively constricts porcine carotid arteriovenous anastomoses mainly via 5-$HT_{1B/1D}$ receptors and should be able to abort migraine headaches. The latter has indeed been confirmed in initial clinical studies in man.

Keywords: Alniditan; Antimigraine drug; Arteriovenous anastomosis; Carotid artery; GR127935; 5-$HT_{1B/1D}$ receptor; Migraine; (Pig)

1. Introduction

The novel indole derivative sumatriptan was introduced several years ago (Humphrey et al., 1988) and since then many studies have established the effectiveness of the drug in the acute treatment of migraine (The Subcutaneous Sumatriptan International Study Group, 1991; Visser et al., 1996). Sumatriptan constricts several large cranial and extracranial blood vessels (see Saxena and Tfelt-Hansen, 1993), including porcine carotid arteriovenous anastomoses (Den Boer et al., 1991; De Vries et al., 1996), via 5-HT_1-like receptors (Humphrey et al., 1990; Hoyer et al., 1994). Using the selective 5-$HT_{1B/1D}$ receptor antagonist GR127935 (Clitherow et al., 1994; Skingle et al., 1996; De Vries et al., 1997), it has been shown that the sumatriptan-sensitive 5-HT_1-like receptors in several tissues (Pauwels, 1996; Skingle et al., 1996; Villalón et al., 1996), including porcine carotid arteriovenous anastomoses (De Vries et al., 1996), are identical to 5-$HT_{1B/1D}$ receptors.

The success of selective 5-$HT_{1B/1D}$ receptor agonists in the treatment of migraine, combined with some shortcomings of sumatriptan (e.g., headache recurrence, coronary artery constriction) has prompted the development of several new compounds acting specifically at this receptor class (Saxena et al., 1997b; Villalón et al., 1997). Alniditan (R091274; Janssen Research Foundation, Belgium) is one such compound. In contrast to other 5-$HT_{1B/1D}$ recep-

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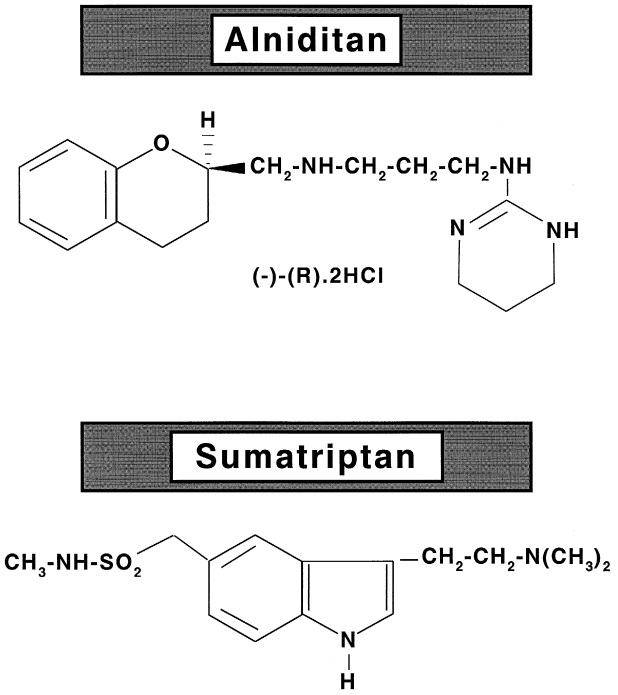

Fig. 1. Chemical structures of alniditan and sumatriptan.

tor agonists, which are all substituted indoles, alniditan is a benzopyran derivative (Fig. 1). Moreover, alniditan displays very high affinities at h5-$HT_{1B/1D}$ receptors, with virtually no affinity at the h5-ht_{1F} receptor (see Table 1) and is inactive at several other receptor classes (Leysen et al., 1996). On the other hand, similar to other 5-$HT_{1B/1D}$ receptor agonists, alniditan constricts isolated cerebral arteries (Janssens et al., 1997), blocks plasma extravasation evoked by trigeminal ganglion stimulation in the rat dura mater (Limmroth et al., 1997) and reduces total carotid blood flow in the dog (Van de Water et al., 1996).

