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Stimulant action of tetraethylammonium on the peristaltic reflex of the guinea-pig isolated ileum

D. B. BELESLIN* AND M. M. RAKIĆ

Department of Pharmacology, Medical Faculty, Beograd, Yugoslavia

1. Tetraethylammonium (TEA) in concentrations below 0·5 mg/ml. depressed or blocked the peristaltic reflex of the guinea-pig isolated ileum: in concentrations above 0·5 mg/ml. it caused a contraction of the longitudinal muscle and restored the peristaltic reflex previously blocked by the lower concentrations.

2. The peristaltic reflex, when blocked by ganglion-blocking agents, morphine and morphine-like agents, 5-hydroxytryptamine, catecholamines or atropine, was restored by high concentrations of TEA.

3. The possible mechanisms of these effects are discussed.

The ganglion-blocking effect of tetraethylammonium (TEA) is well known. Bozler (1949) found that TEA blocks synaptic transmission in the gut and thus inhibits the peristaltic reflex. It has also been shown that high concentrations of TEA cause contraction of the longitudinal muscle of the guinea-pig ileum (Collins, 1948; Trendelenburg, 1961; Rakić & Beleslin, 1966). Rakić & Beleslin (1966) found that high concentrations of TEA not only cause a contraction of the longitudinal muscle but also stimulate the peristaltic activity in the guinea-pig isolated ileum, the lumen of which has been distended for a prolonged period. An attempt has now been made to analyse more fully this stimulant effect of TEA.

Methods

The methods have been described in the preceding paper (Beleslin, 1969). The drugs used were: tetraethylammonium chloride, hexamethonium bromide, azamethonium chloride, 5-hydroxytryptamine creatinine sulphate, morphine sulphate, codeine phosphate, pethidine chloride, methadone hydrochloride, noradrenaline bitartrate, adrenaline hydrochloride and atropine sulphate. All values refer to the salts.

Results

Effects of TEA on the peristaltic reflex

TEA in concentrations below 0·5 mg/ml. depressed or blocked the peristaltic reflex but had no effect on the longitudinal muscle. On the other hand, concentrations of 2–3 mg/ml. caused a contraction of the longitudinal muscle and restored

* Present address: Laboratory of Neuropsychology, Department of Psychology, Purdue University, Lafayette, Indiana 47907, U.S.A.

the peristaltic reflex after it had been blocked by a low concentration. In Fig. 1, TEA (0·25 mg/ml.) blocked the peristaltic reflex, which was at once restored by the addition of TEA 2 mg/ml. The regular and strong peristaltic waves persisted for about 3 min.

Effect on the action of ganglion-blocking agents

TEA (1·5 mg/ml.) restored the peristaltic reflex blocked by azamethonium (0·25 mg/ml.). Strong peristaltic waves continued for about 5 min, during which time the tone of the circular muscle was increased (Fig. 2). In similar experiments, restoration of the peristaltic reflex by higher concentrations of TEA after block by hexamethonium or azamethonium lasted for 2–10 min.

Effect on the action of 5-hydroxytryptamine

TEA (1·5–2 mg/ml.) restored, after a short latency, the peristaltic reflex abolished by 5-hydroxytryptamine. The peristaltic waves were small at first, becoming more regular and strong after a few minutes, and continued for about 10 min. There was also an increase in the tone of the circular and longitudinal muscles.

