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Modifications by sumatriptan and acetylcholine of nitric oxide-mediated neurogenic dilatation in dog cerebral arteries

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Abstract

Canine cerebral arterial strips denuded of endothelium responded to nicotine and transmural electrical stimulation with relaxations, which were abolished by N^G-nitro-L-arginine and methylene blue. Magnitudes of relaxation did not differ in the arteries contracted with prostaglandin $F_{2\alpha}$ and sumatriptan, an effective therapeutic of migraine. Sumatriptan concentration-dependently contracted the arteries responding to 2 Hz stimulation with persistent relaxations, and the concentration of this 5-$HT_{1B/1D/1F}$ receptor agonist to overcome the relaxation averaged 1.06×10^{-7} M. Acetylcholine inhibited the response to nerve stimulation due possibly to its action on prejunctional nitroxidergic nerves; the inhibition did not differ in the arteries contracted with prostaglandin $F_{2\alpha}$ and K^+. It appears that sumatriptan does not interfere with the release of nitric oxide from nerves but counteracts the neurogenic relaxation by functional antagonistic action on smooth muscle. Prejunctional inhibition by muscarinic receptor activation is unlikely associated with opening of neuronal K^+ channels.

Keywords: Sumatriptan; Acetylcholine; Nitroxidergic nerve, nitrergic; Cerebral artery

1. Introduction

Sumatriptan, a 5-$HT_{1B/1D/1F}$ receptor agonist (Hartig et al., 1996; Van den Broek et al., 2000), is regarded as a useful anti-migraine agent (Saxena and Tfelt-Hansen, 2000). Suppression of persistent intracranial vasodilatation, possibly responsible for cluster headache and migraine, by vasoconstriction via 5-HT receptor activation (Humphrey and Feniuk, 1991; Ferrari and Saxena, 1993), especially 5-HT_{1B} subtype (Nilsson et al., 1999; Razzaque et al., 1999), is postulated to underlie the therapeutic action. Nitric oxide (NO) derived from the vasodilator nerve (Toda and Okamura, 1990a, 1992) and endothelium (Katusic, 1992; Toda and Okamura, 1998) dilates cerebral arteries. Since L-N^G-methylarginine hydrochloride, a non-selective NO synthase inhibitor, relieves headaches in migraine patients (Lassen et al., 1997), endogenous NO is suggested to participate in the pathogenesis. Intravenous infusion of nitroglycerin to healthy subjects evokes vascular headache (Iversen et al., 1989). Histamine that dilates primate cerebral arteries via a release of endogenous NO (Toda, 1990) is recognized to provoke migraine attacks (Krabbe and Olesen, 1980). Possibility of neurogenic NO to participate in the migraine headache is also suggested (Ayajiki et al., 1997; Toda 1997). Sumatriptan reportedly inhibits the release of norepinephrine from adrenergic nerves in the isolated rat kidney (Charlton et al., 1986) and of serotonin from the isolated superfused pig brain cortex (Schlicker et al., 1989) by acting on prejunctional 5-HT_1-like receptors. Reduction by sumatriptan of the calcitonin gene-related peptide release from trigeminal nerve terminals is suggested to be attributed to activation of prejunctional 5-HT_1-like receptors (Goadsby and Edvinsson, 1993). However, whether this 5-$HT_{1B/1D/1F}$ receptor agonist acts on prejunctional nitroxidergic nitrergic nerves in cerebral arteries and produces vasoconstriction by interfering with the release of NO remains to be determined.

Suppression by acetylcholine of cerebral vasodilatation caused by nitroxidergic nerve stimulation is mediated by prejunctional muscarinic receptor activation in canine, monkey and porcine cerebral arteries (Toda et al., 1995, 1997; Tanaka et al., 1999; Liu and Lee, 1999), whereas

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α-adrenoceptor and VIP receptors in nerve terminals do not seem to participate in the modulation of neurogenic vasodilatation in cerebral arteries (Toda et al., 1995, 1997). Decreased Ca^{2+} influx may be involved in the inhibitory effect of acetylcholine; however, further mechanisms of action have not been clarified. Recently, Jiang et al. (1999) have suggested that opening of neuronal K^+ channels is involved in the acetylcholine-induced inhibition in isolated guinea pig basilar arteries, on the basis of data obtained with K^+ channel inhibitors. Our preliminary study has indicated that this is not the case in dog and monkey cerebral arteries.

