Regulation of the cyclic AMP concentration in chick brain by β-adrenoreceptors and histamine H_2 receptors

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Several observations have emphasized the importance of cyclic AMP in the functioning of the central nervous system (for review see Drummond, 1973). The majority of studies have utilized *in vitro* preparations to demonstrate an enhanced formation of cerebral cyclic AMP induced by biogenic amines. However, using the neonate chick with its immature blood-brain barrier we have shown that certain biogenic amines increase the concentration of cerebral cyclic AMP *in vivo* (Edwards, Nahorski & Rogers, 1973). In the present study we have attempted to further characterize the receptors involved in these responses.

All experiments were performed on two-day old Rhode Island Red x Sussex Brown hybrid chicks. Receptor blocking agents were injected subcutaneously 30 min before an injection of isoprenaline or histamine into the right jugular vein. The cerebral hemispheres were removed and frozen within 0.5 s using a freeze-blowing technique (Veech, Harris, Veloso & Veech, 1973) to eliminate post-mortem changes in cyclic AMP concentration (Nahorski & Rogers, 1973). Following purification by column chromatography, cyclic AMP was assayed by the protein binding saturation assay of Brown, Albano, Ekins, Sgherzi & Tampion (1971).

Isoprenaline (1 mg/kg) induced a two-fold increase in cerebral cyclic AMP concentration which was completely blocked in chicks pretreated with DL-propranolol (0.5 mg/kg). D-propranolol was at least 10 times less potent than the racemate. Phentolamine (10 mg/kg) did not antagonize the isoprenaline response.

Histamine (10 mg/kg) produced a two- to three-fold increase in brain cyclic AMP. This response was not antagonized by pretreatment with the histamine H_1-receptor antagonist mepyramine in doses of up to 20 mg/kg, but was blocked by the H_2-receptor antagonists burimamide (10 mg/kg) and metiamide (5 mg/kg).

Parallel *in vitro* experiments were performed using 0.37 mm thick slices of chick cerebral hemispheres preincubated for 60 min in Krebs-bicarbonate buffer containing 10 mM glucose. DL-propranolol (10 μM) completely blocked the 20- to 30-fold increase in cyclic AMP induced by isoprenaline (10 μM) whereas D-propranolol (10 μM) and phentolamine (10 μM) were ineffective. The 15- to 20-fold increase in slice cyclic AMP content induced by histamine (10 μM) was unaffected by mepyramine at concentrations of 10-50 μM. On the other hand both burimamide and metiamide (5-50 μM) antagonized the histamine response.

From these observations we suggest that increased cyclic AMP formation in chick cerebral hemispheres can be mediated through stimulation of β-adrenoreceptors and histamine H_2 receptors. In view of the fact that histamine also increases cyclic AMP in gastric tissue (Karppanen & Westermann, 1973) and guinea pig heart (Pöch, Kukovetz & Scholz, 1973) by activation of H_2 receptors, it is possible that histamine H_2 receptors, like β-adrenoreceptors, are linked to adenyl cyclase.

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