Buspirone, but not sumatriptan, induces miosis in humans: Relevance for a serotoninergic pupil control

Background and objective: Drugs that act on the serotoninergic system have been shown to influence the pupil size. However, the 5-hydroxytryptamine (5-HT) receptor type or subtype that affects pupil diameter has not been defined in humans. With a placebo-controlled, double-blind randomized design, we investigated in healthy volunteers the effect on pupil size of buspirone and sumatriptan, which mainly act on 5-HT_{1A}- and the 5-HT_1-like receptors, respectively.

Methods: The pupil area was measured by means of a videopupillometer before and after a single oral administration of placebo or of three different doses of active drugs. Heart rate and arterial blood pressure were recorded after pupil area measurement.

Results: Buspirone (5, 10, and 20 mg) caused a dose-dependent miosis. Sumatriptan (50, 100, and 200 mg) did not affect the pupil size. Twenty milligrams of buspirone reduced the mydriasis induced by pretreatment with homatropine eyedrops. A 20 mg dose of buspirone reduced blood pressure without change in heart rate, whereas buspirone, at doses lower than 20 mg, and sumatriptan did not affect heart rate and blood pressure.

Conclusions: This study suggests that buspirone, but not sumatriptan, the selective agonist of 5-HT_1-like receptors, causes miosis in humans by activation of 5-HT_{1A} receptors, possibly located in the central nervous system where they inhibit iris sympathetic pathways. Measurement of pupil size seems to provide a valuable and sensitive index of 5-HT_{1A} receptor function in humans. (CLIN PHARMACOL THER 1995;57:349-55.)

Marcello Fanciullacci, MD, Riccardo Sicuteri, MD, Massimo Alessandri, MD, and Pierangelo Geppetti, MD *Florence, Italy*

The size of the pupil is determined by a functional balance of the innervation between the autonomically supplied sphincter and the radially arranged dilator muscles of the iris: the constrictor muscle is under the parasympathetic control, whereas the dilator muscle is governed by the adrenergic nerve supply.

There is evidence in humans that drugs that affect 5-hydroxytryptamine (5-HT) function induce pupillary changes. For instance, fenfluramine, which releases 5-HT from synapses, and the 5-HT reuptake inhibitor indalpine cause mydriasis.[1,2] Drugs that act on 5-HT receptors have also been shown to affect pupil size. 5-HT_2 receptor antagonists, such as mianserin,[3,4] ICI 169,369, and ICI 170,809,[5,6] cause a dose-related reduction of pupillary diameter in healthy volunteers. There is no evidence for 5-HT_1 receptors involvement in the regulation of pupil size in humans. 5-HT_1 receptors have been divided in different subtypes, which subserve various responses in different tissues. The definition of which subtype of 5-HT_1 receptor plays a role in a given response in humans is hampered by the heterogeneity of 5-HT_1 receptor subtypes and by the fact that selective drugs for 5-HT_1 receptor subtypes have not been available for clinical studies.

Recently, drugs that exhibit selectivity for 5-HT_1 receptor subtypes have been used in human therapy. Buspirone, a drug that reaches the central nervous system and exerts anxiolytic activity,[7,8] has been characterized as a partial agonist for 5-HT_{1A} receptors.[9,10] The selective agonist of the 5-HT_1-like receptor sumatriptan,[11] which mediates constriction of the cranial blood vessels[12] and inhibits neurogenic inflammatory

From the Institute of Internal Medicine and Therapeutics IV, University of Florence.

Supported by grants 93.00756 and 93.00595.PF41 from the National Research Council (CNR, Rome Italy).

Received for publication June 6, 1994; accepted Sept. 27, 1994.

Reprint requests: Marcello Fanciullacci, MD, Institute of Internal Medicine and Therapeutics IV, University of Florence, Viale Pieraccini 18, 50139 Florence, Italy.

0009-9236/95/$3.00 + 0 **13/1/60932**

Table I. Demographic parameters of the study subjects

	Men	*Women*	*Age range (yr)*	*Mean age (yr)*	*Weight (kg)*
Group 1	4	3	18-40	28.2 ± 4.1	67.5 ± 4.6
Group 2	4	3	20-38	27.5 ± 4.2	68.8 ± 4.5
Group 3	3	3	25-42	31.3 ± 3.8	65.4 ± 4.1

Data are mean values ± SEM. ANOVA and Bonferroni test, all pairwise comparisons.

responses in pial vessels,[13] is being used for the treatment of the attack of migraine and cluster headache.[14,15] In this study we explored the ability of buspirone and sumatriptan to affect pupil size in healthy volunteers. Because buspirone, but not sumatriptan, induced a dose-dependent miosis, an attempt to determine the involvement of the parasympathetic system in the buspirone-induced miosis was also performed.

