nucleotide concentration increased with age. One minute of ischaemia induced an increase of 23.5 p moles/mg protein in the one day old chick and 48 p moles/mg protein in the 28 day old bird compared with the appropriate controls. It is possible, therefore, that the discrepancy between the developmental changes in cyclic AMP obtained in the present study and those obtained in the rat by Schmidt *et al.* (1970) may be due to age dependent post-mortem hypoxic increases in brain cyclic AMP.

In the neonate chick with its immature blood-brain barrier, the systemic administration of β-adrenoceptor agonists has been shown to increase the concentration of cyclic AMP in chick cerebral hemispheres *in vivo* (Edwards, Nahorski & Rogers, 1974). In the present study chicks of varying ages were injected intravenously with isoprenaline (5 μmoles/kg) and were killed by freeze-blowing 3 min later. The isoprenaline-induced increase in cyclic AMP was maximal in three day old chicks (+19.7 p moles/mg protein) but diminished with age (+3.3 p moles/mg protein in 28 day old birds).

^{3}H-noradrenaline was given intravenously to chicks aged 2-28 days, and its penetration into the brain was determined. Brain levels of ^{3}H-noradrenaline at 28 days of age were only 19% of those at two days of age. It is probable, therefore, that the decrease in the *in vivo* cyclic AMP response to isoprenaline with age is due to the development of a blood-brain barrier to catecholamines rather than a change in receptor sensitivity. *In vitro* studies to further substantiate these results are now in progress.

Financial support from the Medical Research Council is gratefully acknowledged.

References

BROWN, B.L., ALBANO, J.D.M., EKINS, R.P., SGHERZI, A.M. & TAMPION, W. (1971). A simple and sensitive saturation assay method for the measurement of adenosine 3',5'-cyclic monophosphate. *Biochem. J.*, **121**, 561-562.

DRUMMOND, G.I. (1973). Metabolism and functions of cyclic AMP in nerve. In: *Progress in Neurobiology*, eds Kerkut, G.A. & Phyllis, J.W. Vol. 2, Part 2, pp. 119-176. Oxford: Pergamon Press.

EBADI, M.S., WEISS, B. & COSTA, E. (1971). Microassay of adenosine 3',5'-monophosphate (cyclic AMP) in brain and other tissues by the luciferin-luciferase system. *J. Neurochem.*, **18**, 183-192.

EDWARDS, C., NAHORSKI, S.R. & ROGERS, K.J. (1974). *In vivo* changes of cerebral cyclic adenosine 3',5'-monophosphate induced by biogenic amines: association with phosphorylase activation. *J. Neurochem.*, **22**, 565-572.

NAHORSKI, S.R. & ROGERS, K.J. (1973). The adenosine 3',5'-monophosphate content of brain tissue obtained by an ultrarapid freezing technique. *Brain Res.*, **51**, 332-336.

SCHMIDT, M.J., PALMER, E.C., DETTBARU, W.D. & ROBISON, G.A. (1970). Cyclic AMP and adenyl cyclase in the developing rat brain. *Dev. Psychobiol.*, **3**(1), 53-67.

Antinociceptive activity in mice after central injections of α- and β-adrenoceptor antagonists

R.D.E. SEWELL* & P.S.J. SPENCER

Department of Applied Pharmacology, UWIST, Cardiff

Recent studies have demonstrated that narcotic agonist and partial agonist analgesic agents interact in a specific way with certain putative central transmitters: thus, the intracerebroventricular (ICV) injection of 5-hydroxytryptamine (5-HT) potentiates whilst the ICV injection of noradrenaline (NA) attenuates the antinociceptive activity of these agents in experimental animals (Sewell & Spencer, 1974). The present study sets out to characterize more fully the nature of this attenuation by ICV-administered NA.

Nociceptive sensitivity was measured repeatedly at fixed intervals in ICI-derived albino mice weighing 18-22 g, using the tail-immersion method described in the earlier report. It had already been demonstrated that the centrally-acting α-sympathomimetic agent clonidine possessed antinociceptive activity in experimental animals (Schmitt, Le Douarec & Petillot, 1974), and this has been confirmed by the present authors using the tail-immersion test in mice. However, when clonidine was given by ICV injection (0.5 μg/animal), it possessed only marginal antinociceptive activity, and furthermore substantially attenuated the antinociceptive effect of morphine (3 mg/kg) when given concurrently. The α-adrenergic antagonist phentolamine (10 μg/animal, ICV) exhibited antinociceptive activity when given alone and significantly potentiated the activity of a subcutaneously administered concurrent dose of morphine (3 mg/kg) or pentazocine (15 mg/kg). The antinociceptive activity of subcutaneously

administered clonidine (300 μg/kg) on the other hand was significantly antagonized by phentolamine (5 μg/animal, ICV).