The present study was undertaken to determine the prejunctional action of sumatriptan and the interaction of neurogenic NO and sumatriptan in isolated dog cerebral arteries denuded of the endothelium, in which acetylcholine inhibits nitroxidergic nerve function prejunctionally. In addition, whether the prejunctional inhibitory effect of acetylcholine is ascribable to K^+ channel opening was elucidated. Sumatriptan reportedly opens K^+ channels (Le Grand et al., 1998).

2. Materials and methods

2.1. Preparation and experimental protocol

Beagle dogs of either sex, weighing 9 to 14 kg, were used for the present study. The Animal Care and Use committee at our University approved the use of dog blood vessels.

Dogs were anesthetized with sodium pentobarbital (30 mg/kg, i. v.) and killed by bleeding from the carotid arteries. The brain was removed, and the middle cerebral and basilar arteries were isolated. The arteries were helically cut into strips of approx. 20 mm long, and the endothelium was removed by gently rubbing the intimal surface by cotton ball. Endothelial denudation was verified by abolishment of the relaxation induced by 10^{-8} M substance P. The specimen was vertically fixed between hooks in a muscle bath (20 ml capacity) containing the modified Ringer-Locke solution of the following composition (mM): NaCl 120, KCl 5.4, $CaCl_2$ 2.2, $MgCl_2$ 1.0, $NaHCO_3$ 25.0, and dextrose, 5.6. The bathing media were maintained at 37 ± 0.3°C and aerated with mixture of 95% O_2 and 5% CO_2; the pH of the solution was 7.38 to 7.43. The hook fixing the upper end of the strips was connected to the lever of a force-displacement transducer, and the resting tension was adjusted to 1.5 g, which is optimal for inducing the maximal contraction. Some of the strips were placed between stimulating electrodes (Toda et al., 1997). Electrical stimulation was transmurally applied every 10 min by 0.2 ms square pulses of supra-maximal intensity at 5 Hz for 40 s. For continuous electrical stimulation, a frequency of 2 Hz was used. Before the start of experiments, the arterial strips were allowed to equilibrate for 60–90 min in the bathing media, during which time the fluids were replaced three times every about 10 min.

Isometric mechanical responses were displayed on an ink-writing oscillograph. The arteries were partially contracted with prostaglandin $F_{2\alpha}$, sumatriptan or K^+ to obtain relaxations to transmural electrical stimulation (5 Hz), nicotine (10^{-4} M) or NO (10^{-7} M). In some strips contracted with prostaglandin $F_{2\alpha}$, in which persistent relaxations were induced by the stimulation at 2 Hz, concentration–response curves of sumatriptan were obtained, and the concentration enough to cancel the neurogenic relaxation was determined from the curves in each strip. Inhibitory effects of acetylcholine on the response to 5 Hz stimulation were compared in the arterial strips contracted with prostaglandin $F_{2\alpha}$ and K^+. Papaverine (10^{-4} M) was added at the end of the experiments to attain the maximal relaxation, and relaxations induced by the electrical stimulation or chemical agents were presented as relative values to those due to papaverine.

