was $1.63 \pm 0.18$ ng.cm$^{-2}$ min$^{-1}$ ($n = 36$). PS injected at the doses of 50, 75, and 150 mg/kg caused increases in ACh output of 57%, 83% and 313% respectively. PE, 150 mg/kg, only caused a 50% increase and PC had no effect. The increase only occurred in the two samples collected following the phospholipid administration. When calcium was removed from the Ringer solution and substituted with magnesium the spontaneous ACh output was decreased and the increase induced by PS was either prevented or strongly reduced.

It has been shown by Mongar & Svec (1972) that PS potentiates the histamine release by antigen from three sensitized rat tissues. This effect is calcium dependent. It therefore seems possible that a number of secretory processes at peripheral and central levels might be affected by PS through a mechanism in which calcium plays an important role.

We thank Fidia Laboratories Abano Terme, Italy for the supply of purified phospholipids. This work was supported by CNR grant No. 74.00250.04.

### References

HEMSWORTH, B.A. & NEAL, M.J. (1968). The effect of central stimulant drugs on the release of acetylcholine from the cerebral cortex. *Br. J. Pharmac.*, **32**, 543-550.

MONGAR, J.L. & SVEC, P. (1972). The effect of phospholipids on anaphylactic histamine release. *Br. J. Pharmac.*, **46**, 741-752.

## Developmental changes in the sensitivity of neurohormone-stimulated cyclic AMP formation in chick cerebral hemispheres

S.R. NAHORSKI, WENDY PATTON* & K.J. ROGERS

*Department of Pharmacology, University of Sheffield*

In a previous study from this laboratory we reported that in the *in vivo* 3′-5′-adenosine cyclic monophosphate (cyclic AMP) content of chick cerebral hemispheres decreased with increasing age (Nahorski, Rees & Rogers, 1975). Moreover, whereas the responsiveness of the cerebral cyclic AMP system to isoprenaline and histamine *in vivo* fell throughout the post-natal period, the post mortem ischaemic increase in the cyclic nucleotide became progressively larger with age. In the present experiments we have used *in vitro* techniques in an attempt to elucidate possible mechanisms for these developmental changes in sensitivity.

Experiments were performed on Rhode Island Red X Sussex Brown chicks and embryos at various stages during their perinatal development. Cerebral hemisphere slices (0.37 mm thick) were preincubated for 60 min in a Krebs-bicarbonate buffer containing 10 mM glucose and following exposure of the slices to various agonists, the cyclic AMP content of the tissue was determined by a protein-binding assay. Responsiveness to isoprenaline and histamine in the slices became evident at 17 days embryonic age whereas a response to adenosine was observed at 15 days embryonic age. By means of dose-response curves it was found that the maximal cyclic AMP response to isoprenaline (493 p moles/mg protein) and histamine (524 p moles/mg protein) occurred at 3 days postnatal age and then declined during the first postnatal month. The largest increase in the nucleotide concentration following exposure to adenosine was observed at 19 days embryonic age (211 p moles/mg protein) and this response was maintained throughout the period studied. Despite the apparent developmental alterations in the maximum response to different agonists, the $ED_{50}$ for each of the agonists was similar at all ages studied.

The activity of adenylate cyclase in cerebral homogenates of chicks of various ages was assayed in the presence and absence of 10 mM NaF. Significant basal activity was observed in 15 day old embryos and this increased at least 4 fold by 21 days postnatal age. NaF only significantly stimulated enzyme activity in tissue from the oldest birds. Ethyleneglycolbis (β-aminoethyl)-*N*, *N*′-tetracetic acid (EGTA) markedly suppressed enzyme activity and in the presence of this $Ca^{++}$ chelator no developmental changes in adenylate cyclase activity were observed. Phosphodiesterase activity was determined using low (1 μM cyclic AMP) substrate concentrations. Enzyme activity increased from $949 \pm 82$ p moles cyclic AMP hydrolysed min$^{-1}$ mg$^{-1}$ protein at 15 days embryonic age to $4529 \pm 153$ p moles cyclic AMP hydrolysed min$^{-1}$ mg$^{-1}$ protein at 4 weeks post hatch.