In the present study, we analysed the effects of alniditan in the porcine carotid vascular bed, with particular emphasis on the arteriovenous anastomotic fraction, since constriction of cranial arteriovenous anastomoses has previously been shown to be of high predictive value for antimigraine activity (e.g., Saxena, 1995; Saxena et al., 1997b). Additionally, we established the contribution of 5-$HT_{1B/1D}$ receptors by analysing the alniditan-induced carotid vascular effects in pigs pre-treated with GR127935 or corresponding volumes of physiological saline.

Table 1
pK_i values of alniditan, sumatriptan and GR127935 at 5-HT_1 receptor subtypes

	h5-HT_{1A}	h5-HT_{1B}	h5-HT_{1D}	h5-ht_{1E}	h5-ht_{1F}
Alniditan[a]	8.42	8.96	9.40	6.62	6.44
Sumatriptan[a]	6.43	7.82	8.46	5.80	7.85
GR127935[b]	7.16	9.56	9.73	5.93	7.34

[a]Data from Leysen et al. (1996); [b]Pauwels, P.J. (personal communication).

2. Materials and methods

2.1. General

After an overnight fast, 16 pigs (Yorkshire × Landrace; 10–15 kg) were anaesthetised with azaperone (160 mg, i.m.), midazolan hydrochloride (5 mg, i.m.) and metomidate (200 mg, i.v.), intubated and connected to a respirator (BEAR 2E, BeMeds, Baar, Switzerland) for intermittent positive pressure ventilation with a mixture of room air and oxygen. Respiratory rate, tidal volume and oxygen supply were adjusted to keep arterial blood gas values within physiological limits (pH: 7.35–7.48; pCO_2: 35–48 mmHg; pO_2: 100–120 mmHg). Anaesthesia was maintained with a continuous i.v. infusion of pentobarbitone sodium at 20 mg kg^{-1} min^{-1}. With this anaesthetic regimen, arteriovenous anastomotic blood flow is considerably higher than that in pigs in a conscious state or under thiopentone anaesthesia (Den Boer et al., 1993).

Catheters were placed in the inferior vena cava via the left femoral vein for the administration of drugs and in the aortic arch via the left femoral artery for the measurement of arterial blood pressure (Combitrans disposable pressure transducer; Braun, Melsungen, Germany) and the withdrawal of arterial blood for determining blood gases (ABL-510, Radiometer, Copenhagen, Denmark). The common carotid arteries, external jugular veins and vagus nerves were identified and both vagi and the accompanying cervical sympathetic nerves were cut between two ligatures. Another catheter was placed in the right external jugular vein for the withdrawal of venous blood samples, while the right common carotid artery was dissected free and a needle was inserted against the direction of blood flow for the administration and uniform mixing of radioactive microspheres. Blood flow was measured in the right common carotid artery with a flow probe (internal diameter: 2.5 mm) connected to a sine-wave electromagnetic flow meter (Transflow 601-system, Skalar, Delft, The Netherlands). Heart rate was measured with a tachograph (CRW, Erasmus University, Rotterdam, The Netherlands) triggered by electrocardiographic signals.

Arterial blood pressure, heart rate and carotid blood flow were continuously monitored on a polygraph (CRW, Erasmus University). Body temperature was kept at about 37°C and the animals were continuously infused with saline to compensate for fluid losses during the experiment.

2.2. Distribution of carotid blood flow

The distribution of common carotid blood flow was determined with 15 ± 1 (S.D.) μm diameter microspheres

labelled with either ^{141}Ce, ^{113}Sn, ^{95}Nb, ^{103}Ru or ^{46}Sc (NEN Dupont, Boston, USA). For each measurement, a suspension of about 200 000 microspheres, labelled with one of the isotopes, was mixed and injected into the carotid artery. At the end of the experiment, the animal was killed, using an overdose of pentobarbital, and the heart, kidneys, lungs and the different cranial tissues were dissected out, weighed and put in vials. The radioactivity in these vials was counted for 5–10 min in a γ-scintillation counter (Packard, Minaxi autogamma 5000), using suitable windows for discriminating the different isotopes. All data were processed by a set of specially designed programs (Saxena et al., 1980), using a personal computer.

The fraction of carotid blood flow distributed to the different tissues was calculated by multiplying the ratio of tissue and total radioactivities by the total common carotid blood flow at the time of the injection of microspheres. Since little or no radioactivity was detected in the heart and kidneys, all microspheres trapped in lungs reached this tissue from the venous side after escaping via carotid arteriovenous anastomoses. Therefore, the amount of radioactivity in the lungs was used as an *index* of the arteriovenous anastomotic fraction of carotid blood flow (Saxena and Verdouw, 1982).

