3. Lignocaine (0.02–6.0 mM) was used to assess local anaesthetic actions. Lignocaine only depressed the IPSP and the EPSP (at 0.2–0.6 mM) and depressed the action potential at 0.9–6.0 mM. E_m and R_m were anaffected.

All these general anaesthetics appear to prolong inhibition at the lower concentrations and this is likely to produce anaesthesia *in vivo*. With halothane, ketamine and urethane the depression of the EPSP probably contributes to the anaesthetic action.

References

SCHOLFIELD, C.N. (1976). A depolarizing inhibitory post-synaptic potential in mammalian brain slices. *J. Physiol. (Lond.)*, **263**, 120P.

SCHOLFIELD, C.N. (1977). Prolongation of post-synaptic inhibition by barbiturates. *Br. J. Pharmac.*, **59**, 507P.

Effect of vasoactive intestinal peptide (VIP) and other neuropeptides on cAMP accumulation in brain slices

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Various peptides may act as neurotransmitters or neuromodulators in the central nervous system; these include substance P, neurotensin, vasoactive intestinal peptide (VIP), the hypothalamic releasing factors and the enkephalins and endorphins. Recent findings have demonstrated the selective distribution of such peptides in brain, their localization in nerve terminals and their release from such terminals. The postsynaptic actions of a number of neurotransmitters seem to be mediated through cAMP or cGMP (Greengard, 1976). Furthermore, several of the peptides listed above have been reported to stimulate adenylate cyclase activity (Duffy, Wong & Powell, 1975; Robberecht, Conlon & Gardner, 1976). Therefore, a number of peptides, reported to be present in relatively high concentrations in specific rat brain regions, were examined to determine their effect on cAMP and cGMP accumulation in slices of various regions of rat brain and on cell free adenylate cyclase activity in homogenates.

Substance P, luteinizing hormone releasing factor, thyrotropin releasing factor, somatostatin, neurotensin and glucagon at concentrations up to 100 μM were without effect on any of these tests in a number of brain regions. When slices (prepared according to the method of Forn, Kreuger & Greengard, 1974) from these same brain regions were incubated in the presence of VIP (0.5 μM), however, a statistically significant increase (40 to 100% over basal) in the accumulation of cAMP was observed. There were no changes in cGMP levels and no increase in cAMP was seen in cerebellar slices. A small increase in cell free adenylate cyclase activity could be demonstrated in the presence of VIP (0.5 μM). When slices were incubated in the presence of the phosphodiesterase inhibitor isobutylmethylxanthine (2 mM) a three to six fold increase in basal levels of cAMP was observed but VIP was able to elicit a further increase in cAMP, indicating that its effects on cAMP accumulation are probably due to activation of adenylate cyclase. The increase in cAMP in tissue slices by VIP was diminished in media lacking calcium or media containing high calcium concentrations (4.0 mM). When tissue slices were incubated in the presence of VIP and the antagonist drugs propranolol (10 μM), phenoxybenzamine (50 μM), α-flupenthixol (1 μM), fluphenazine (50 μM) and naloxone (1 μM), no alterations in the VIP induced increase in cAMP were observed. Furthermore, when VIP was incubated in the presence of a variety of compounds which stimulate cAMP formation, dopamine (100 μM), noradrenaline (10 μM), prostaglandin E_1 (5 μM), morphine (1 μM), isoprenaline (1 μM) or adenosine (50 μM) the VIP induced increase in cAMP levels was additive to that caused by each of these agents.

These results further support a role for VIP as a neurotransmitter or neuromodulator in the central nervous system and suggests that, as in the periphery, its central actions may be mediated through an adenylate cyclase/cAMP system.

References

DUFFY, M.J., WONG, J. & POWELL, D. (1975). Stimulation of adenylate cyclase activity in different areas of human brain by Substance P. *Neuropharmacol.*, **14**, 615–618.

FORN, J., KREUGER, B.K. & GREENGARD, P. (1974). Adenosine 3′,5′-monophosphate content in rat caudate nucleus: demonstrations of dopaminergic and adrenergic receptors. *Science*, **186**, 1118–1120.

GREENGARD, P. (1976). Possible role for cyclic nucleotides and phosphorylated membrane proteins in postsynaptic actions of neurotransmitters, *Nature (Lond.)*, **260**, 101–108.

ROBBERECHT, P., CONLON, T.P. & GARDNER, J.D. (1976). Interaction of porcine vasoactive intestinal peptide with dispersed pancreatic acinar cells from the guinea pig. *J. Biol. Chem.*, **251**, 4635–4639.