Short report

Calcium channel antagonism by pizotifen

STEPHEN J PEROUTKA,* SUZANNE B BANGHART,† GEORGE S ALLEN†

From the Departments of Neurology* and Neurosurgery,† The Johns Hopkins Hospital, Baltimore, Maryland, USA

SUMMARY Pizotifen is a clinically effective anti-migraine agent with potent anti-serotonin and anti-histamine properties. Pizotifen is equipotent in blocking contractions of the canine basilar artery induced by serotonin, norepinephrine or calcium chloride. As a result, the primary action of pizotifen in the canine basilar artery system appears to be calcium channel blockade and not selective antagonism of serotonin or norepinephrine. Calcium channel blocking ability may be related to the clinical efficacy of pizotifen in the treatment of migraine.

Specific calcium channel blockers such as flunarizine, verapamil and nimodipine have recently been shown to be effective in the prophylactic treatment of migraine.¹⁻⁶ On the other hand, pizotifen is a clinically effective anti-migraine agent but has no known calcium channel blocking abilities. Instead, its efficacy in the treatment of migraine has been attributed to its potent anti-serotonin and anti-histamine properties.⁷ However, pizotifen is structurally similar to cyproheptadine and amitriptyline, two other traditional anti-migraine agents which have recently been shown to possess calcium channel antagonist properties.^{8,9} Because of the structural similarity and anti-migraine efficacy of these agents, the present study investigated the ability of pizotifen to inhibit calcium-dependent contractions of the canine basilar artery.

Materials and methods

Canine basilar artery contractions were studied using an *in vitro* chamber system described in previous publications.^{9,10} Briefly, dogs of both sexes were killed by rapid exsanguination. The brains were removed and the basilar artery dissected free at room temperature. The vessel was divided into eight segments, each of which was mounted on parallel prongs inside two four-pronged chambers. The chambers

were filled with 50 ml of a modified Krebs buffer. The buffer was adjusted to a pH of 7.4 ± 0.05 , continually oxygenated and maintained at 37°C. Cumulative dose-response curves for serotonin were repeated until a stable response had occurred. Pizotifen was then incubated with the artery for five minutes prior to the addition of serotonin, norepinephrine or calcium chloride. The concentration of pizotifen needed to block 50% of the contraction (IC_{50}) normally obtained in the presence of 100 nM serotonin, 1 μ M norepinephrine or 0.5 mM calcium chloride was calculated by log-probit analysis. Each experiment was performed nine to twelve times using basilar artery segments from three or four dogs.

Results

Dose response curves for serotonin were obtained in the absence and presence of varying concentrations of pizotifen (fig). At 10^{-7} M pizotifen, the maximal response to serotonin (C_{max}) is decreased to approximately 70% of the control value. However, the K_{ED50} value for serotonin is not significantly different between the control (16 nM) and 10^{-7} M pizotifen (10 nM) contractions, a finding which suggests that the drug antagonism is non-competitive. At 10^{-6} M pizotifen, less than 35% of the initial C_{max} is obtained with concentrations of serotonin as high as 10^{-6} M. Only a minimal serotonin induced contraction could be obtained in the presence of 10^{-5} M pizotifen.

A sustained contraction of the canine basilar artery can also be produced by 1 μ M norepinephrine or by the addition of 0.5 mM calcium chloride to an initially calcium free buffer. Micromo-

Address for reprint requests: Dr SJ Peroutka, Department of Neurology, Stanford University Medical Center, Stanford, Ca. 94305, USA.

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Fig 1 Pizotifen antagonism of serotonin-induced contractions of canine basilar artery segments. Pizotifen ($\circ$ 10^{-8} M; $\square$ 10^{-7} M; $\blacksquare$ 10^{-6} M) was incubated for ten minutes with canine basilar artery segments prior to the addition of increasing concentrations of 5-HT. Data shown are the results of a single experiment which was repeated eight times.

lar concentrations of pizotifen block serotonin, norepinephrine and calcium induced contractions of the canine basilar artery. As shown in the table, the IC_{50} values for pizotifen were calculated for each of the three types of agonist induced contraction. Serotonin ($290 \text{ nM} \pm 80$), norepinephrine (120 ± 34) and calcium chloride (350 ± 90) induced contractions were inhibited to a similar degree by equimolar concentrations of pizotifen.

Discussion

The major finding of the present study is that pizotifen inhibits induced contractions of the canine basilar artery via a blockade of the calcium channel. Both serotonin and norepinephrine induced contractions of the canine basilar artery are dependent upon the entrance of extracellular calcium via specific membrane channels to initiate intracellular contractile systems.^{10,11} Although pizotifen is a potent serotonin antagonist,¹² it has no known adrenolytic activity.⁷ However, in the present study, pizotifen was essentially equipotent in blocking contractions of the canine basilar artery induced by serotonin, norepinephrine and calcium, a property shared by other calcium channel antagonists.¹¹ This

Table 1 Inhibition of agonist induced contractions of canine basilar artery by pizotifen

Agonist	IC_{50} (nM)
Serotonin	290 ± 80
Norepinephrine	190 ± 50
Calcium chloride	350 ± 90

represents the first demonstration of calcium channel antagonism by pizotifen, an agent whose previous vasoactive properties and anti-migraine efficacy were attributed to its anti-serotonin and/or anti-histamine properties.^{7,13}

The ability of pizotifen to block calcium channels in the canine basilar artery system may relate to its effectiveness in the prophylactic treatment of migraine. At the present time, three traditional anti-migraine agents (pizotifen, cyproheptadine, amitriptyline) have been shown to possess calcium channel blocking abilities.^{8,9} In addition, a number of recent studies have documented the beneficial effects of selective calcium channel blockers in migraine therapy.¹⁻⁶ Thus, the clinical efficacy of pizotifen in migraine prophylaxis may derive from its ability to block calcium channels located in vascular smooth muscle. Future clinical and physiological studies will determine whether the calcium channel antagonists, as a group of agents, are effective in the treatment of migraine.

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