2.3. Experimental protocol

After a stabilisation period of about 1 h, the animals were divided into three groups. In the first group ($n = 4$), values of heart rate, mean arterial blood pressure, carotid blood flow and its distribution, as well as arterial and jugular venous blood gases were measured at baseline, and after four consecutive injections of physiological saline (0.5 ml, every 20 min). The second and third groups of animals ($n = 6$ each) were pre-treated with saline (i.v.) or GR127935 (0.5 mg kg^{-1}, i.v.), respectively, given over a period of 5 min at a rate of 1 ml min^{-1}. After a waiting period of 15 min, baseline values of heart rate, mean arterial blood pressure, carotid blood flow and its distribution, as well as arterial and jugular venous blood gases were measured. Subsequently, these groups of animals received sequential i.v. doses of alniditan (3, 10, 30 and 100 μg kg^{-1}) every 20 min. Fifteen minutes after each dose of alniditan, all haemodynamic variables were assessed again.

2.4. Data presentation and statistical analysis

All data have been expressed as means ± S.E.M. The significance of the difference between the variables within one group was evaluated with Duncan's new multiple range test, once an analysis of variance (randomised block design) had revealed that the samples represented different populations (Steel and Torrie, 1980). The changes caused by alniditan in saline and GR127935-pre-treated groups at corresponding doses were compared by using Student's unpaired *t*-test. Statistical significance was accepted at $P < 0.05$ (two-tailed). In the saline-pre-treated group, the dose of alniditan eliciting a 50% decrease (ED_{50}) in arteriovenous anastomotic blood flow or vascular conductance was calculated using linear regression analysis.

2.5. Drugs

Apart from the anaesthetics, azaperone, metomidate (both from Janssen Pharmaceuticals, Beerse, Belgium),

Table 2
Values of heart rate, mean arterial blood pressure and differences in arterial and jugular venous oxygen saturation at baseline and after consecutive injections (0.5 ml) of saline (control; $n = 4$) or sequential doses of alniditan

Pre-treatment	Baseline	Alniditan (μg kg^{-1}, i.v.)			
		3	10	30	100
Heart rate (beats min^{-1})					
Control	97 ± 4	96 ± 3	96 ± 3	95 ± 3	93 ± 2
Saline	95 ± 4	93 ± 4*	92 ± 4*	91 ± 4*	91 ± 4*
GR127935	99 ± 3	97 ± 3*	96 ± 3*	94 ± 3*	93 ± 3*
Mean arterial blood pressure (mmHg)					
Control	102 ± 4	99 ± 5	97 ± 3	96 ± 3	99 ± 5
Saline	95 ± 3	95 ± 4	90 ± 4*	80 ± 3*	73 ± 3*
GR127935	92 ± 2	87 ± 2*	82 ± 1*	76 ± 2*	72 ± 2*
Arterial–jugular venous oxygen saturation difference (%)					
Control	4.0 ± 1.0	4.3 ± 1.4	4.4 ± 1.2	5.8 ± 1.3	6.3 ± 1.7
Saline	4.6 ± 1.3	7.8 ± 2.3	9.7 ± 3.2*	13.1 ± 3.4*	14.6 ± 3.8*
GR127935	10.1 ± 2.2	11.6 ± 2.5	12.4 ± 2.5*	13.1 ± 2.4*$^{+}$	14.7 ± 2.4*$^{+}$

The effects of alniditan were analysed in animals pre-treated with saline ($n = 6$) or GR127935 (0.5 mg kg^{-1}; $n = 6$).
All values have been presented as means ± S.E.M. *, $P < 0.05$ vs. baseline. +, $P < 0.05$ vs. response by corresponding dose of alniditan in animals pre-treated with saline.

midazolan hydrochloride (Hoffmann La Roche, Mijdrecht, The Netherlands) and pentobarbitone sodium (Apharmo, Arnhem, The Netherlands), the compounds used in this study were: alniditan ((−)-(*R*)-*N*-[(3,4-dihydro-2*H*-1-benzopyran-2-yl)methyl]-*N*-(1,4,5,6-tetrahydro-2-pyrimidinyl)-1,3-propanediamine dihydrochloride), GR127935 (*N*-[methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadia-zol-3-yl) [1,1-biphenyl]-4-carboxamide hydrochloride; both provided by Janssen Research Foundation, Beerse, Belgium) and heparin sodium (Leo Pharmaceutical Products, Weesp, The Netherlands) to prevent clotting of the catheters. GR127935 was dissolved by heating the dispersion in distilled water to about 70°C and then allowing to cool down to room temperature, whereas alniditan was dissolved in physiological saline. All doses refer to the respective salts.