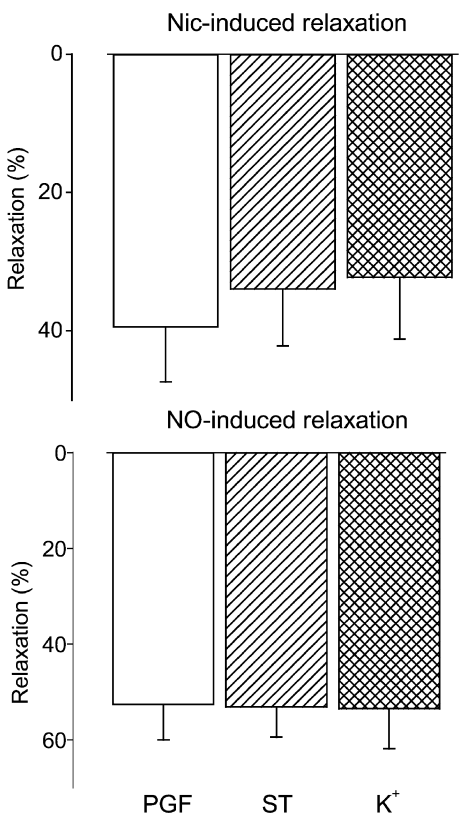

Fig. 1. Relaxations induced by nicotine (Nic, 10^{-4} M, upper panel) and NO (10^{-7} M, lower) of canine cerebral arterial strips denuded of the endothelium and contracted with prostaglandin $F_{2\alpha}$ (PGF, 10^{-6} M), sumatriptan (ST, 1 to 5×10^{-7} M) or K^+ (12 to 15 mM). The ordinate represents the response relative to that induced by 10^{-4} M papaverine that produced the maximal relaxation. The values with different vasoconstrictor agents were obtained from the same strips. Preparations used were from six separate dogs. Vertical bars denote S.E.M.

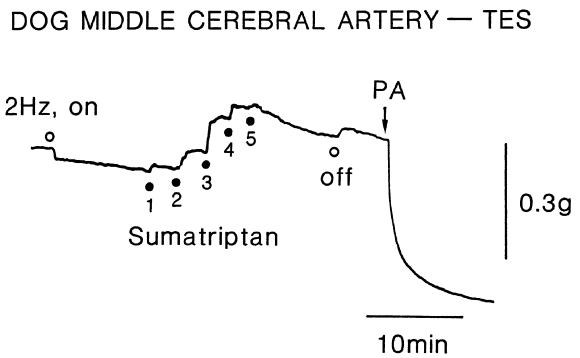

Fig. 2. Tracing of the response to sumatriptan at various concentrations under relaxations induced by persistent transmural electrical stimulation (TES, 2 Hz from 'on' to 'off') in an endothelium-denuded strip contracted with prostaglandin $F_{2\alpha}$. Concentrations of sumatriptan from 1 to 5 indicate 2×10^{-8}, 10^{-7}, 5×10^{-7}, 2×10^{-6} and 10^{-5} M, respectively. PA represents 10^{-4} M papaverine that produced the maximal relaxation.

2.2. Statistics and drugs used

The results shown in the text and figures are expressed as mean values ± S.E.M. Statistical analyses were made using the Student's paired and unpaired *t*-tests for two groups and Tukey's test after one-way analysis of variance for three or more groups. Drugs used were nicotine (base), hexamethonium bromide, methylene blue, L-arginine (Nacalai Tesque, Kyoto, Japan), N^G-nitro-L-arginine (Peptide Institute, Minoh, Japan), acetylcholine chloride (Daiichi Pharmaceutical, Tokyo), atropine sulfate (Tanabe, Osaka, Japan), sumatriptan (Glaxo Group Research, Greenford, UK), tetrodotoxin (Sankyo, Tokyo), prostaglandin $F_{2\alpha}$ (Pharmacia-Upjohn, Tokyo), and papaverine hydrochloride (Dainippon, Osaka). Responses to NO were obtained by adding the $NaNO_2$ solution adjusted at pH 2 (Furchgott, 1988), and concentrations of acidified $NaNO_2$ in the bathing media were expressed as those of NO.

