5-Hydroxytryptamine: Source of Activator Calcium in Human Basilar Arteries

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SUMMARY We performed experiments in human cerebral arteries to determine the source of activator calcium during contractions induced by 5-hydroxytryptamine. Rings of human basilar artery obtained at autopsy were mounted for isometric tension recording in organ baths filled with a physiological salt solution. Contractile responses to 5-hydroxytryptamine were virtually abolished in Ca**+-free solution, and inhibited significantly by nimodipine. In both cases, the depression of the response to 5-hydroxytryptamine was comparable to that seen when KCl was used to contract the vessels. These experiments demonstrate that 5-hydroxytryptamine mediates contraction of the smooth muscle in human basilar artery by increasing membrane permeability to extracellular calcium.

ALTHOUGH 5-HYDROXYTRYPTAMINE is a potent constrictor of cerebral arteries from numerous animal species, its mechanism for making Ca++ available to activate the contractile proteins appears to be species-dependent. While contractions to 5-hydroxytryptamine in dog and rabbit basilar arteries depend upon the influx of extracellular Ca++ in the bovine basilar artery they are not associated with transmembrane Ca++ influx, suggesting that the ion is made available by mobilization of intracellular stores. The availability of calcium entry blockers with a relative specificity for cerebrovascular smooth muscle, provides a method for determining the Ca++-dependency of the contractile responses to neurohumoral mediators implicated in clinical conditions such as cerebral vasospasm. In view of the role that 5-hydroxytryptamine may play in such pathological situations, we performed experiments to determine the source of activator Ca++ during 5-hydroxytryptamine-induced contractions in isolated human basilar arteries.

Methods

Basilar arteries were removed from cadavers (ages 44–79 years) donated to the Mayo Foundation for the purpose of medical science. The vessels were obtained between 4 and 23 hours after death. After removal, the arteries were cleaned of connective tissue and cut into 3 mm rings. The rings were placed in organ chambers (25 ml volume) and attached to strain gauges (Statham UC2) for isometric tension recording. Experiments were performed at 37°C in a physiological salt solution. Contractile responses to 5-hydroxytryptamine were virtually abolished in Ca++-free solution, and inhibited significantly by nimodipine. In both cases, the depression of the response to 5-hydroxytryptamine was comparable to that seen when KCl was used to contract the vessels. These experiments demonstrate that 5-hydroxytryptamine mediates contraction of the smooth muscle in human basilar artery by increasing membrane permeability to extracellular calcium.

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tions were achieved by overflowing the organ chamber with high K+ solutions kept in a reservoir at 37°C.

For statistical analysis, Student's t-test for paired observation was used. P values less than 0.05 were considered to be statistically significant.

Results

In rings from 6 arteries, dose-response curves to 5-hydroxytryptamine and KCl were performed in control solution (2.5 mM Ca++) and in Ca++-free solution following 10 min exposure to Ca++-free solution containing 2mM EGTA. In the absence of extracellular Ca++, the two agonists did not cause significant increases in tension (fig. 1).

When contractions were obtained with 5-hydroxytryptamine (4 x 10^-6M) or KCl (20 mM), the addition of increasing concentrations of nimodipine caused a concentration-dependent relaxation. At 10^-8M, nimodipine caused significant relaxation of contractions induced by 5-hydroxytryptamine. At the higher concentrations of antagonist used (10^-8 and 10^-7M), contractions caused by 5-hydroxytryptamine and KCl were markedly inhibited (fig. 2).

Discussion

Previous investigators have shown that 5-hydroxytryptamine contracts human cerebral arteries.13-15 In human pial arteries, this contraction can be attenuated by the calcium channel blocking agent nifedipine.16 The present experiments concur with this report, and demonstrate that in the human basilar artery, 5-hydroxytryptamine mediates contraction by increasing membrane permeability to extracellular calcium. In this respect, human basilar arteries resemble canine and rabbit,1-3 but not bovine2 cerebral arteries. As in all other blood vessels tested so far,10-12 the contractile response to KCl was also dependent upon extracellular calcium. The observation that both Ca++-free solution and nimodipine also markedly depressed responses to 5-hydroxytryptamine, suggests that mobilization of intracellular Ca++ stores must play at best a minor role in the contractile response to the monoamine.

It has been reported that calcium channel blocking agents increase cerebral blood flow in animal models3 and humans17 after acute ischemic stroke, and can prevent or alleviate cerebral vasospasm.18,19 High extracellular K+ concentrations and 5-hydroxytryptamine-induced constriction, respectively, have been implicated as possible spasmogenic agents in these pathologies.5,7-9 The present study predicts that calcium channel blocking agents should be particularly effective to treat increased cerebrovascular tone caused by these agents.

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References


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**Graphs:**
- Figure 1: Effect of incubation in Ca++-free solution on the concentration-contraction curves to KCl and 5-hydroxytryptamine (5-HT) in isolated human basilar arteries. Data shown as means (n = 6) ± SEM, and expressed as percent of the contraction obtained with the largest concentration of each agonist. * = the effect of Ca++-free + 2 mM EGTA solution is statistically significant.
- Figure 2: Effect of increasing concentrations of the Ca++ entry blocker nimodipine on contractions of human basilar arteries evoked by the ED50 of either KCl or 5-hydroxytryptamine (5-HT). Data shown as means (n = 6) ± SEM, and expressed as percent of the initial contraction. * = the effect of nimodipine is statistically significant.
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