2.6. Ethical approval

The Ethics Committee of the Erasmus University Rotterdam dealing with the use of animals in scientific experiments approved the protocol for this investigation.

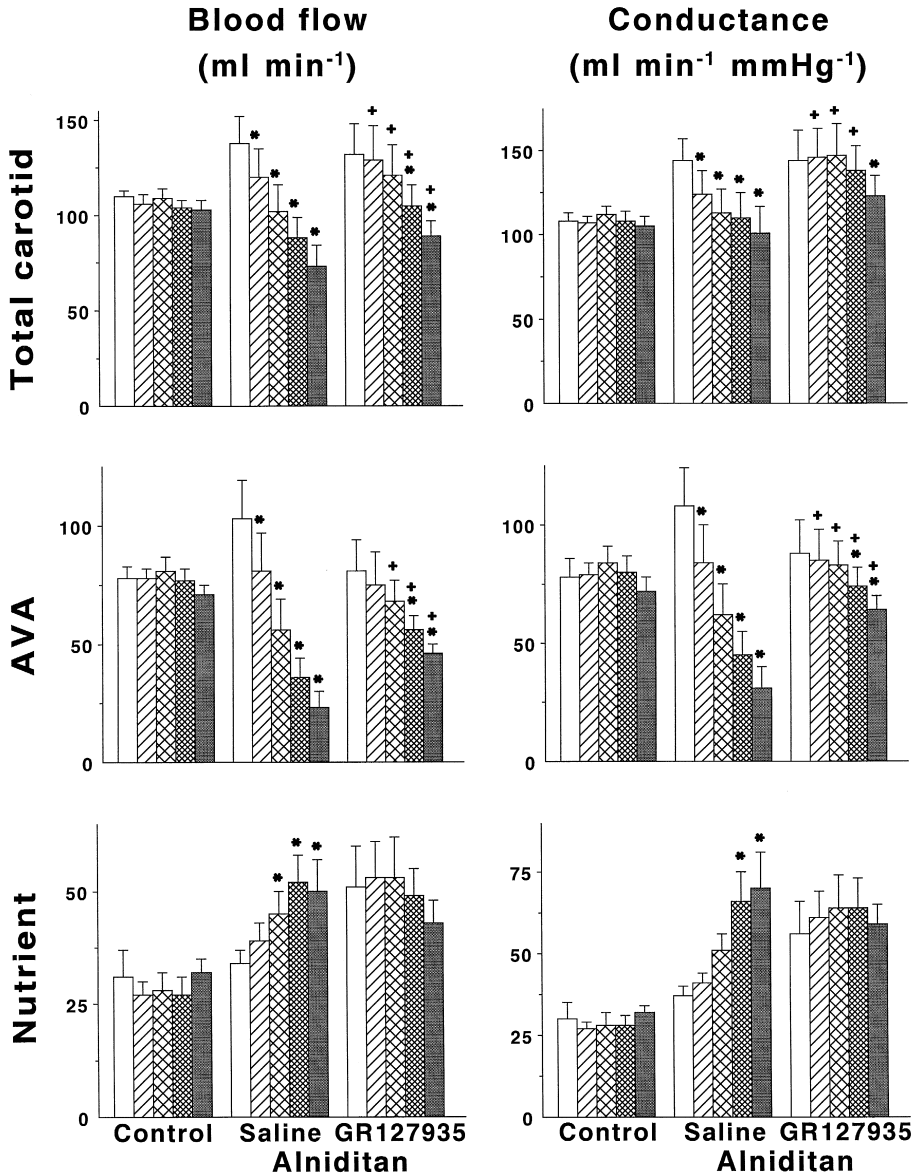

Fig. 2. Values of total carotid, arteriovenous anastomotic (AVA) and nutrient blood flow (left panels) and conductance (right panels) at baseline, and after four consecutive injections of 0.5 ml saline (control; $n = 4$) or alniditan (3, 10, 30 and 100 μg kg^{-1}, i.v.). The effects of alniditan were analysed in animals pre-treated with either saline ($n = 6$) or GR127935 (0.5 mg kg^{-1}; $n = 6$). From left to right, the bars signify values before (baseline) and after the 4 doses of saline (control animals) or alniditan (saline- or GR127935-pre-treated animals). All values are presented as means ± S.E.M. *, $P < 0.05$ vs. baseline. +, $P < 0.05$ vs. response by corresponding dose in animals pre-treated with saline.