The results suggest that in the embryonic and neonatal periods the development of cerebral neurohormone receptors coupled to adenylate cyclase may precede the development of

functional transmitter input leading to "supersensitive" responses to exogenous agonists. This resembles the supersensitivity demonstrated in cerebral tissue to isoprenaline after chemical denervation. (Nahorski & Rogers, 1975).

Financial support from the Medical Research Council is gratefully acknowledged.

**References**

NAHORSKI, S.R., REES, M.W. & ROGERS, K.J. (1975). Cyclic AMP in developing chick brain: changes with ischaemia and catecholamine administration. *Br. J. Pharmac.*, **54**, 255-256P.

NAHORSKI, S.R. & ROGERS, K.J. (1975). Altered sensitivity of β-adrenoceptor-mediated cyclic AMP formation in brain. *Br. J. Pharmac.* (in press).

## A primate model of acute dystonic reaction to neuroleptics

G.M. ANLEZARK*, C.D. MARSDEN & B.S. MELDRUM

*Department of Neurology, Institute of Psychiatry, London, SE5 8AF*

A small proportion of patients (5% or less) treated with classical neuroleptic drugs of the butyrophenone and phenothiazine series develop acute dystonic reactions in the initial few days of therapy. The mechanism by which these reactions are produced is unknown, but the antipsychotic action of neuroleptics is thought to be due to blockade of central dopamine synapses.

In the course of testing the neuroleptics haloperidol (0.6-1.2 mg/kg i.v.) and pimozide (0.1-2.5 mg/kg i.v.) in the photosensitive Senegalese baboon, *Papio papio*, we discovered that three animals showed a dystonic response (Meldrum, Anlezark & Trimble, 1975). One animal showed the abnormal response only after the highest dose of pimozide and was not used in the subsequent experiments. The other two invariably showed the response with all doses tested. The normal response to neuroleptics in these baboons was sedation and a reduction in spontaneous motor behaviour lasting up to 5 hours. The abnormal response was characterized by episodes of compulsive gnawing, tongue protrusion, neck extension and trunk twisting and by licking accompanied by salivation and hyperventilation lasting up to 7 hours. This dystonic reaction was also produced by chlorpromazine (5 and 25 mg/kg i.m.), but not by thioridazine (3 and 7 mg/kg i.v.). It was abolished by the anticholinergics benztropine (0.2 mg/kg i.v.) and hyoscine (20 and 50 μg/kg i.v.). This is analogous to the situation in human patients, in whom anticholinergic drugs dramatically abolish acute dystonic reactions to neuroleptics. Thioridazine is a potent antipsychotic which has few extrapyramidal side effects, perhaps because it possesses high inherent anti-muscarinic activity (Miller & Hiley, 1974).

In acute experiments, the neuroleptics cause increased turnover and release of dopamine in the rat striatum (Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970), and dystonic postures and movements are provoked by L-DOPA in some patients with Parkinson's disease. A possible explanation of dystonic reactions to neuroleptic drugs is that the dopamine release that they cause activates dopaminergic synapses not blocked by the neuroleptics. If this is so, depletion of central dopamine by reserpine or the tyrosine hydroxylase inhibitor, α-methyl-p-tyrosine (AMPT) should reduce or abolish the abnormal responses. Pretreatment with AMPT alone (200 mg/kg i.p. in a single dose or 150 mg/kg i.p. x 3) had little effect on the dystonic response to haloperidol (1 mg/kg i.v.), but pretreatment with reserpine (2 mg/kg i.p.) and AMPT (200 mg/kg i.p. or 150 mg/kg i.p. x 2) decreased the severity of the dystonic response to haloperidol and delayed its onset.

**References**

ANDÉN, N-E., BUTCHER, H., CORRODI, H., FUXE, K. & UNGERSTEDT, U. (1970). Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmac.*, **19**, 303-314.

MELDRUM, B.S., ANLEZARK, G.M. & TRIMBLE, M. (1975). Drugs modifying dopaminergic activity and behaviour, the EEG and epilepsy in *Papio papio*. *Eur. J. Pharmac.*, **32**, 203-213.

MILLER, R.J. & HILEY, C.R. (1974). Anti-muscarinic properties of neuroleptics and drug-induced Parkinsonism. *Nature, Lond.*, **248**, 596-597.