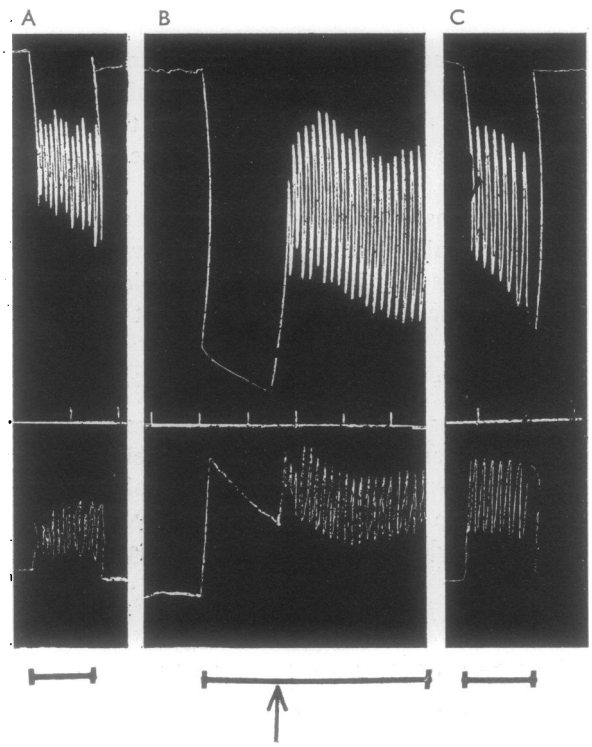

FIG. 1. Guinea-pig isolated ileum. Tracings in this and subsequent figures: Intraluminal volume changes shown in upper record, increase in volume downwards; contractions and relaxations of longitudinal muscle in lower record, contractions upwards. At horizontal bars, intraluminal pressure raised to 30 mm H_2O. Between A and B, TEA (0·25 mg/ml.) and at arrow TEA (2 mg/ml.) were added to the bath. Between B and C, TEA washed out. Time marker in min.

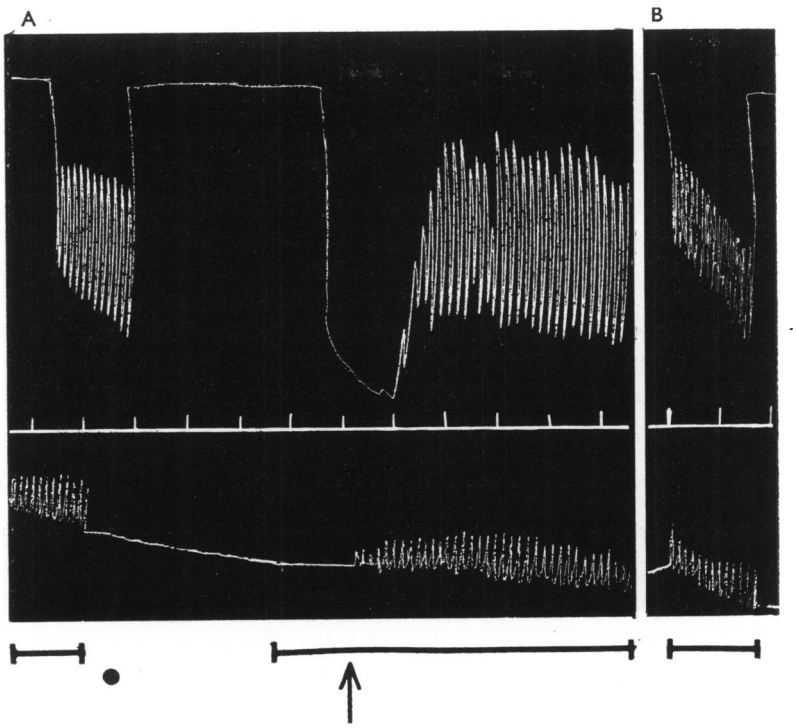

FIG. 2. Guinea-pig isolated ileum. At horizontal bars, intraluminal pressure raised to 25 mm H_2O. At ●, azamethonium (0·25 mg/ml.) and at arrow, TEA (1·5 mg/ml.) were added to the bath. Between A and B, both azamethonium and TEA washed out. Time marker in min.