3. Results

3.1. Systemic haemodynamics and arterio-jugular venous oxygen difference

As shown in Table 2, the baseline values of heart rate and blood pressure in the three groups of animals did not differ. In control animals, infusions of saline did not produce any changes in systemic haemodynamics or arterio-jugular venous oxygen saturation difference. Alniditan caused a small decrease in heart rate (maximum change: $-4 \pm 1\%$) and a more pronounced hypotensive effect (maximum change: $-23 \pm 5\%$). Similar decreases in heart rate (maximum change: $-6 \pm 1\%$) and blood pressure (maximum change: $-21 \pm 2\%$) were observed with alniditan in animals pre-treated with GR127935 (0.5 mg kg^{-1}, i.v.).

Alniditan produced a dose-dependent increase in the arteriovenous oxygen saturation difference (maximum change: $252 \pm 78\%$), which seems to be attenuated in animals treated with GR127935 (maximum change: $57 \pm 14\%$). However, it should be pointed out that, compared to the saline-pre-treated animals, the baseline values of arterio-jugular venous oxygen saturation difference in the group of animals pre-treated with GR127935 was higher (Table 2). This higher baseline value, most likely due to the previously described partial agonist properties of GR127935 at receptors mediating arteriovenous anastomotic constriction (De Vries et al., 1996), may have reduced the window for further increase in the arterio-jugular venous oxygen saturation difference by alniditan.

3.2. Carotid haemodynamics

As shown in Fig. 2 (absolute values) and Fig. 3 (percent changes from baseline), infusions of physiological saline did not produce any changes in the carotid haemodynamics. Alniditan dose-dependently decreased total carotid and arteriovenous anastomotic blood flow and concomitant conductance values; nutrient blood flow and conductance increased. The dose of alniditan that was needed to decrease baseline values of arteriovenous anastomotic blood flow and conductance by 50% (ED_{50}) was found to be 18.6 ± 5.6 μg kg^{-1} (51 ± 16 nmol kg^{-1}) and 23.9 ± 7.5 μg kg^{-1} (64 ± 20 nmol kg^{-1}), respectively. The maximum changes observed in total carotid, arteriovenous anastomotic and nutrient conductance with the highest dose of alniditan were -31 ± 6, -72 ± 5 and $+103 \pm 39\%$, respectively. As observed earlier (De Vries et al., 1996), the baseline values of arteriovenous anastomotic blood flow and conductance in the animals pre-treated with GR127935 were slightly lower than in those pre-treated with saline, but statistical significance was not reached ($P < 0.05$) in the present series of experiments. After treatment with GR127935, the carotid haemodynamic effects of alniditan were potently and significantly antagonised (see Figs. 2