3. Results

3.1. Responses to nicotine or transmural electrical stimulation as affected by sumatriptan or K^+

In helical strips of canine cerebral arteries contracted with prostaglandin $F_{2\alpha}$ (10^{-6} M), nicotine (10^{-4} M) and NO (10^{-7} M) elicited moderate relaxations. The nicotine-induced relaxation was abolished by hexamethonium (10^{-5} M, $n=4$) and methylene blue (10^{-5} M, $n=3$), whereas the response to NO was unaffected by the ganglionic blocker but was abolished by methylene blue. N^G-nitro-L-arginine (10^{-5} M) abolished only the relaxation induced by nicotine ($n=4$), and L-arginine (3×10^{-3} M) restored the response. After the responses to nicotine and NO were determined to be reproducible, the strips were contracted with sumatriptan or K^+ and the responses to nicotine and NO were obtained. Contractions to sumatriptan (1 to 5×10^{-7} M) or K^+ (12 to 15 mM) were adjusted to match those induced by prostaglandin $F_{2\alpha}$. Fig. 1 summarizes the quantitative data on nicotine and NO in arterial strips contracted with different vasoconstrictors. The responses did not significantly differ.

The cerebroarterial strips contracted with prostaglandin $F_{2\alpha}$ responded to transmural electrical stimulation at frequencies of 2 and 5 Hz with relaxations, which were abolished by tetrodotoxin (3×10^{-7} M in all strips used), methylene blue (10^{-5} M, $n=3$) and N^G-nitro-L-arginine (10^{-5} M, $n=4$). The mean value of relaxations induced by nerve stimulation at 5 Hz, a frequency that elicits reproducible responses of cerebral arteries (Toda et al., 1997), was 23.5 ± 6.1% ($n=5$) in prostaglandin $F_{2\alpha}$ (10^{-6} M)-contracted strips. In the same strips contracted with sumatriptan (1-5×10^{-7} M) to a similar extent, the value was 28.0 ± 6.7% (128.8 ± 16.1% by paired comparison,

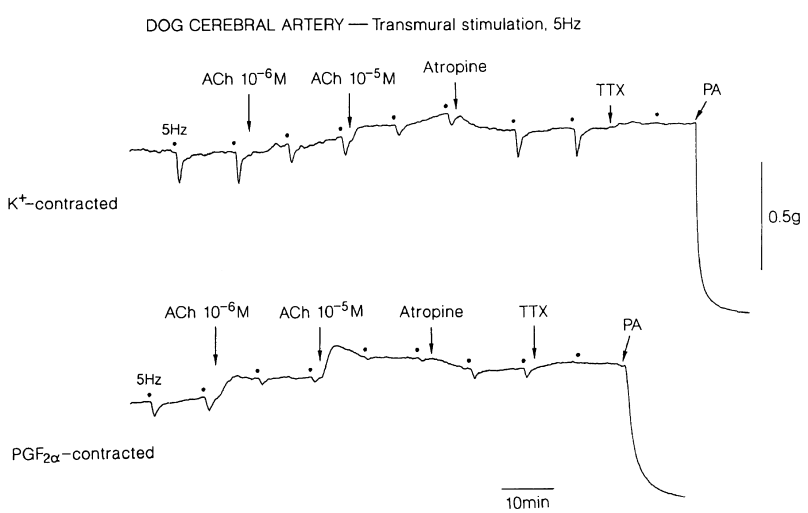

Fig. 3. Modifications by acetylcholine (ACh, 10^{-6} and 10^{-5} M) and atropine (10^{-7} M) of the relaxant response to transmural electrical stimulation at 5 Hz for 40 s in endothelium-denuded strips from the same dog, contracted either with K^+ (upper tracing) or prostaglandin $F_{2\alpha}$ (lower). Dots above the tracings denote the application of electrical stimulation. TTX, 3×10^{-7} M tetrodotoxin; PA, 10^{-4} M papaverine.

$n = 5$, $P > 0.05$). In the strips showing relaxations in response to persistent nerve stimulation at 2 Hz, the addition of sumatriptan (2×10^{-8} to 10^{-5} M) produced a concentration-related contraction (Fig. 2). The concentration of this agonist to overcome the neurogenic relaxation averaged $[1.06 \pm 0.42] \times 10^{-7}$ M ($n = 5$). After the nerve stimulation was turned off in the strips contracted by the highest concentration of sumatriptan, the arterial tone was raised, as shown in Fig. 2.

