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Two separate cholinergic mechanisms for regulation of oxytocin release

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The oxytocinergic neurones of the lactating rat generate every 5–15 min during suckling a synchronized and brief (2–4 s) burst of action potentials (Lincoln & Wakerley, 1975). Each period of accelerated firing (> 40 spikes/s) discharges a pulse of oxytocin (0.5–1.0 mU) from the neurohypophysis; this circulates to the mammary gland and initiates the ejection of milk. The hypothalamic neurones of the supraoptic and paraventricular nuclei, which synthesize and release oxytocin, are excited by iontophoretically applied acetylcholine (Dreifuss & Kelly, 1972) and cholinomimetics stimulate the release of neurohypophysial hormones (Kuhn & McCann, 1971). It is possible, therefore, that acetylcholine may be an essential synaptic transmitter in the pathway for reflex milk ejection. This was examined by the application of cholinolytics to rats that were reflexly milk ejecting, under urethane anaesthesia.

Lactating rats (250–350 g), separated from their young for 20 h at 8–10 days post-partum, were anaesthetized with urethane (1.2 g/kg, i.p.). Intramammary and arterial pressures were recorded, as described elsewhere (Tribollet, Clarke, Dreifuss & Lincoln, 1977). Three hours later, whilst the animal was still anaesthetized, a hungry litter of young were applied to the nipples. The first milk ejection occurred after 20–40 min, and thereafter milk ejections recurred approximately every 6 minutes. Cholinolytics (atropine, hyoscine, mecamylamine and hexamethonium) were injected into the saphenous vein, in a volume of about 0.3 ml. Cholinomimetics (carbachol and bethanecol) were injected into the lateral cerebral ventricle in a volume of 1 µl; the solutions were made isotonic with NaCl.

Atropine and hyoscine, muscarinic antagonists, failed to abolish the milk-ejection reflex of the rat when given in doses up to 100 mg/kg (0/22). Mecamylamine (0.5–2.0 mg/kg) and hexamethonium (5–10 mg/kg), nicotinic antagonists, caused a substantial delay in the recurrence of milk ejection (27/45). This inhibition was dose-dependent and recovery was obtained.

Both the cholinomimetics, carbachol (0.01–0.2 µg) and bethanecol (0.2–4.0 µg), when injected into the lateral ventricle caused a large prolonged release of both oxytocin and vasopressin, as observed through changes in intramammary and blood pressures (36/46). This release was abolished by atropine (0.1–1.0 mg/kg) applied systemically (11/11). Mecamylamine had no effect at 5 mg/kg (0/8).

A direct action of these drugs on the neurohypophysis or mammary glands was unlikely for the responses to intravenous injections of oxytocin and to endogenous oxytocin released by electrical stimulation of the neurohypophysis remained unaltered. Thus, the milk-ejection reflex of the rat appears to contain an excitatory cholinergic relay of the nicotinic type, placed somewhere other than at the level of the oxytocinergic neurone. By contrast, the response to intraventricular cholinomimetics is muscarinic in type.

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