Responses of the isolated sphincter of Oddi from the guinea-pig to field stimulation

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Recent reviews (Persson, 1972; Sarles, 1974; Tansy, Innes, Martin & Kendall, 1974) have highlighted the uncertainties concerning the control of the terminal portion of the common bile duct. The present study was undertaken to investigate the neurally mediated responses of the guinea-pig sphincter of Oddi to field stimulation and their modification by drugs.

The choledochoduodenal junction of the guinea-pig is anatomically noteworthy. The lower end of the common bile duct expands into a large oval pouch lying on the serosal surface of the duodenum. From the caudal end of the pouch a small duct passes directly into the duodenum (Higgins, 1927).

Male guinea-pigs (200 to 1,000 g) were stunned, bled and the terminal portion of the common bile duct and surrounding duodenal areas were removed. A polyethylene cannula (1 mm i.d.) was passed, via the common bile duct, into the pouch and ligated. The duodenum was trimmed to the limits of the pouch. The cannula was attached to a Y-tube one arm of which was connected to a pressure transducer linked to a polygraph, the other was perfused with Krebs solution at the rate of 0.024 ml/min. The preparation was then placed in a bath of Krebs solution maintained at 37° C and bubbled with 5% CO_2 in oxygen. Field stimulation was applied via two platinum loop electrodes (2 cm apart at 50 V, 40 Hz and 0.2 ms pulse width.

The preparations exhibited resting perfusion pressures of 1 to 6 cm H_2O with approximately one third showing spontaneous activity. Field stimulation resulted in changes in perfusion pressure of up to 25 cm H_2O. The increase in resistance to perfusion with field stimulation was abolished by tetrodotoxin (1 μg/ml) and lignocaine (117 μg/ml). This stimulation response was also much reduced in 30 of 44 preparations by atropine (28 ng/ml) or hyoscine (152 ng/ml). Acetylcholine (0.05 to 50 μg/ml) and carbachol (1 to 5 μg/ml) produced increases in perfusion pressure whilst neostigmine (10 to 100 μg/ml) caused an increase in spontaneous activity and a sustained increase in perfusion pressure. Propranolol (5 μg/ml), phentolamine (140 ng/ml) or guanethidine (1.9 μg/ml) did not affect the response to field stimulation. Noradrenaline (0.5 to 2 μg/ml) in a single instance increased perfusion pressure. Isoprenaline (0.5 to 2 μg/ml) consistently inhibited activity in spontaneously active preparations. Nicotine (0.5 to 16 μg/ml) caused a small rise in perfusion pressure in 3 out of 11 preparations. This response was blocked by hexamethonium (10 μg/ml).

In this preparation, therefore, there is evidence of cholinergic neurones having a motor function, but little evidence for significant adrenergic motor control.

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Peptide hormones and the extinction of conditioned taste aversion

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When a rat is subjected to the unpleasant effects of a drug contingent upon drinking a distinctively flavoured novel solution, it acquires a strong aversion to the taste of that solution (Rozin & Kalat, 1971). This phenomenon is commonly called 'conditioned taste aversion'.

Rats, which were deprived of water for 23.30 h, were allowed to drink a 5% glucose solution ('sugar water') in a single 15 min session. Lithium chloride (LiCl, 0.15 M 10 ml/kg i.p.) injected 30, 60 or 120 min after the conclusion of the drinking session induced strong avoidance of the sugar water at subsequent sessions. Avoidance was less as the interval between drinking and drug treatment

was increased. Conditioned taste aversion only occurs when the test solution is novel. It was found that LiCl, given 30 min after the drinking session, could not induce avoidance for tap water or sugar water if the rats had previously been given either of these solutions in the absence of LiCl treatment.

De Wied and coworkers (de Wied, 1969; Garrud, Gray & de Wied, 1974) have shown that ACTH-analogues modulate the extinction of shock or appetite motivated behaviour. It was therefore deemed of interest to study the effects of these analogues on the extinction of conditioned taste aversion. In each experiment eight groups of ten rats were used. Two groups received extinction sessions (a single 15 min session/day) during which time the rats were allowed free access to sugar water contained in a drinking tube. These animals had the choice between drinking the aversive solution or not drinking at all ('forced extinction'). Two other groups had the choice of either tap water or sugar water (preference test). Extinction in the preference test took much longer than forced extinction (approximately 3 weeks *versus* 3 days). In addition, two control groups which had been treated with saline instead of LiCl, were subjected to the forced extinction test and two other control groups to the preference test. In each block of two groups, one group was injected s.c. with a drug 1 h prior to daily extinction sessions whereas the other group was treated with placebo. In the first experiment the effects of ACTH (adrenocorticotrophic hormone)-analogue, $ACTH_{4\text{-}10}$, were studied. $ACTH_{4\text{-}10}$ is known to delay the extinction of shock and appetite motivated behaviour (de Wied, 1969; Garrud, Gray & de Wied, 1974). In the conditioned taste aversion test, it was found that 100 μg $ACTH_{4\text{-}10}$/rat delayed the extinction in the preference test, but did not affect forced extinction. The peptide did not influence the fluid intake of the control groups.

When the phenylalanine residue in position seven of the sequence $ACTH_{4\text{-}10}$ is replaced by its D-isomer ($ACTH_{4\text{-}10\,7D\,Phe}$) extinction of shock and appetite motivated behaviour is facilitated (de Wied, 1969; Garrud, Gray & de Wied, 1974). However, $ACTH_{4\text{-}10}$ and $ACTH_{4\text{-}10\,7D\,Phe}$ have a similar effect on passive avoidance behaviour: both compounds potentiate weak passive avoidance responses (Greven & de Wied, 1973). It appeared that $ACTH_{4\text{-}10\,7D\,Phe}$ (100 μg/rat) delayed the extinction of conditioned taste aversion in the preference test. The peptide did not alter forced extinction or fluid intake of the control groups. The finding that $ACTH_{4\text{-}10}$ and $ACTH_{4\text{-}10\,7D\,Phe}$ had similar effects suggests that extinction of conditioned taste aversion is not completely comparable to extinction of shock motivated (active) avoidance responses.

α-MSH (melanocyte stimulating hormone) and ACTH share the amino acid sequence 4-10. Like ACTH, α-MSH delays the extinction of shock and appetite motivated behaviour (de Wied, 1969; Kastin, Dempsey, LeBlanc, Dyster-Aas & Schally, 1974). It was shown that 100 μg/rat α-MSH similarly delayed the extinction of conditioned taste aversion in the preference test but not in the forced extinction test. In contrast, melanocyte stimulating hormone release inhibiting factor (MIF; 100 μg/rat), which according to Sandman, Alexander & Kastin (1973) exerts behavioural effects similar to α-MSH, was without effect.

It is concluded that extinction of conditioned taste aversion can be modulated by the administration of peptide hormones or hormonal analogues

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