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Further evidence for an electrogenic sodium pump in a mammalian sympathetic ganglion.

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After ganglion cells of superior cervical ganglia from rabbit, rat or kitten have been depolarized by acetylcholine or carbachol, removal of the depolarizing agent results in a large hyperpolarization (Pascoe, 1956; Brown, 1966; Kosterlitz, Lees & Wallis, 1968). Since Kosterlitz *et al.* (1968) found that the rates of onset and decay of this hyperpolarization recorded by the sucrose-gap method were reduced in a potassium-free solution, they suggested that the potential was generated as a result of active extrusion of Na^+ by an electrogenic sodium pump, which requires extracellular K^+.

Further evidence shows that: (*a*) the hyperpolarization is still present when the membrane potential approaches E_K and its magnitude is not linearly related to the ratio $[K^+]_i/[K^+]_o$; (*b*) it cannot be attributed to movement of Cl^-; (*c*) is prevented by ouabain (10 μM); (*d*) it is reduced when $[Na^+]_o$ or $[Ca^{2+}]_o$ is reduced; (*e*) its rates of onset and decay are reduced in a glucose-free solution.

However, a diffusion barrier round the cells might allow an electrically neutral pump to generate the potential if the potassium ion concentration within the barrier fell. This possibility is excluded by the following experiment: in potassium-free solution, acetylcholine causes a depolarization, which is followed slowly by a small hyperpolarization; when now $[K^+]_o$ is raised to 6 mM, a large, rapid hyperpolarization

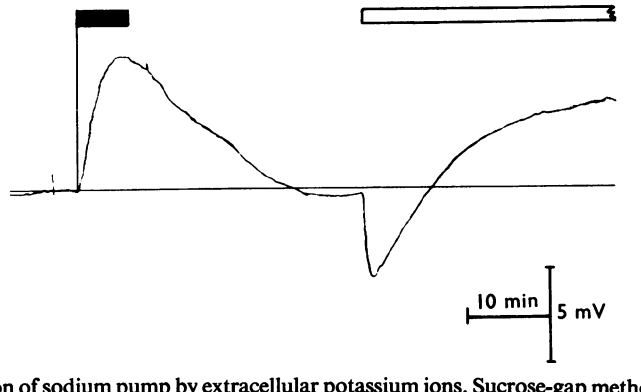

FIG. 1. Activation of sodium pump by extracellular potassium ions. Sucrose-gap method of recording; depolarization of ganglion upwards. Ganglion bathed in potassium-free Krebs solution for 23 min before commencement of record. Eserine (60 μM) present throughout the experiment. Black bar, ganglion exposed to acetylcholine 110 μM. White bar, $[K^+]$ of Krebs solution bathing ganglion raised to 6 mM. Note that the resting potential in the presence of 6 mM K^+ was eventually −4·6 mV, of which about 40% was due to d.c. drift.

occurs (Fig. 1). We conclude that an electrogenic sodium pump is operating which requires extracellular K^+ to activate it. Cs^+ is much less effective than K^+ in stimulating the pump as has been shown for the rat superior cervical ganglion by Brown, Brownstein & Scholfield (1969).

By the sucrose-gap method, the mechanism underlying the production of the drug-induced hyperpolarization is compared with the hyperpolarization of ganglion cells evoked by orthodromic excitation, the P wave or slow IPSP. Unlike the drug-induced hyperpolarization, the P wave has a component whose amplitude increases in potassium-free solution (Kosterlitz *et al.*, 1968). Furthermore, in confirmation of the findings of Kobayashi & Libet (1968) and Libet & Kobayashi (1969), the amplitude of the *P* wave is not readily diminished by ouabain.

This work was supported by U.S. Public Health Service Grant NB 03026 from the National Institute of Neurological Diseases and Stroke.

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The effects of morphine-like substances and their antagonists on transmission at the neuro-effector junction of the myenteric plexus-longitudinal muscle preparation of the guinea-pig ileum.

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It has been shown (Gyang & Kosterlitz, 1966; Kosterlitz & Watt, 1968) that, in the guinea-pig ileum, narcotic analgesic drugs have both agonist and antagonist properties and that the pharmacological effects depend on the ratio of agonist to antagonist potency. There are only a few compounds which are pure antagonists devoid of agonist activity, for example, naloxone. The order of agonist and antagonist potencies as determined on the guinea-pig ileum are in good agreement with observations made in man. This fact has made it possible to use the guinea-pig ileum for the prediction of agonist and antagonist activities of new compounds (Kosterlitz & Watt, personal communication).

Since this method depends on the effects of the narcotic analgesic drugs on impulse transmission at the myenteric plexus-longitudinal muscle junction, it was of interest to investigate more fully the factors which influence the release of acetylcholine and the response of the longitudinal muscle to the transmitter. It has been shown (Paton & Zar, 1968; Cowie, Kosterlitz & Watt, 1968) that morphine in low concentrations depresses the acetylcholine output when the myenteric plexus-longitudinal muscle