METHODS

Subjects. The study was performed in 20 healthy volunteers in accordance with the principles of the Declaration of Helsinki. Study subjects had no abnormalities shown by routine history and physical examination. Subjects had taken no medications for at least 2 weeks before the study. They were randomly divided into three groups, and the groups were very similar in age, sex, and weight distribution (Table I). The study was approved by the Ethics Committee of our Institute, and subjects gave their written informed consent before entry to the study.

Experimental procedure. All testing started at 9 AM. The subjects were allowed to have a light breakfast at least 2 hours before the onset of the investigation. Pupil areas were measured by use of an electronic, monocular infrared pupillometer consisting of a camera head (Iriscorder c301, Hamamatsu City, Japan) that included television camera, infrared light, eye-fix lamp, and chin and forehead rest table; a control unit (Iriscorder c301); and television monitor (model PM-125 A, Ikegami, Tokyo, Japan). The measurement of the pupil areas was performed according the method previously reported.[16] Measurements were done in a soundproof room after 5 minutes of pupil adaptation to obtain the standard light conditions. Subjects were seated in front of the television camera with the head and chin supported by the rest table in a comfortable position. They were asked to fix the eye on the green-light produced by the eye-fix lamp, which appeared in the lens of the television camera and acted as a fixation target. The distance between the eye under observation and the lens was 11 cm. The pupillometer used a closed-circuit television system and a low-intensity, completely invisible infrared light source that illuminates the eye without any inconvenience to the subject. The television monitor display allowed easy setting for image pick-up and fully automatic processing in the pupil area measurement.

Immediately after pupil measurements, subjects were placed in the supine position, heart rate determined from a single precordial derivation ECG, and systolic and diastolic blood pressures measured by use of a mercury sphygmomanometer were recorded. Subjects were asked to indicate if they had any symptom during the study.

Experimental design. The study had a placebo-controlled, double-blind randomized design. The pupil area of one eye, chosen at random, was evaluated in each subject immediately before and every 30 minutes for a period of 150 minutes after the single oral intake of placebo or drugs. In four sessions separated by 4 to 7 days, group 1 received placebo (four half-tablets of placebo), 5 mg buspirone (three half-tablets of placebo and one half-tablet of the active drug), 10 mg buspirone (two half-tablets of placebo and two half-tablets of the active drug), or 20 mg buspirone (four half-tablets of active drug). Group 2 was treated with placebo or sumatriptan (50, 100, and 200 mg) according to the same modalities described above for buspirone.

After the measurement of the baseline pupil area, subjects of group 3 were instilled in one eye, chosen at random, with 50 μl of an aqueous solution containing 1% homatropine hydrobromide, a dose capable of abolishing the pupillary light reflex.[17] Thirty minutes after instillation of homatropine the pupil reflex to the light was no longer present, and the pupil size of the treated eye was measured again, which was considered the baseline value (time 0). Immediately after that, subjects received 20 mg buspirone (two tablets) or placebo (two tablets) in a randomized and double-blind manner, and the pupil size was measured thereafter every 30 minutes for 150 minutes. At least 4 days were allowed to elapse between buspirone or placebo administration.