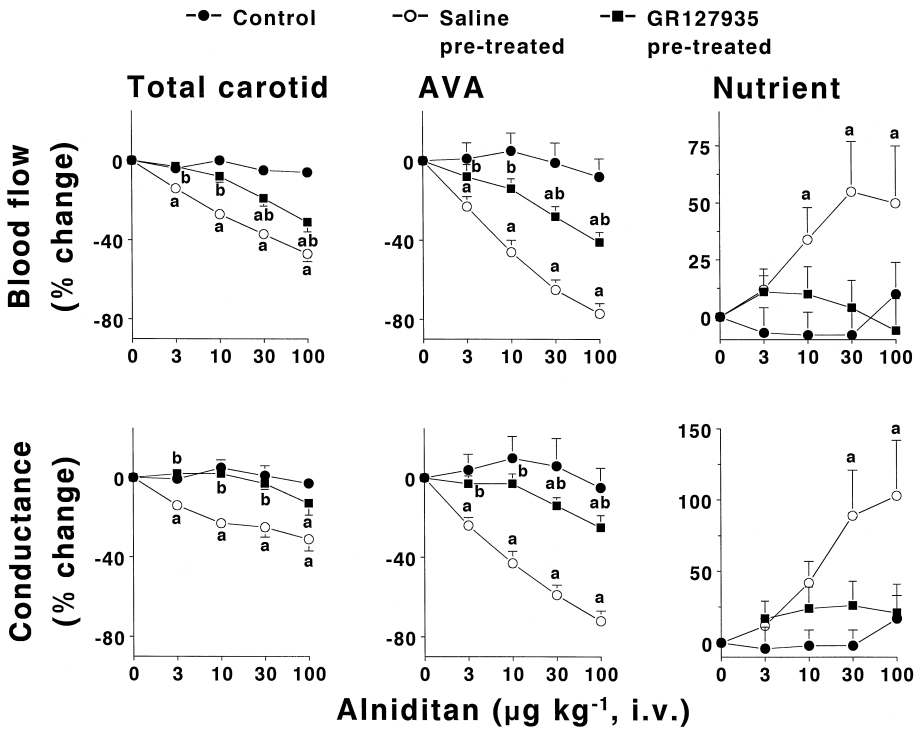

Fig. 3. Percent changes from baseline values in total carotid, arteriovenous anastomotic (AVA) and nutrient blood flow (upper panels) and conductance (lower panels) after four consecutive injections of 0.5 ml saline (control; $n = 4$) or alniditan (3, 10, 30 and 100 μg kg^{-1}, i.v.). The effects of alniditan were analysed in animals pre-treated with either saline ($n = 6$) or GR127935 (0.5 mg kg^{-1}; $n = 6$). All values are presented as means ± S.E.M. (a) $P < 0.05$ vs. baseline. (b) $P < 0.05$ vs. corresponding dose in animals pre-treated with saline.