3.2. Modification by acetylcholine of the response to transmural electrical stimulation

In prostaglandin $F_{2\alpha}$-contracted arterial strips, transmural stimulation at 5 Hz for 40 s caused reproducible relaxations which were inhibited concentration-dependently by the addition of acetylcholine (10^{-6} and 10^{-5} M). The effect was reversed by atropine (10^{-7} M) (Fig. 3, lower tracing). Paired comparisons of the inhibitory effect of acetylcholine were made in two arterial strips obtained from the same dogs which were contracted either with prostaglandin $F_{2\alpha}$ (10^{-6} M) or K^+ (12 to 15 mM). In K^+-contracted strips, acetylcholine attenuated the neurogenic relaxation, and atropine restored the response (Fig. 3, upper tracing), as seen in the strips contracted with prostaglandin $F_{2\alpha}$. The quantitative data are presented in Fig. 4. The inhibition by acetylcholine did not significantly differ in the K^+- and prostaglandin $F_{2\alpha}$-contracted arterial strips.

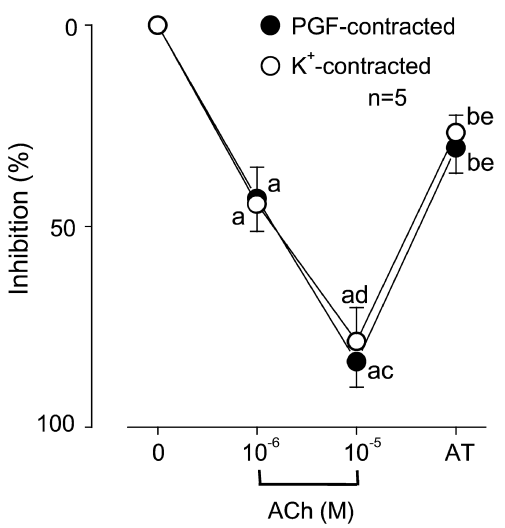

Fig. 4. Comparison of inhibitory effects of acetylcholine (ACh) on the response to transmural electrical stimulation in canine cerebral arterial strips contracted with prostaglandin $F_{2\alpha}$ and K^+. The ordinate represents the percentage of inhibition of the neurogenic response. Significantly different from control, $^{a}P < 0.01$, $^{b}P < 0.05$; significantly different from the value with 10^{-6} M acetylcholine, $^{c}P < 0.01$, $^{d}P < 0.05$; significantly different from the value with 10^{-5} M, $^{e}P < 0.01$ (Tukey's test). AT, 10^{-7} M atropine; *n*, number of strips from separate dogs. The values were obtained from different strips isolated from the same dog. Vertical bars represent S.E.M.

4. Discussion

Transmural electrical stimulation and nicotine produce relaxations of cerebral arteries from dogs, monkeys, humans and pigs (Toda and Okamura, 1990a,b; Toda, 1993; Lee and Sarwinski, 1991; Tanaka et al., 1999), which are recognized to be mediated by NO released from vasodilator nerves. The fact that the nicotine-induced relaxation, being sensitive to hexamethonium, and the response to electrical stimulation, abolished by tetrodotoxin, were depressed by N^G-nitro-L-arginine, an NO synthase inhibitor, and methylene blue, an inhibitor of soluble guanylate cyclase, indicates the involvement of neurogenic NO in the responses obtained in the present study. Relaxations induced by nicotine, electrical nerve stimulation and exogenous NO did not differ in the arteries contracted with sumatriptan, an agonist of 5-$HT_{1B/1D/1F}$ receptor subtypes, from those contracted with prostaglandin $F_{2\alpha}$. Similar results were also obtained in our preliminary study on cerebral arteries isolated from Japanese monkeys (N. Toda et al., unpublished data). These findings suggest that activation of the 5-HT receptors does not modify the effect of NO on smooth muscle and the synthesis or release of NO in nerve terminals. Prejunctional 5-HT receptor stimulation interferes with the release of norepinephrine in the isolated pig coronary artery (Molderings et al., 1989) and perfused rat kidney (Charlton et al., 1986) and serotonin or calcitonin gene-related peptide in the brain (Schlicker et al., 1989; Goadsby and Edvinsson, 1993). Sumatriptan reportedly hyperpolarizes membrane potential via opening Ca^{2+}-dependent K^+ channel in cultured glioma cells (Le Grand et al., 1998); thus, the triptan might prejunctionally inhibit nitroxidergic nerve function in the cerebral artery. However, the relaxation induced by nitroxidergic nerve stimulation in the dog cerebral artery was not inhibited by sumatriptan (present study). Therefore, impairment of tonic release of NO from vasodilator nerves does not seem to participate in the cerebral vasoconstriction induced by sumatriptan in vivo.