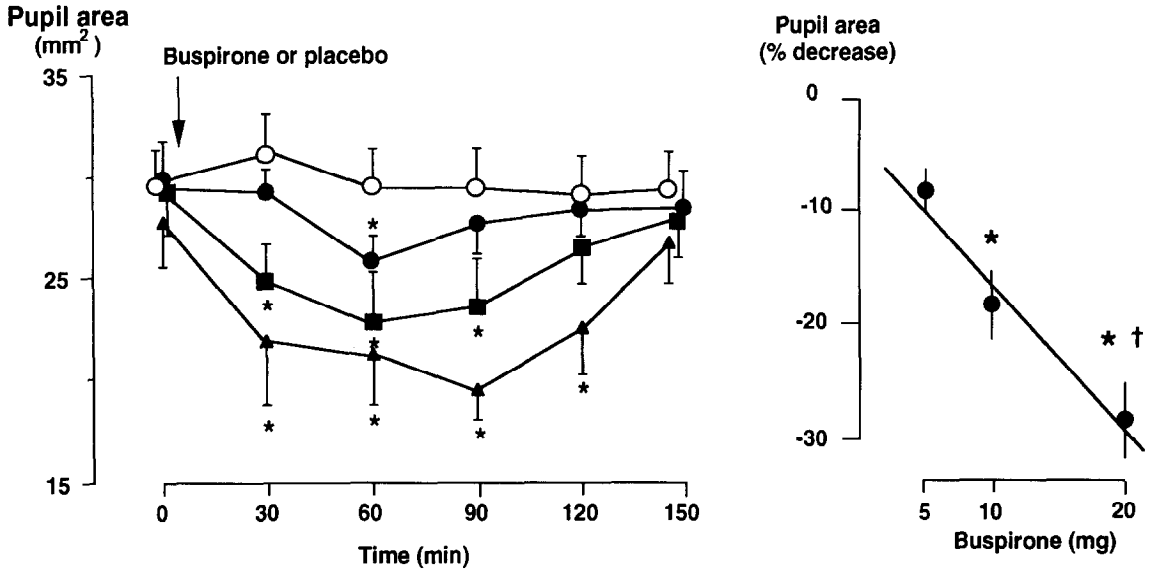

Fig. 1. Left panel, Effect of orally administered buspirone (5 mg, *solid circles;* 10 mg, *solid squares;* and 20 mg, *solid triangles*) or placebo *(open circles)* on pupil area in seven healthy subjects. Buspirone or placebo was given immediately after the measurement of baseline value (time 0). *$p < 0.05$ versus placebo; ANOVA and Bonferroni test. **Right panel,** Dose-response curve of the miotic action of buspirone on seven healthy volunteers. The values are mean ± SEM of the maximal miotic responses expressed as percentage differences of basal values. *$p < 0.05$ versus 5 mg buspirone; †$p < 0.05$ versus 10 mg buspirone; ANOVA and Bonferroni test.

Statistical analysis. All values are mean ± SEM. ANOVA and the Bonferroni test were used to establish whether significant differences were present between the values of placebo and of the three doses of the drug at each time point. Comparisons between the effect of buspirone and placebo in eyes treated with homatropine were performed with the Student *t* test for paired data. Changes were considered to be significant when $p < 0.05$.

Drugs. The drugs used for this study were buspirone chloridrate (10 mg tablet; Axoren, Glaxo SpA, Verona, Italy), sumatriptan succinate (100 mg tablet; Imigran, Glaxo SpA), and homatropine hydrobromide eyedrops (Omatropine, Allergan, Pomezia, Italy). Placebo tablets for buspirone and sumatriptan were prepared at the Pharmacy of the University Hospital (Florence, Italy) and contained all the compounds present in the tablets of buspirone and sumatriptan, respectively, with the exception of the active drugs. Tablets were administered to the patients enveloped in a wafer.

RESULTS

Drug effects. No difference was observed between baseline values of pupil areas measured before the administration of buspirone and placebo. Administration of buspirone was associated with a dose-dependent decrease in the pupil size (Fig. 1). A significant decrease of the pupil area in comparison with values obtained after the administration of placebo was observed at 30 through 120 minutes after the intake of 20 mg buspirone. After the administration of 10 mg buspirone a significant decrease of the pupil area was found at 30, 60, and 90 minutes after drug administration. The pupil area was significantly reduced in subjects treated with 5 mg buspirone only 60 minutes after the drug intake (Fig. 1, *left panel*). When maximal miotic effects produced by each dose of buspirone (calculated as percentage differences of basal values) were considered, a clear cut dose-response curve was shown (Fig. 1, *right panel*). No difference was observed between baseline pupillary values before sumatriptan and placebo. The values of the pupil area in subjects treated with 50, 100, or 200 mg sumatriptan were not statistically different from the values obtained in subjects treated with placebo at any time of observation (Table II).