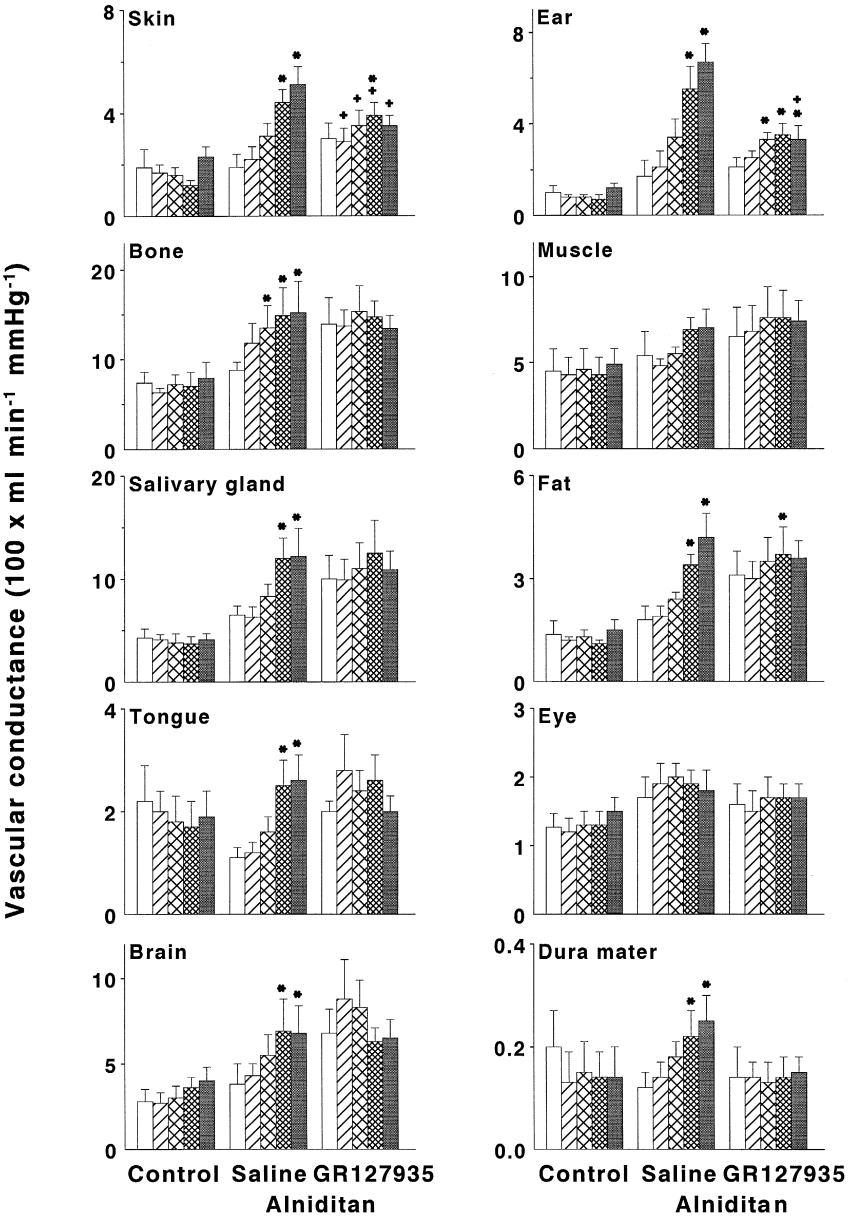

Fig. 4. Values of carotid vascular conductance in different cranial tissues at baseline, and after four consecutive injections of 0.5 ml saline (control; $n = 4$) or alniditan (3, 10, 30 and 100 μg kg^{-1}, i.v.). The effects of alniditan were analysed in animals pre-treated with either saline ($n = 6$) or GR127935 (0.5 mg kg^{-1}; $n = 6$). From left to right, the bars signify values before (baseline) and after the 4 doses of saline (control animals) or alniditan (saline- or GR127935-pre-treated animals). All values are presented as means ± S.E.M. $*$, $P < 0.05$ vs. baseline. $+$, $P < 0.05$ vs. response by corresponding dose in animals pre-treated with saline.

and 3); the highest dose of alniditan (100 μg kg^{-1}) changed baseline conductance values only by $-13 \pm 6\%$ (total carotid), $-25 \pm 6\%$ (arteriovenous anastomotic) and $+21 \pm 20\%$ (nutrient).

The complete distribution of carotid blood flow in the three groups of animals is shown in Fig. 4. Alniditan produced significant increases in vascular conductance to the skin, ear, bone, salivary gland, fat, tongue, brain and dura mater; no changes were observed in the muscles and eyes. The corresponding volumes of saline did not produce changes in blood flow or conductance values. In animals treated with GR127935, alniditan increased vascular conductance only in the skin, ear and fat; these changes were, in the case of skin and ear, significantly less than the changes obtained in control animals (Fig. 4).

4. Discussion

4.1. Systemic haemodynamics

Alniditan seemed to cause a small bradycardic effect (maximum change: 4–6%), similar to that reported with

some other 5-$HT_{1B/1D}$ receptor agonists sumatriptan (Feniuk et al., 1989; De Vries et al., 1996), avitriptan (Saxena et al., 1997a) and GMC2021 (3-[2-(dimethylanimo)ethyl]-5-[trifluoromethyl)sulfonyl]oxy] [1*H*]indole oxalate) (Saxena et al., 1996a). Unlike in the anaesthetised dogs (Van de Water et al., 1996), alniditan however caused a more pronounced hypotension in the anaesthetised pigs (Table 2). The mechanism involved in the hypotensive action of alniditan is not clear. Since this effect was not attenuated by GR127935, the role of 5-$HT_{1B/1D}$ receptors seems unlikely. Activation of central 5-HT_{1A} receptor activation (Dreteler et al., 1989; Saxena and Villalón, 1990) also seems uncertain. Although alniditan displays high affinity at 5-HT_{1A} receptors (Table 1), subcutaneously administered [^{3}H]alniditan does not seem to occupy central receptors in the guinea-pig, probably because of poor penetration into the brain (Bonaventura et al., 1997). In any case, systemic haemodynamic changes were not observed with alniditan in clinical studies (De Beukelaar, F., personal communication; Goldstein et al., 1996).

4.2. Carotid haemodynamics

As previously observed with several other 5-$HT_{1B/1D}$ receptor agonists, like sumatriptan (Den Boer et al., 1991; De Vries et al., 1996), avitriptan (Saxena et al., 1997a), GMC2021 (Saxena et al., 1996a) and S20749 (Saxena et al., 1996b), alniditan dose-dependently decreased total porcine carotid blood flow and conductance. Corresponding volumes of physiological saline were devoid of this effect. This alniditan-induced decrease of total carotid blood flow and conductance was exclusively attributable to a constrictor action on the cephalic arteriovenous anastomoses; the nutrient vascular bed in fact slightly dilated. In keeping with this, alniditan increased the arterio-jugular venous oxygen saturation difference.

