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Letter to the Editor

Calcitonin gene-related peptide activates non-adrenergic, non-cholinergic relaxations of the rat isolated duodenum

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Calcitonin gene-related peptide (CGRP) is a newly discovered sensory neuropeptide (Rosenfeld et al 1983) widely distributed in various viscera and particularly, the gastrointestinal tract and cardiovascular system (Clague et al 1985; Sternini & Brecha 1985; Mulderry et al 1985). CGRP possesses a potent inhibitory action on smooth muscle contractility: for instance it is a potent vasodilator and potentiates the inflammatory oedema induced by mediators of increased vascular permeability (Brain et al 1985, 1986; Edvinsson et al 1985). However, CGRP may affect muscle motility indirectly also, e.g. by activating neural elements. In fact, exogenous CGRP produces a contraction of the guinea-pig isolated ileum, which is abolished by hyoscine plus mepyramine (Tippins et al 1984). We now report that rat synthetic CGRP produces neurogenic non-adrenergic, non-cholinergic (NANC) relaxation of the rat isolated duodenum.

Segments of rat duodenum were excised from male albino rats, Wistar–Morini strain, 340–360 g, and mounted in an isolated organ bath containing Krebs solution gassed with 95% O_2 and 5% CO_2 (Maggi et al 1984; Manzini et al 1985). Tension was recorded from the longitudinal muscle by means of an isometric transducer connected to a Basile 7050 Unirecord.

CGRP (1–100 nM, n = 10) produced a transient relaxation of the rat isolated duodenum (Fig. 1) (EC 50 5 nM, 95% CL 3–9 mM). The relaxant effect of CGRP 0·1 μM amounted to 60–80% of that produced in the same preparation by DMPP (0·1 mM) or noradrenaline (1 μM). CGRP (0·1 μM)-induced relaxation was unaffected by atropine (3 μM) plus guanethidine (3 μM, n = 6) but was significantly reduced (about 40%) by tetrodotoxin (TTX, 1 μM, n = 6), thus indicating the partial involvement of a neurogenic NANC mechanism.

Previous studies suggested that ATP might be one of the transmitter(s) and/or cotransmitters released by intrinsic NANC neurons in the rat duodenum (Maggi et al 1984; Manzini et al 1985). Therefore we studied the effect of ATP-desensitization on CGRP-induced relaxation.

Previous exposure to ATP (1 mM, 2 min before) reduced by about 40% (n = 6) the amplitude of CGRP (0·1 μM)-induced relaxation (Fig. 1 upper panel) while that produced by noradrenaline (1 μM) was unaffected. A second exposure to ATP (1 mM, 2 min later without washing) produced a relaxation with an amplitude of about 50% compared with the first, indicating desensitization. Repeated exposure to ATP (1 mM at 2 min intervals up to 5 mM, n = 6) did not reduce further its relaxant effect or produce a greater reduction in

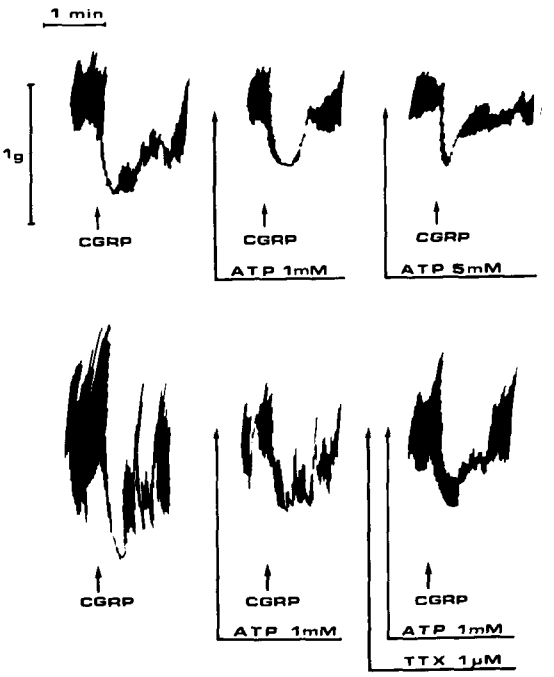

FIG. 1. Upper panels. Effect of ATP-desensitization on CGRP (0·1 μM)-induced relaxation of the rat isolated duodenum. ATP 1 mM was added to the organ bath 2 min before the challenge with CGRP. ATP 5 mM was added cumulatively to the organ bath (five consecutive challenges with ATP 1 mM at 2 min intervals without washing). Note that ATP 5 mM did not produce a greater reduction of CGRP-induced relaxation than ATP 1 mM. Lower panels. Effect of ATP-desensitization (1 mM, 2 min before) or ATP-desensitization plus TTX (1 μM) on the CGRP-induced relaxations of the rat isolated duodenum.

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CGRP-induced relaxation than that produced by ATP 1 mM (Fig. 1).

In other experiments, we studied the effect of ATP desensitization (1 mM, 2 min before) on CGRP-induced relaxation either in the absence or in the presence of TTX (1 μM, Fig. 1, n = 6). In preparations desensitized to ATP, the prior addition of TTX did not produce a greater reduction of CGRP-induced relaxation than ATP alone (Fig. 1). The observation that (i) TTX and ATP-desensitization reduced CGRP-induced relaxation to a similar extent (about 40%) and (ii) the antagonistic effect of TTX and ATP were non-cumulative (Fig. 1 lower panel) is consistent with the hypothesis that the neuronal (TTX-sensitive) component of CGRP-induced relaxation may involve release of endogenous ATP from intramural NANC neurons.

In the rat isolated duodenum the relaxant effect of CGRP could thus involve two components, i.e. an indirect, TTX-sensitive one, by activating intramural nerves, as already described for the guinea pig ileum (Tippins et al 1985), and a direct TTX-resistant component, maybe similar to that responsible for the direct vasodilatation of cat cerebral vessels (Edvinsson et al 1985).

CGRP neurons and fibres have been demonstrated in the rat duodenum, and in the myenteric plexus CGRP fibres form a network around certain intramural neurons (Clague et al 1985; Sternini et al 1985). NANC relaxations of the longitudinal muscle of the rat isolated duodenum can be elicited not only by electrical or chemical stimulation of intramural NANC neurons (Maggi et al 1984; Manzini et al 1985), but also by physiological-like stimuli such as increase in intraluminal pressure (Holman & Hughes 1965) or chemical stimulation (capsaicin) of sensory nerves (Maggi et al 1986). The potential role of endogenous CGRP in regulating duodenal motility in this animal species requires further study.

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