Buspirone at 5 mg and 10 mg and sumatriptan at all the dose levels tested did not affect baseline blood pressure and heart rate (data not shown). Reduction in

Table II. Effect of orally administered sumatriptan or placebo on pupil area (in square millimeters) in seven healthy subjects

Time (min)	*Effect after placebo*	*Effect after sumatriptan*		
		50 mg	*100 mg*	*200 mg*
0	27.2 ± 2.5	26.5 ± 3.1	26.3 ± 3.1	28.9 ± 2.3
30	27.7 ± 2.4	27.8 ± 3.4	25.8 ± 3.7	23.4 ± 3.8
60	26.2 ± 2.5	25.4 ± 2.9	24.5 ± 2.8	24.5 ± 2.7
90	25.3 ± 3.1	26.7 ± 3.2	27.4 ± 2.5	23.9 ± 3.5
120	27.4 ± 2.4	24.8 ± 2.9	27.8 ± 3.0	26.6 ± 3.5
150	28.2 ± 2.8	25.3 ± 2.1	26.0 ± 2.3	26.1 ± 2.9

Sumatriptan or placebo were given immediately after the measurement of baseline value (time 0). ANOVA and Bonferroni test, comparisons against placebo at each time point.

systolic and diastolic blood pressure, without changes in heart rate, was observed 60 and 90 minutes after the administration of 20 mg buspirone (data not shown). The maximal decrease was observed at 60 minutes: systolic and diastolic blood pressures were 128 ± 3.5 mm Hg and 79 ± 3 mm Hg, respectively, after placebo and 108 ± 2.1 mm Hg ($p < 0.05$) and 68 ± 1 mm Hg ($p < 0.05$), respectively, after buspirone. Dizziness and weakness were reported by two of the seven subjects treated with 10 mg buspirone and by all subjects after 20 mg buspirone. Three of the seven subjects treated with 200 mg sumatriptan reported nausea and dizziness.

Effect of buspirone on homatropine-induced mydriasis. The mean baseline pupil areas before homatropine and before the administration of placebo or buspirone were not statistically different (Fig. 2). As expected, 30 minutes after homatropine instillation, a marked dilation of the pupil size was observed (Fig. 2) and the physiologic miosis in response to the light was lost in all the subjects, thus indicating complete blockade of the cholinergic muscarinic receptors in the treated eye. In this condition 20 mg buspirone caused a significant reduction of the pupil area at 30 through 90 minutes after the oral intake of the drug in the homatropine-treated eye (Fig. 2). In the homatropine study, five of the six subjects treated with 20 mg buspirone reported dizziness and weakness.

DISCUSSION

In this study we measured pupil size for 150 minutes after oral administration of buspirone and sumatriptan in humans. We found that during this period of observation, which is sufficient for both drugs to reach their peak plasma levels,[18,19] buspirone, but not sumatriptan, reduced pupil size. Plasma level of buspirone and sumatriptan were not measured in the present study. In the absence of pharmacokinetic data, we can not exclude that the lack of effect of sumatriptan may reflect incomplete absorption of the drug. However, it is likely that sumatriptan absoption was substantially unaltered in our normal volunteers. It is possible that the pupillary effect induced by buspirone and the lack of effect of sumatriptan reflects their different pharmacologic profiles of action.

Sumatriptan has weak activity on 5-HT_{1A} receptors[20,21] and poorly penetrates into the brain,[22,23] where 5-HT_{1A} receptors are predominantly located.[9] Therefore, activation of 5-HT_{1A} receptors seems to be of little relevance to the clinical action of sumatriptan. There is evidence that the primary site of action of sumatriptan is at the level of the blood vessel wall because this drug has marked agonistic activity on 5-HT_1-like receptors, which contract cranial vessels[12] and inhibit neuropeptide release from perivascular endings of primary sensory fibers.[13] The high affinity of sumatriptan for 5-HT_{1D} binding sites observed in vitro in brain tissue homogenates suggests that 5-HT_1-like receptors are functionally the same as the brain 5-HT_{1D} receptors.[24,25] The 5-HT_1-like receptors that cause inhibition of neurotransmitter release have also been identified on sympathetic nerve terminals.[26] The observation that sumatriptan did not cause miosis or cardiovascular effects seems to exclude the existence of 5-HT_1-like or 5-HT_{1D} receptors, which inhibit norepinephrine release from the iris and cardiovascular sympathetic nerve terminals in humans. Our results are consistent with previous study that showed no clinically significant effect of 8 and 16 mg subcutaneous sumatriptan on pupil diameter, measured with photographs, heart rate, and blood pressure.[27]