The effects of alniditan on carotid haemodynamic were apparently unrelated to the fall in blood pressure for several reasons. The carotid haemodynamic effects were observed earlier than the hypotensive response (see Table 1 and Fig. 2) and they were clearly attenuated by GR127935, which did not affect the hypotensive response (see Table 1 and Fig. 3). The animals used in the present study had been subjected to bilateral vagosympathectomy, thus, largely avoiding reflex changes due to hypotension. Moreover, in dogs, where alniditan did not cause hypotension, the drug also selectively decreased carotid blood flow, with a concomitant increase in the arterio-jugular oxygen saturation difference (Van de Water et al., 1996).

As expected from its high binding affinity at the 5-HT_1 receptor subtypes (Table 1), alniditan yielded an ED_{50} (dose producing a 50% decrease in arteriovenous anastomotic conductance) of 64 ± 20 nmol kg^{-1}. The ED_{50} value of alniditan was lower than that obtained previously with sumatriptan (156 ± 54 nmol kg^{-1}; De Vries et al., 1996). Similarly, Van de Water et al. (1996) have recently shown that alniditan was approximately 2.6-fold more potent than sumatriptan in eliciting vasoconstriction in the canine carotid vascular bed. Since the alniditan-induced arteriovenous anastomotic constriction was potently antagonised by GR127935, this effect is mainly mediated by 5-$HT_{1B/1D}$ receptors. The absence of 5-HT_{1D} receptor mRNA in cephalic blood vessels indicates that the 5-HT_{1B} receptor, of which mRNA is abundantly expressed in the cranial vasculature (Bouchelet et al., 1996), is probably responsible for the constriction of arteriovenous anastomoses. The recent development of SB-216641 and BRL-15572, ligands relatively selective for the 5-HT_{1B} and 5-HT_{1D} receptor subtypes, respectively (Price et al., 1997; Schlicker et al., 1997), will help to confirm the latter suggestion. Although Bouchelet et al. (1996) also reported 5-ht_{1F} receptor transcript expression in cranial blood vessels, this receptor is unlikely to be involved, in view of the low affinity displayed by alniditan at this receptor (Table 1). As 0.5 mg kg^{-1} of GR127935, a dose that abolished the sumatriptan-induced arteriovenous anastomotic constriction (De Vries et al., 1996), did not completely block the alniditan-induced carotid haemodynamic changes, it may be that receptors other than 5-$HT_{1B/1D}$ subtypes are involved. Indeed, this also seems to be the case for the ergot- and 5-HT-induced arteriovenous anastomotic constriction (De Vries et al., 1998). On the other hand, it is possible that higher doses of GR127935 may be needed for a complete blockade of the alniditan-induced changes. Unfortunately, the partial agonist property of the GR127935 (present results; De Vries et al., 1996) precludes the use of higher doses of this antagonist.

Similar to sumatriptan (De Vries et al., 1996), alniditan produced a dilatation in carotid arterioles (nutrient vascular bed), which was observed in many cranial tissues (see Fig. 4). This dilatation, being sensitive to antagonism by GR127935, seems to be due to activation of 5-$HT_{1B/1D}$ receptors. It is noteworthy that Schoeffter and Hoyer (1990) have reported of 5-HT receptors similar to 5-$HT_{1B/1D}$ subtypes mediating endothelium-dependent relaxations in porcine isolated coronary artery, although it may also be argued that the nutrient dilatation is an indirect consequence of the closure of arteriovenous anastomoses.

4.3. Conclusions

The present results show that alniditan selectively constricts porcine carotid arteriovenous anastomoses, with an approximately 3-times higher potency compared to sumatriptan. Since dilatation of cephalic arteriovenous anastomoses has been implicated in the pathophysiology of migraine headache (Heyck, 1969; Ferrari and Saxena, 1993; Saxena, 1995) and the constriction of these cranial structures seems to be of high predictive value for antimigraine activity (Saxena et al., 1997b), alniditan should be effective in the treatment of migraine. Indeed, preliminary studies have shown that alniditan successfully aborts mi-

graine headache, with high response rates and low recurrence frequencies (Goldstein et al., 1996; Dahlöf and De Beukelaar, 1997). Larger trials will be needed to confirm this. Interestingly, the clinical effectiveness of alniditan, which is, in contrast to sumatriptan, virtually devoid of affinity at the h5-ht$_{1F}$ receptor, implies that an action at the 5-ht$_{1F}$ receptor is not essential for antimigraine activity.

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