The effect of Apamin® on nonadrenergic, noncholinergic nervous vasodilatations in the cat small intestine[1]

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Summary. The intestinal vasodilation evoked by mechanical mucosal stimulation or by transmural electrical field stimulation was abolished by close i.a. injection of Apamin, a polypeptide originally isolated from bee venom. Apamin also blocked the vasodilatation induced by close i.a. infusion of vasoactive intestinal polypeptide (VIP). It is suggested that Apamin is a VIP receptor antagonist.

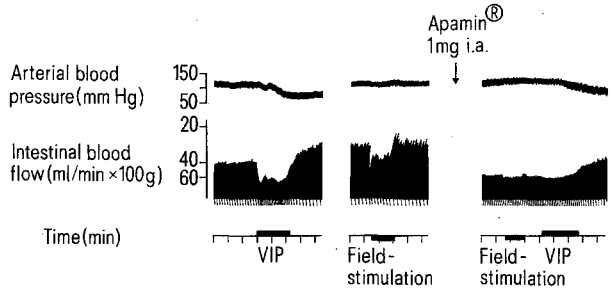
It is well established that the nervous control of gastrointestinal function is in part mediated via nonadrenergic, noncholinergic neurones. One such mechanism that has been studied fairly extensively in this laboratory is the reflex intestinal vasodilatation elicited by mechanical stimulation of the mucosa or by transmural electrical field stimulation[2]. Evidence has been reported suggesting that this vasodilatation is induced via the release of vasoactive intestinal polypeptide (VIP) from nerves in close contact with the smooth muscle cells of the intestinal vessels[3,4]. In this report experiments are described which show that this reflex intestinal hyperemia can be abolished by Apamin®, a polypeptide originally isolated from bee venom[5].

Methods. The experiments were performed on cats deprived of food for 24 h with free access to water. The animals were anaestethized with chloralose (50 mg/kg b.wt). Venous outflow from a denervated segment of the jejunum weighing about 15 g was recorded by an optical drop recorder unit operating an ordinate writer. Arterial blood pressure was recorded from the left femoral artery by a pressure transducer (Staham P23AC). All recordings were made on a Grass polygraph. In some experiments an intestinal vasodilatation was elicited by mechanical stimulation of the intestinal mucosa by pulling a short piece of rubber tubing back and forth through the lumen. In other experiments the intestinal hyperemia was induced by transmural electrical field stimulation as described in detail by Biber et al.[6]. Apamin® (Serva Feinbiochemica) was administered close i.a. according to the method described by Biber et al.[7]. VIP (purchased from professor V. Mutt, Stockholm, Sweden) was infused through a catheter in a branch to the superior mesenteric artery.

Results. Figure 1 illustrates a representative experiment. The upper recording shows arterial blood pressure and the lower, blood flow from an isolated intestinal segment as monitored by an ordinate writer. The downward deflections of the lower recording gives every 10th drop as counted automatically by the drop recording unit. The left and middle panels illustrate the effects of a close i.a. infusion of VIP and transmural electrical field stimulation, respectively, before administration of Apamin. The right panel shows the effects of the same experimental manipulations after 1 mg Apamin given close i.a. It can be seen that the intestinal vasodilatations induced by VIP and an electrical field were almost completely abolished after giving Apamin. Similar results were obtained with regard to the vasodilatation elecited by mechanical mucosal stimulation. However, the vascular effects produced by electrical stimulation of the regional sympathetic vasoconstrictor fibres or by close i.a. infusion of the vasodilator drug isoprenaline were unchanged after Apamin administration (not shown in figure).

Discussion. Apamin is a polypeptide of known composition containing 18 amino acid residues. In the present study it was demonstrated that Apamin blocked the vasodilatations evoked by transmural electrical field stimulation, by mechanical mucosal stimualtion or by i.a. infusions of VIP. The vascular effects elicited by electrical stimulation of the regional vasoconstrictor nerves, or by the vasodilator drug isoprenaline, remained unchanged after Apamin administration arguing against Apamin having an unspecific effect on nervous transmission or on vascular smooth muscles. The reported observations are in full agreement with our earlier findings indicating that VIP is a neurotransmitter in the nervous reflex involved in the vasodilatation evoked by mechanical mucosal stimulation or by transmural electrical field stimulation[3,4]. These observations are also in agreement with the recent study reporting the Apamin blockade of the noncholinergic and nonadrenergic relaxation of taenia coli seen upon electrical field stimulation[8].

VIP and Apamin are both basic polypeptides with a molecular mass of the same order of magnitude. Based on the observations reported in this study it is proposed that Apamin is a receptor blocking agent for VIP. Studies to test this hypothesis further are in progress in this laboratory.



Left and middle panels: The effects on arterial blood pressure and intestinal blood flow of a close i.a. infusion of vasoactive intestinal polypeptide (VIP; 3 µg/min) and transmural electrical field stimulation (2.5 V, 20 msec, 20 Hz), respectively. Right panel: The effects of the same experimental procedures 10–15 min after close i.a. administration of 1 mg Apamin. Note that the rate of blood flow is inversely proportional to the height of the ordinate writer. Downward deflections of blood flow recordings indicate every 10th drop counted.

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