The principal finding of this study is that buspirone provokes a dose-dependent miotic effect. Miosis induced by buspirone, at the highest dose tested, was evident as early as 30 minutes after the drug intake and reached a maximum within 60 minutes. Pharma-

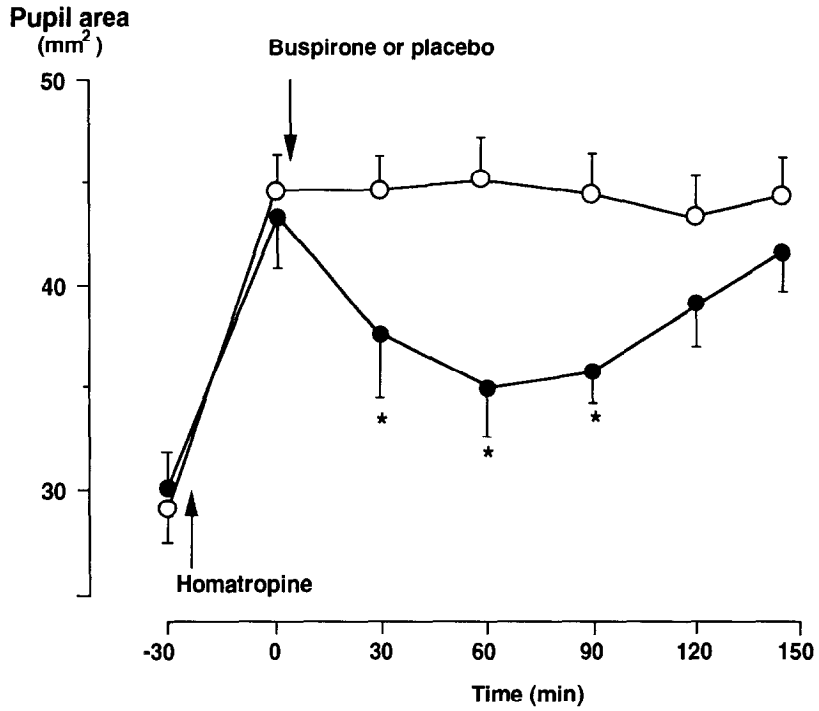

Fig. 2. Effect of orally administered buspirone (20 mg, *solid circles*) or placebo *(open circles)* on mydriasis induced by homatropine (1%, 50 μl) eyedrops in six healthy volunteers. Buspirone or placebo was given immediately after the measurement of pupil areas (time 0) recorded 30 minutes after homatropine instillation. $*p < 0.05$ versus placebo; Student t test.

cokinetic data in humans show that oral buspirone is rapidly absorbed, reaching a maximal concentration within an hour after dosing and with a plasma elimination half-life of 2½ to 3½ hours.[18] Therefore the time course of the effect of buspirone on pupil size is in good agreement with the pharmacokinetic parameters of this drug.

Buspirone is extensively and rapidly metabolized to 1-pyrimidinylpiperazine,[18] which is a potent antagonist of α_2-adrenergic receptors.[28] α_2-Adrenergic receptor agonists such as clonidine cause miosis in humans.[29] However, there is no evidence that α_2-adrenergic receptor antagonists decrease pupil size, and it is unlikely that the miotic effect of buspirone is caused by the α_2-adrenergic receptor antagonist activity of its metabolite. Buspirone exhibits some affinity for dopamine D_2-receptors. However, buspirone affinity for 5-HT_{1A} receptors is 16-fold higher than that for dopamine D_2-receptors,[8] and there is no evidence for an action of dopaminergic agents on pupil size. Buspirone is a partial agonist for 5-HT_{1A} receptors. Because buspirone is a highly liposoluble molecule and rapidly accumulates in the brain, its clinical anxiolytic value is attributed to activation of 5-HT_{1A} receptors in the brain.[8,18,30] The present findings suggest that the ability of buspirone to cause miosis in humans is attributable to its agonistic activity on 5-HT_{1A} receptors.