Sumatriptan is a potent cerebral vasoconstrictor (Nilsson et al., 1999; Van den Broek et al., 2000); stimulation of 5-HT_{1B} receptor subtypes on smooth muscle of the human cerebral artery appears to participate in the contraction. In the present study, sumatriptan concentration-dependently contracted dog cerebral arteries that had been relaxed by persistent electrical stimulation of nerves. Stimulation of the pterygopalatine ganglion or greater superficial petrosal nerve induces dilatation of middle cerebral and posterior communicating arteries of 10–20%, compared to the size before stimulation, in anesthetized dogs that is mediated by NO from parasympathetic postganglionic neurons innervating the arteries (Toda et al., 2000). The concentration of sumatriptan, enough to reverse the neurogenic relaxation, was 1.06×10^{-7} M. It has been reported that the mean value of maximal concentration of

unbound sumatriptan in plasma of migraine patients receiving doses sufficient to relieve headaches is 72 ng/ml (approx. 2.44×10^{-7} M) (Saxena and Tfelt-Hansen, 2000). Despite an inability to reduce the release of NO from vasodilator nerves, sumatriptan may counteract the neurogenic relaxation by acting directly on smooth muscle. Clinical studies support the contention that the vasoconstriction is an important component of the anti-migraine action of triptans (Friberg et al., 1991; Limmroth et al., 1996).

Prejunctional muscarinic receptor activation interferes with the response of cerebral arteries to nitroxidergic nerves (Toda et al., 1995; Tanaka et al., 1999). Although involvement of muscarinic M_2 receptor subtypes and decreased Ca^{2+} influx into nerve terminals are speculated (Toda et al., 1997; Liu and Lee, 1999), further mechanisms have not been elucidated. Recent study by Jiang et al. (1999) suggests that K^+ channel opening is involved in the prejunctional action of acetylcholine on the basis of findings obtained with K^+ channel inhibitors in isolated guinea pig basilar arteries. However, the present study with dog cerebral arteries does not support this hypothesis, since the effect of acetylcholine was not inhibited in the arteries contracted with K^+ in concentrations that are enough to abolish the endothelium-dependent, NO-independent relaxation induced by K^+ channel opening substances in the monkey lingual artery (Ayajiki et al., 1999). On the other hand, it is reported that NO derived from nerves relaxes guinea pig basilar arteries possibly by a mediation of voltage-dependent K^+ channel opening (Jiang et al., 1998). This is not the case in dog cerebral arteries, because the stimulation-induced relaxation was not significantly influenced in K^+-contracted arteries, compared to those contracted with prostaglandin $F_{2\alpha}$, and methylene blue abolished the response.

It may be concluded that sumatriptan does not interfere with the release of NO from vasodilator nerves but acts directly on smooth muscle as a functional antagonist to cerebral vasodilatation associated with neurogenic NO, possibly responsible for migraine and cluster headaches. Inhibitory effect of acetylcholine on the release of NO from vasodilator nerves does not seem to be due to opening of neuronal K^+ channel in dog cerebral arteries.

References

Ayajiki, K., Okamura, T., Toda, N., 1997. Flunarizine, an anti-migraine agent, impairs nitroxidergic nerve function in cerebral arteries. Eur. J. Pharmacol. 329, 49–53.

Ayajiki, K., Okamura, T., Fujioka, H., Imaoka, S., Funae, Y., Toda, N., 1999. Involvement of CYP3A-derived arachidonic acid metabolite(s) in responses to endothelium-derived K^+ channel opening substance in monkey lingual artery. Br. J. Pharmacol. 128, 802–808.