The β-adrenergic antagonist propranolol possesses no antinociceptive activity when peripherally administered (Cicero, Meyer & Smithloff, 1974). However, when given alone, propranolol (10 μg/animal, ICV) exhibited some antinociceptive effect but it did not potentiate the activity of concurrent subcutaneous doses of morphine (2.5 mg/kg), pentazocine (15 mg/kg) or clonidine (300 μg/kg, s.c.).

Cicero *et al.* (1974) have shown previously that peripherally-administered α-adrenergic antagonists enhance the antinociceptive effects of morphine in mice. The present study shows this is also true when these agents are restricted to the central nervous system by virtue of their ICV route of injection; also, that the antinociceptive activity of a partial agonist is also enhanced, whilst that of clonidine is attenuated. Whilst the enhancement of the action of narcotic agonists and partial agonists by α-adrenergic antagonists is entirely consistent with the previously demonstrated effects of ICV NA, the significance of the antinociceptive effect of ICV propranolol requires further study.

We are indebted to Messrs Boehringer & Sohn, Ingelheim, for generous financial assistance.

References

CICERO, T.J., MEYER, E.R. & SMITHLOFF, B.R. (1974). Alpha adrenergic blocking agents: antinociceptive activity and enhancement of morphine-induced analgesia. *J. Pharmac. exp. Ther.*, **189**, 72-82.

SCHMITT, H., Le DOUAREC, J.C. & PETILLOT, N. (1974). Antinociceptive effects of some α-sympathomimetic agents. *Neuropharmacology*, **13**, 289-294.

SEWELL, R.D.E. & SPENCER, P.S.J. (1974). Modification of the antinociceptive activity of narcotic agonists and antagonists by intraventricular injection of biogenic amines in mice. *Br. J. Pharmac.*, **51**, 140-141P.

The uptake of mescaline by rat brain synaptosomes

P. BEVAN

Department of Psychiatry, University of Edinburgh, Morningside Park, Edinburgh EH10 5HF

It has previously been reported that single cortical neurones can respond with excitation or depression to microelectrophoretically applied mescaline (Bevan, Bradshaw, Roberts & Szabadi, 1974). It has also been reported that these neuronal responses can be potentiated by the tricyclic antidepressant desipramine (Bevan, Bradshaw & Szabadi, 1975). It is of interest to know whether this potentiation could be due to the blockade of the uptake of mescaline into presynaptic terminals. Iversen (1967) has reported that mescaline has a very low affinity for noradrenaline uptake mechanisms in the periphery, but there are no data concerning the uptake of mescaline into brain tissue.

I have therefore examined the uptake of (^{14}C)-mescaline (specific activity 5.2 mCi/mmole, New England Nuclear Corpn) and, for the purposes of comparison, (^{14}C)-(−)-noradrenaline (specific activity 5.0 mCi/mmole, Radiochemical Centre Ltd.) into synaptosomes prepared from rat cerebral cortex according to the method of Thornburg & Moore (1973). After incubation, the mescaline or noradrenaline content of each sample was assessed by liquid scintillation spectrometry, and the protein content determined using the method of Lowry, Rosebrough, Farr & Randall (1951). The uptake of mescaline or noradrenaline was thus expressed as pmoles/mg protein for each sample. All values are expressed as mean ± s.e.

In agreement with earlier reports, for example, Horn, Coyle & Snyder (1971), the accumulation of noradrenaline was found to be a temperature-dependent process (K_m = 0.628 ± 0.033 μM, V_m= 192.3 ± 7.4 pmoles/mg protein). Mescaline was also accumulated by an active uptake process (K_m= 1.24 ± 0.27 μM, V_m= 26.34 ± 8.02 pmoles/mg protein); however, for equivalent concentrations, the uptake of mescaline was much lower than that of noradrenaline. For example, at a concentration of 0.628 μM, the K_m of noradrenaline, the uptake of mescaline was 10% the uptake of noradrenaline.

The effect of desipramine on the uptake of noradrenaline and on the uptake of mescaline was then examined. Desipramine competitively inhibited the uptake of noradrenaline (K_i desipramine = 0.0499 ± 0.0052 μM). However, desipramine, within a concentration range 0.05-5 μM, did not affect the uptake of mescaline.

The effect of mescaline on the uptake of noradrenaline was also examined. Mescaline was found to inhibit the active accumulation of noradrenaline in a non-competititive manner (K_i mescaline = 10.548 ± 0.697 μM).