Regarding the mechanism by which activation of 5-HT_{1A} receptors by buspirone reduces pupil size, it must be also noted that the miotic response to buspirone was unaffected by pretreatment of the eye with homatropine, which blocked the miotic response to the light. Therefore the miotic effect of buspirone, a drug essentially inactive on muscarinic cholinergic receptors,[8] cannot be attributed to a cholinergic mechanism. Hence, the most likely hypothesis is that buspirone induces miosis by inhibiting the sympathetic discharge to the iris dilator smooth muscle. There is growing evidence, in experimental animals, that drugs that act on 5-HT_{1A} receptors located in the medullary region of the brain induce inhibition of sympathetic outflow and thus a decrease in sympathetic tone to the vasculature.[31,32] These effects are reverted by 5-HT_{1A} antagonists.[33] Administration of the selective 5-HT_{1A} receptor agonist flesinoxan to hypertensive patients and normotensive volunteers was found to decrease blood pressure without reflex tachycardia.[34] In our

study a low dose of buspirone was already able to induce miosis without any cardiovascular change, whereas when a higher dose of buspirone was used, the miosis was associated to hypotension. The observation that buspirone caused miosis and hypotension is fully consistent with the ability of buspirone to inhibit sympathetic discharge centrally.

In conclusion, the results can be taken to indicate that measurement of the miotic effect of buspirone seems to be a particularly sensitive method to determine the pharmacologic activity of this drug. We propose that a serotoninergic mechanism mediated by central 5-HT_{1A} receptors plays a role in the control of pupil size by inhibition of sympathetic outflow. In agreement with this hypothesis, the monitoring of the pupil size seems to represent a good model for the study of central 5-HT_{1A} receptors in a clinical setting. However, definitive proof for the role of 5-HT_{1A} receptor activation on buspirone-induced miosis could be obtained only by the use of selective antagonists for this subtype of 5-HT_1 receptors, which, however, are not currently available for clinical use.

References

1. Kramer R, Rubicek M, Turner P. The role of norfenfluramine in fenfluramine-induced mydriasis. J Pharm Pharmacol 1973;25:575-6.
2. Brion N, Culig J, Turner P. Indalpine effects on pupil diameter. Therapie 1985;40:9-11.
3. Kopera H. Anticholinergic and blood pressure effects of mianserin, amitriptyline and placebo. Br J Clin Pharmacol 1978;5:29S-34S.
4. Shur E, Checkley S, Delgado I. Failure of mianserin to affect autonomic function in the pupils of depressed patients. Acta Psychiatr Scand 1983;67:50-5.
5. Millson DS, Haworth SJ, Rushton A, Wilkinson D, Hobson S, Harry J. The effects of a 5-HT_2 receptors antagonist (ICI 169,369) on changes in waking EEG, pupillary responses and state of arousal in human volunteers. Br J Clin Pharmacol 1991;32:444-54.
6. Millson DS, Jessup CL, Swaisland A, Haworth S, Rushton A, Harry JD. The effects of a selective 5-HT_2 receptor antagonist (ICI 170,809) on platelet aggregation and pupillary responses in healthy volunteers. Br J Clin Pharmacol 1992;33:281-8.
7. Carli M, Prontera C, Samanin R. Evidence that 5-tryptaminergic neurones are involved in the anxiolytic activity of buspirone. Br J Pharmacol 1989;96:829-36.
8. Peroutka SJ. Selective interaction of novel anxiolytics with 5-hydroxytryptamine$_{1A}$ receptors. Biol Psychiatry 1985;20:971-9.
9. Andrade R, Nicoll RA. Novel anxiolytic discriminates between postsynaptic serotonin receptors mediating different physiological responses on single neurons of the rat hyppocampus. Naunyn Schmidebergs Arch Pharmacol 1987;336:5-10.
10. Gozlan S, Metzikawy S, Pichat L, Glowinski J, Hamon M. Identification of presynaptic serotonin autoreceptors using a new ligand: ^{3}H-PAT. Nature 1983;305:140-2.
11. Humphrey PPA, Feniuk W, Perren MJ, Oxford AW, Coates IH, Butina D. GR43175, a selective agonist for the 5-HT_1-like receptor in dog isolated saphenous vein. Br J Pharmacol 1988;94:1123-32.
12. Feniuk W, Humphrey PPA, Perren MJ. The selective carotid arterial vasoconstrictor action of sumatriptan in anaesthetized dogs. Br J Pharmacol 1989;96:83-90.
13. Buzzi MG, Moskowitz MA. The antimigraine drug sumatriptan (GR 43175) selectively blocks neurogenic plasma extravasation from blood vessels in dura mater. Br J Pharmacol 1990;99:202-6.
14. Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. N Engl J Med 1991;325:316-21.
15. Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. N Engl J Med 1991;325:322-6.
16. Fanciullacci M, Alessandri M, Pietrini U, Briccolani-Bandini E, Beatrice S. Long-term ergotamine abuse: effect on adrenergically induced mydriasis. Clin Pharmacol Ther 1992;5:302-7.
17. Alessandri M, Pietrini U, Fusco BM, Nicolodi M, Fanciullacci M. Possible non-muscarinic miotic action of echotiophate iodide in humans. Pharmacol Res 1989; 21:285-91.
18. Gammans RE, Mayol RF, Labudde JA. Metabolism and disposition of buspirone. Am J Med 1988;80: 41-51.
19. Dechant KL, Clissold SP. Sumatriptan: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the acute treatment of migraine and cluster headache. Drugs 1992;43:776-98.
20. Van Wijngaarden I, Tulp MTM, Soudijn W. The concept of selectivity in 5-HT receptor research. Eur J Pharmacol 1990;188:301-12.
21. McCarthy BG, Peroutka SJ. Comparative neuropharmacology of didihydroergotamine and sumatriptan (GR43175). Headache 1989;29:420-2.
22. Skingle M, Birch PJ, Leighton GE, Humphrey PPA. Lack of antinociceptive activity of sumatriptan in rodents. Cephalalgia 1990;10:207-12.
23. Dixon CM, Saynor DA, Andrew PD, Oxford J, Bradbury J, Tarbit MH. Disposition of sumatriptan in laboratory animals and humans. Drug Metab Dispos 1993;21:761-9.
24. Peroutka SJ, McCarthy BG. Sumatriptan (GR 43175) interacts selectively with 5-HT_{1B} and 5-HT_{1D} binding sites. Br J Pharmacol 1989;163:133-6.
25. Hoyer D, Middlemiss DN. Species differences in the pharmacology of terminal 5-HT autoreceptors in mammalian brain. Trends Pharmacol Sci 1989;10:131-2.
26. Feniuk W, Humphrey PPA, Watts AD. Presynaptic in-