Charlton, K.G., Bond, R.A., Clarke, D.E., 1986. An inhibitory prejunctional 5-HT_1-like receptor in the isolated perfused rat kidney. Naunyn-Schmiedeberg's Arch. Pharmacol. 332, 8–15.

Ferrari, M.D., Saxena, P.R., 1993. Clinical and experimental effects of sumatriptan in humans. Trends Pharmacol. Sci. 14, 129–133.

Friberg, L., Olesen, J., Iversen, H.K., Sperling, B., 1991. Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. Lancet 338, 13–17.

Furchgott, R.F., 1988. Studies on relaxation of rabbit aorta by sodium nitrite: the basis for the proposal that the acid activatable inhibitory factor from bovine retractor penis is inorganic nitrite and the endothelium-derived relaxing factor is nitric oxide. In: Vanhoutte, P. (Ed.), Vasodilatation. Raven Press, New York, pp. 401–414.

Goadsby, P.J., Edvinsson, L., 1993. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neurpeptide changes seen in humans and cats. Ann. Neurol. 33, 48–56.

Hartig, P.R., Hoyer, D., Humphrey, P.P.A., Martin, G.R., 1996. Alignment of receptor nomenclature with the human genome: classification of 5-HT_{1B} and 5-HT_{1D} receptor subtypes. Trends Pharmacol. Sci. 17, 103–105.

Humphrey, P.P.A., Feniuk, W., 1991. Mode of action of the anti-migraine drug sumatriptan. Trends Pharmacol. Sci. 12, 444–446.

Iversen, H.K., Olesen, J., Tfelt-Hansen, P., 1989. Intravenous nitroglycerin as an experimental model of vascular headache. Basic characteristics. Pain 38, 17–24.

Jiang, F., Guang, C., Rand, M.J., 1998. Role of potassium channels in the nitrergic nerve stimulation-induced vasodilatation in the guinea-pig isolated basilar artery. Br. J. Pharmacol. 123, 106–112.

Jiang, F., Guang, C., Rand, M.J., 1999. Cholinergic prejunctional inhibition of nitrergic neurotransmission in the guinea-pig isolated basilar artery. Clin. Exp. Pharmacol. Physiol. 26, 364–370.

Katusic, Z.S., 1992. Endothelial L-arginine pathway and regional cerebral arterial reactivity to vasopressin. Am. J. Physiol. 262, H1557–H1562.

Krabbe, A.E., Olesen, J., 1980. Headache-provocation by continuous intravenous infusion of histamine: clinical results and receptor mechanisms. Pain 8, 253–259.

Lassen, L.H., Ashina, M., Christiansen, I., Ulrich, V., Olesen, J., 1997. Nitric oxide synthase inhibition in migraine. Lancet 349, 401–402.

Lee, T.J.F., Sarwinski, S.J., 1991. Nitric oxidergic neurogenic vasodilation in the porcine basilar artery. Blood Vessels 28, 407–412.

Le Grand, B., Panissie, A., Pauwels, P.J., John, G.W., 1998. Activation of recombinant h 5-HT_{1B} and h 5-HT_{1D} receptors stably expressed in C6 glioma cells produces increases in Ca^{2+}-dependent K^+ current. Naunyn-Schmiedeberg's Arch. Pharmacol. 358, 608–615.

Limmroth, V., May, A., Auerbach, P., Wosnitza, G., Eppe, T., Diener, H.C., 1996. Changes in cerebral blood flow velocity after treatment with sumatriptan or placebo and implications for the pathophysiology of migraine. J. Neurol. Sci. 138, 60–65.

Liu, J., Lee, T.J.F., 1999. Mechanism of prejunctional muscarinic receptor-mediated inhibition of neurogenic vasodilation in cerebral arteries. Am. J. Physiol. 276, H194–H204.