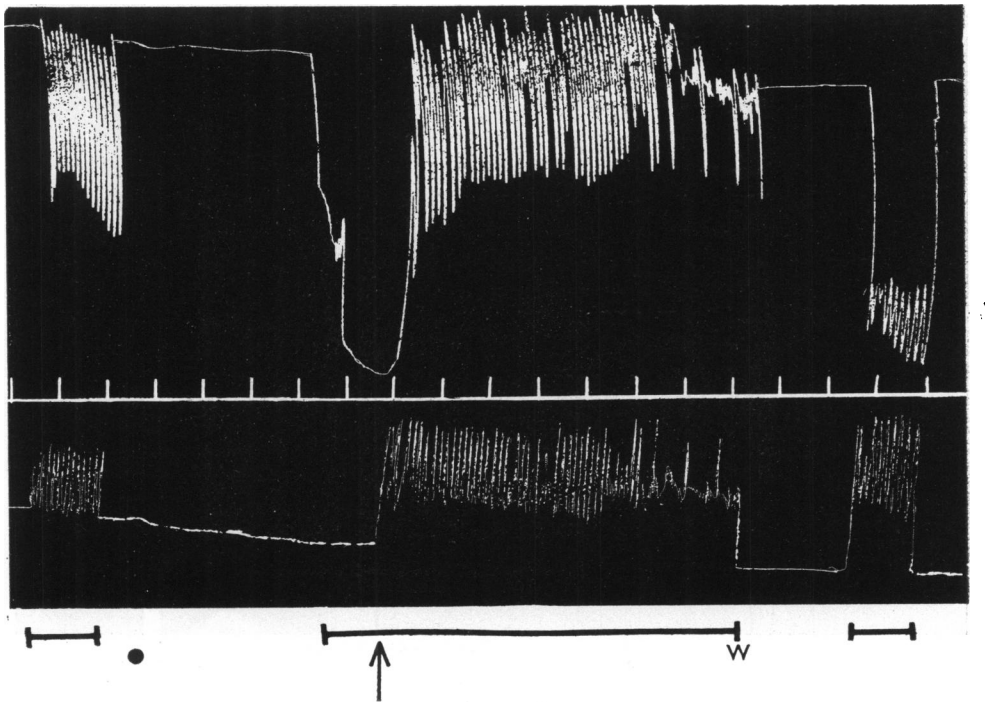

FIG. 3. Guinea-pig isolated ileum. At horizontal bars, intraluminal pressure raised to 30 mm water. At ●, methadone (0·2 μg/ml.) and at arrow, TEA (2·5 mg/ml.) were added to the bath; at W, both methadone and TEA washed out. Time marker in min.

Effect on the action of morphine and morphine-like agents

TEA (1·5–2·5 mg/ml.) restored the peristaltic reflex blocked by methadone morphine, pethidine, or codeine. For instance, addition of TEA (2·5 mg/ml.) to the bath immediately restored the peristaltic reflex blocked by methadone (0·2 μg/ml.) (Fig. 3). The peristaltic waves were irregular and showed incomplete relaxation; during this time, the tone of the circular muscle was increased more than that of the longitudinal muscle. In the presence of pethidine (2 μg/ml.), TEA caused very irregular peristaltic waves with little relaxation between contractions on the other hand, when the reflex was blocked by morphine (0·3 μg/ml.), the peristaltic waves elicited by TEA were regular. The effect of TEA on peristaltic activity blocked by morphine or morphine-like agents lasted for 5–12 min.

Effect on the action of catecholamines

The inhibition of the peristaltic reflex by noradrenaline and adrenaline was antagonized by TEA (1·5–3 mg/ml.). After a short latent period, peristaltic waves of varying amplitude appeared and lasted for about 10 min.

