

lowered GABA levels compared with controls ($P < 0.001$, t -tests); the DRN lesioned rats had no amino acid levels significantly different from controls.

References

- CLARK, R.M. & COLLINS, G.G.S. (1976). The release of endogenous amino acids from the rat visual cortex. *J. Physiol. (Lond.)*, **262**, 283–400.
- FILE, S.E. & HYDE, J.R.G. (1978). Can social interaction be used to measure anxiety? *Br. J. Pharmac.*, **62**, 19–24.

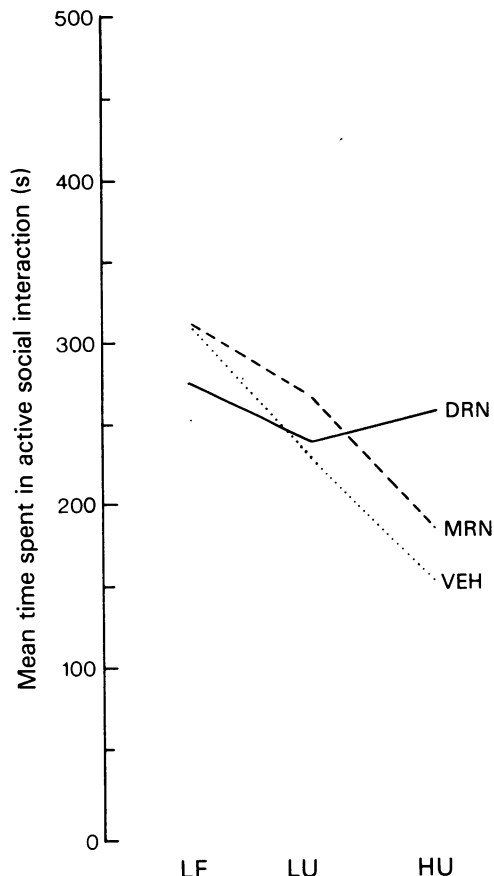


Figure 1. Mean time(s) spent in active social interaction in the low light, familiar (LF), low light, unfamiliar (LU) and high light, unfamiliar (HU), by vehicle controls (VEH), MRN and DRN lesioned rats. Six pairs of rats were tested in each condition, and no pair was tested more than once.

A functional antagonism between benzodiazepines and ACTH?

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Behavioural experiments carried out in this laboratory have implied an anxiety inducing role for ACTH which can be counteracted by chronic treatment with anxiety relieving drugs. Furthermore these experiments have suggested that this interaction involves serotonin containing neurones originating in the Dorsal Raphe Nucleus (Collins, File, Hyde & MacLeod, 1978; File & Vellucci, 1978). It seemed of value therefore to conduct electrophysiological and biochemical experiments in order to assess these interactions in a suitable system at the neuronal level.

Possible ACTH, benzodiazepine, and neurotran-

smmitter interactions were investigated *in vitro* using slices of several limbic areas from the rat brain employing conventional neurochemical techniques (Starr, James & Gayten, 1978). Flurazepam (FZ; 10^{-7} – 10^{-5} M) produced an increase in spontaneous but a decrease in potassium-evoked release of [3 H]-5HT from amygdaloid but not hippocampal slices. Although ACTH had no effect on 5HT release, the peptide (10^{-7} – 10^{-5} M) antagonized the modulating action of FZ. ACTH and FZ, in the doses used, had no effect on the release of radiolabelled GABA, noradrenaline or acetylcholine.

The spontaneous activity of neurons in the cortico-medial region of the amygdala in urethane anaesthetized rats was depressed by the iontophoretic application of γ -aminobutyric acid (GABA) and chlor-diazepoxide (CDP). Mixed effects were observed with 5-HT and ACTH but the majority of cells encountered were inhibited by both compounds (87 and 61% respectively). The inhibitions evoked by 5-HT were susceptible to antagonism by ACTH (15 out of 28 tests) and CDP (12 out of 15 tests). Surprisingly,

we could often antagonise GABA evoked inhibitions by the simultaneous application of ACTH (13 out of 21 tests). Conversely, CDP often potentiated GABA evoked inhibitions of the same neurone (5 out of 10 tests). Perhaps the most interesting observation is that we have been able to reproduce the neurochemical evidence of antagonism between CDP and ACTH. Thus we were able to reversibly block ACTH evoked inhibitions by the simultaneous application of CDP (4 out of 6 tests).