Molderings, G.J., Göthert, M., Fink, K., Roth, E., Schlicker, E., 1989. Inhibition of noradrenaline release in the pig coronary artery via a novel serotonin receptor. Eur. J. Pharmacol. 164, 213–222.

Nilsson, T., Longmore, J., Shaw, D., Olesen, I.J., Edvinsson, L., 1999. Contractile 5-HT_{1B} receptors in human cerebral arteries: pharmacological characterization and localization with immunocytochemistry. Br. J. Pharmacol. 128, 1133–1140.

Razzaque, Z., Heald, M.A., Pickard, J.D., Maskell, L., Beer, M.S., Hill, R.G., Longmore, J., 1999. Vasoconstriction in human isolated middle meningeal arteries: determining the contribution of 5-HT_{1B}- and 5-HT_{1F}-receptor activation. Br. J. Clin. Pharmacol. 47, 75–82.

Saxena, P.R., Tfelt-Hansen, P., 2000. Triptans, 5-$HT_{1B/1D}$ receptor agonists in the acute treatment of migraine. In: Olesen, J., Tfelt-Hansen, P., Welch, K.M.A. (Eds.), The Headaches. 2nd edn. Lippincott-Raven Publishers, Philadelphia, pp. 411–438.

Schlicker, E., Fink, K., Göthert, M., Hoyer, D., Moldrings, G., Roschke, I., Schoeffter, P., 1989. The pharmacological properties of the presynaptic serotonin autoreceptor in the pig brain cortex conform to the

5-HT_{1D} receptor subtype. Naunyn-Schmiedeberg's Arch. Pharmacol. 340, 45–51.

Tanaka, T., Okamura, T., Handa, J., Toda, N., 1999. Neurogenic vasodilation mediated by nitric oxide in porcine cerebral arteries. J. Cardiovasc. Pharmacol. 33, 56–64.

Toda, N., 1990. Mechanism underlying responses to histamine of isolated monkey and human cerebral arteries. Am. J. Physiol. 258, H311–H317.

Toda, N., 1993. Mediation by nitric oxide of neurally-induced human cerebral artery relaxation. Experientia 49, 51–53.

Toda, N., 1997. Nitroxidergic nerve in cranial arteries. In: Olesen, J., Edvinsson, L. (Eds.), Headache Pathogenesis: Monoamines, Neuropeptides, Purines, and Nitric Oxide. Lippincott-Raven Publishers, Philadelphia, pp. 241–245.

Toda, N., Okamura, T., 1990a. Possible role of nitric oxide in transmitting information from vasodilator nerve to cerebroarterial muscle. Biochem. Biophys. Res. Commun. 170, 308–313.

Toda, N., Okamura, T., 1990b. Mechanism underlying the response to vasodilator nerve stimulation in isolated dog and monkey cerebral arteries. Am. J. Physiol. 259, H1511–H1517.

Toda, N., Okamura, T., 1992. Regulation by nitroxidergic nerve of arterial tone. News Physiol. Sci. 7, 148–152.

Toda, N., Okamura, T., 1998. Cerebral vasodilators. Jpn. J. Pharmacol. 76, 349–367.

Toda, N., Uchiyama, M., Okamura, T., 1995. Prejunctional modulation of nitroxidergic nerve function in canine cerebral arteries. Brain Res. 700, 213–218.

Toda, N., Ayajiki, K., Okamura, T., 1997. Inhibition of nitroxidergic nerve function by neurogenic acetylcholine in monkey cerebral arteries. J. Physiol 498, 453–461.

Toda, N., Ayajiki, K., Tanaka, T., Okamura, T., 2000. Preganglionic and postgangionic neurons responsible for cerebral vasodilatation mediated by nitric oxide in anesthetized dogs. J. Cerebral Blood Flow Metab. 20, 700–708.

Van den Broek, R.W.M., Van Den Brink, A.M., de Vries, R., Bogers, A.J.J.C., Stegmann, A.P.A., Avezaat, C.J., Saxena, P.R., 2000. Pharmacological analysis of contractile effects of eletriptan and sumatriptan on human isolated blood vessels. Eur. J. Pharmacol. 407, 165–173.