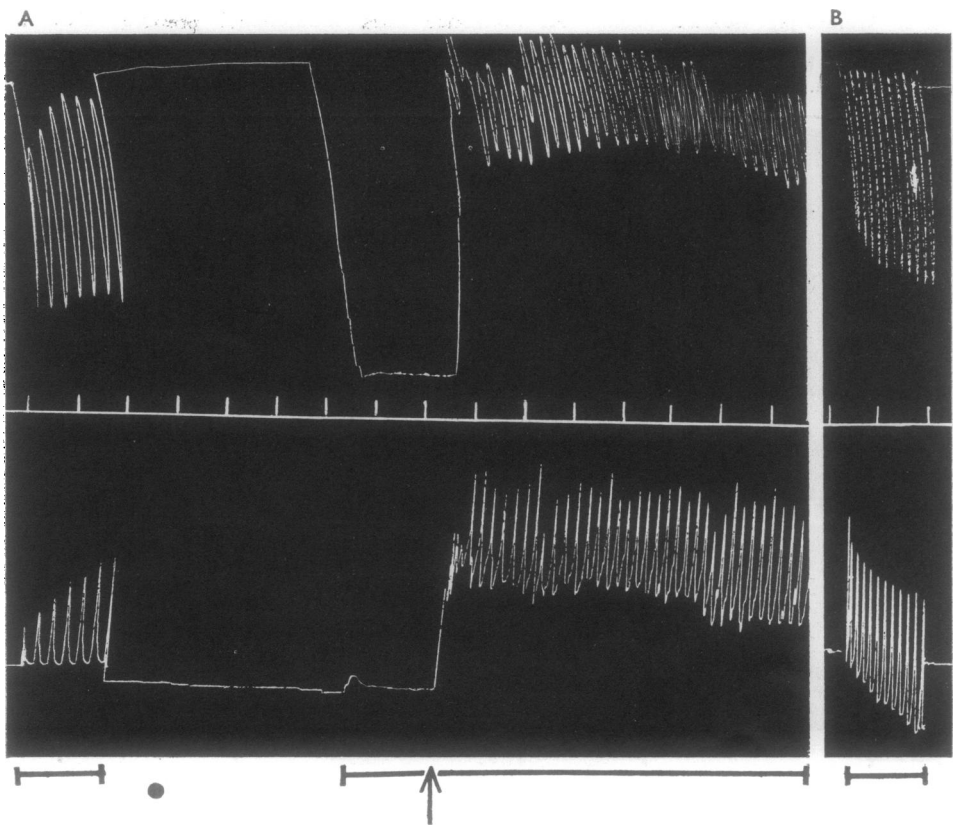

FIG. 4. Guinea-pig isolated ileum. At horizontal bars, intraluminal pressure raised to 30 mm water. At ●, atropine (0·5 μg/ml.) and at arrow, TEA (2·0 mg/ml.) were added to the bath. Between A and B, both atropine and TEA washed out. Time marker in min.

Effect on the action of atropine

The peristaltic reflex blocked by atropine (0·5 μg/ml.) was restored by TEA (2–2·5 mg/ml.). The peristaltic waves appeared immediately after the addition of TEA to the bath and continued for about 8 min (Fig. 4). There was first a strong contraction of both muscle layers, followed by small waves which later became more regular.

Discussion

The stimulant action of TEA on the smooth muscle of many tissues has already been described (Acheson & Moe, 1946; Collins, 1948; Čapek & Knesslovà, 1959; Trendelenburg, 1961). Stone, Entwisle & Loew (1951) found that TEA in high doses released from the cat adrenal medulla catecholamines which caused a rise in the arterial blood pressure and a contraction of the nictitating membrane.

Bozler (1949) obtained a block of the peristaltic reflex by low concentrations of TEA. While our present experiments confirm these observations, they show that high concentrations of TEA cause contraction of the longitudinal muscle and stimulate peristaltic activity. Moreover, high concentrations of TEA restore the peristaltic reflex blocked by hexamethonium, azamethonium, morphine, morphine-like agents, 5-hydroxytryptamine, catecholamines and atropine. These findings are in good agreement with those of Kensler (1950), Stovner (1957) and Collier & Exley (1963), who found that, when the neuromuscular transmission is blocked by *d*-tubocurarine or by low Ca^{2+}, TEA has a restoring effect. Stovner (1957) suggested that TEA increases the release of acetylcholine from the presynaptic nerve endings, a suggestion which was confirmed experimentally by Collier & Exley (1963). TEA also enhances the acetylcholine output of the perfused superior cervical ganglion (Douglas & Lywood, 1961). The restoration of the peristaltic reflex by TEA after block by various drugs may be due to an increased release of acetylcholine from nerve end terminals and direct stimulation of the smooth muscle. Feldberg & Lin (1949) showed that increased muscular tone may facilitate the initiation of peristaltic waves. An effect of TEA on post-synaptic membranes may also be a contributing factor; the stimulant effect of high concentrations of TEA on the peristaltic reflex blocked by low concentrations of TEA, hexamethonium or azamethonium suggest that TEA acts on the same receptors in the enteric ganglia as the other blocking agents.

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