Using two different pharmacological techniques we have been able to corroborate the earlier behavioural data showing an antagonism between ACTH and benzodiazepines. Thus, if ACTH is an endogenous anxiogenic compound then a functional antagonism with benzodiazepines would provide one possible clue to the mode of action of anxiolytic agents.

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References

- COLLINS, G.G.S., FILE, S.E., HYDE, J.R.G. & MACLEOD, N.K. (1978). The effects of 5,7-dihydroxytryptamine lesions of the median and of the dorsal raphe nuclei on social interaction in the rat. *Br. J. Pharmac.* Communication this meeting.
- FILE, S.E. & VELLUCCI, S.V. (1978). Studies on the role of ACTH and of 5-HT in anxiety, using an animal model. *J. Pharm. Pharmac.*, **30**, 105–110.
- STARR, M.S., JAMES, T.A. & GAYTLEN, D. (1978). Behavioural depressant and antinociceptive properties of substance P in the mouse: possible implications of brain monoamines. *Eur. J. Pharmac.*, **48**, 203–212.

Inactivation of released norepinephrine in rat tail artery by neuronal uptake

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Neuronal uptake of endogenously released norepinephrine plays an important role in transmitter disposition in vascular smooth muscle. Recent evidence (Verbeuren, Janssens & Vanhoutte, 1978) suggests that this neuronal pump operates mainly between nerve impulses and is inactivated during depolarization of the nerve endings. This allows for optimal diffusion of transmitter. If this reasoning is correct, an inhibitor of neuronal reuptake, such as cocaine, should differentially alter the contractile response to low and high frequency stimulation. This hypothesis was tested in the present study by comparing the contractile responses of rat tail artery strips to electrical stimulation in the presence and absence of cocaine. Adult male albino rats were killed by a blow to the head and tail arteries were obtained. The artery was cut helically into strips; the strips were mounted in organ baths between two platinum wire electrodes; and isometric contractions were recorded. Cumulative addition of cocaine to the bath produced contraction of the strips. This contractile response was blocked by

phentolamine (10 μ M) and was dependent upon the concentration of cocaine (10^{-8} to 10^{-4} M). Acute denervation of the strips with 6-hydroxydopamine (10 min, pH 4.0) reduced the contractile effect of cocaine. Contractions in response to low frequency field stimulation (0.1 to 1.0 Hz) were significantly potentiated by cocaine (10^{-6} M). Those in response to high frequency stimulation (2 to 16 Hz) were not significantly altered by the presence of cocaine. Cocaine produced a marked slowing of relaxation in tail artery strips contracted by field stimulation (1 and 16 Hz). This effect was concentration dependent (10^{-8} to 10^{-4} M); the relative magnitude of the interval of time required to reach half maximal relaxation was not different for low or high frequency stimulation. These results indicate: (1) contraction in response to cocaine alone probably results from the inhibition of uptake of spontaneously released norepinephrine; (2) the amine uptake mechanism in rat tail artery is differentially affected at low and high frequency electrical stimulation suggesting that neuronal uptake is not operative during the nerve impulse; and (3) the neuronal uptake of transmitter following electrical stimulation is an important disposition mechanism in rat tail artery.

Reference

- VERBEUREN, T.J., JANSSENS, W.J. & VANHOUTTE, P.M. (1978). Effects of moderate acidosis on adrenergic neurotransmission in canine saphenous veins. *J. Pharmac. exp. Ther.*, **206**, 105–114.

Could harmaline generate tremor by affecting 5HT release?

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Whole body tremor can be generated by rhythmical and synchronous activity in the inferior olivary nucleus and such activity can be induced by harmaline, presumably by modification of electrotonic