hibitory action of 5-hydroxytryptamine in dog isolated saphenous vein. Br J Pharmacol 1979;67:247-54.

27. Sullivan JT, Preston KL, Testa MP, Busch M, Jasinski DR. Psychoactivity and abuse potential of sumatriptan. CLIN PHARMACOL THER 1992;52:635-42.
28. Blier P, Curet O, Chaput Y, de Montigny C. Tandospirone and its metabolite 1-(2-pyrimidyl)-piperazine-II: effects of acute administration of 1-PP and long-term administration of tandospirone on noradrenergic neurotransmission. Neuropharmacology 1991;30:691-701.
29. Fanciullacci M, Pietrini U, Fusco BM, Alessandri M, Marabini S, Sicuteri F. Does anisocoria by clonidine reflect a central sympathetic dysfunction in cluster headache? Clin Neuropharmacol 1989;11:52-62.
30. Temple DL, Yevich JP, New JS. Buspirone: chemical profile of a class of anxioselective agents. J Clin Psychiatry 1982;43:4-9.
31. Ramage AG, Fozard JR. Evidence that the 5-HT_{1A} receptor agonists, 8-OH-DPAT and isapirone, have central hypotensive action that differs from that of clonidine in anaesthetized cats. Eur J Pharmacol 1987; 138:179-91.
32. Connor HE, Humphrey PPA, Feniuk W. Serotonin receptors: therapeutic prospects in cardiovascualr disease. Trends Cardiovasc Med 1991;1:205-10.
33. McCall RB, Patel BN, Harris LT. Effect of serotonin$_1$ and serotonin$_2$ receptor agonists and antagonists on blood pressure, heart rate and sympathetic activity. J Pharmacol Exp Ther 1987;242:1152-9.
34. De Voogd JM, Prager G. Early clinical experience with flesinoxan, a new selective 5-HT_{1A} receptor agonist. In: Saxena PR, Wallis DI, Wouters W, Bevan P, eds. Cardiovascular pharmacology of 5-hydroxytryptamine. Dordrecht: Kluwer, 1990:355-9.