Costa, 1975). The M.E.D. was calculated at the time of maximum activity.

The anticonvulsant dose (AC_{50}) of GABA-like agonist compounds was determined against 3-mercaptopropionic acid-induced seizures (50 mg/kg; i.p.) using groups of 6 female mice of the CBA strain (18–20 g). Mice were considered to be protected if no tonic seizure was seen within 10 min of injection of the convulsant agent.

Our results are summarised in Table 1 which also gives the routes of injection and pretreatment times for the standard drugs which we have examined. These data provide a useful profile of the *in vivo* activity of potential GABA-like drugs. Of considerable interest was the finding that muscimol, in contrast to the other putative GABA agonists and in common with GABA antagonists, potentiated harmaline tremor.

References

BIGGIO, G., BRODIE, B.B., COSTA, E. & GUIDOTTI, A. (1977). Mechanisms by which diazepam, muscimol and other drugs change the content of cGMP in cerebellar cortex. *Proc. Natl. Acad. Sci.*, **74**, 3592–6.

COSTA, E., GUIDOTTI, A. & MAO, C.C. (1975). Evidence for involvement of GABA in the action of benzodiazepines: studies on rat cerebellum. In *Advances in Biochem. Psychopharmac.*, **14**, Eds. Costa, E. and Greengard, P. pp. 113–130. New York: Raven Press.

DOGGETT, N.S. (1973). Possible involvement of a dopaminergic pathway in depressant effects of ouabain on the central nervous system. *Neuropharmac.*, **12**, 213–220.

HAEFELY, W., KULCSÁR, A., MÖHLER, H., PIERI, L., POLC, P. & SCHAFFNER, R. (1975). Possible involvement of GABA in the central actions of benzodiazepines. In *Advances in Biochem. Psychopharmac.*, **14**, Eds. Costa, E. and Greengard, P. pp. 131–151. New York: Raven Press.

MAO, C.C., GUIDOTTI, A. & COSTA, E. (1975). Inhibition by diazepam of the tremor and the increase of cerebellar cGMP content elicited by harmaline. *Brain Res.*, **83**, 516–9.

ZETLER, G. (1968). Cataleptic state and hypothermia in mice, caused by central cholinergic stimulation and antagonised by anticholinergic and antidepressant drugs. *Int. J. Neuropharmac.*, **7**, 325–335

The effect of neurotoxic lesions on neuronal systems in rat striatum

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Neurotoxic lesions have been extensively used to study the localization of neuronal systems in the rat striatum as well as providing animal models of Parkinsonism and Huntington's chorea (DuVoisin, 1976; Coyle & Schwarcz, 1977).

In the present study, 6-hydroxydopamine (6-OHDA) lesions of rat striatal dopaminergic afferents and kainic acid (KA) lesions of striatal cell bodies have been used to study the location of dopamine (DA), acetylcholine (ACh), α-aminobutyric acid (GABA) and glutamate containing neurones in rat striatum.

Male Sprague-Dawley rats (150-200 g) were injected unilaterally with either KA (2.5 μg/1 μl saline) into the striatum (Waddington & Cross, 1978) or with 6-OHDA (8 μg/4 μl saline ascorbate) into the lateral hypothalamus (Waddington & Crow, 1978). At 3 or 7 weeks after the lesion rats were decapitated and striata dissected out. Lesioned and unlesioned striata were compared for (a) the activities of the neurotransmitter synthesizing enzymes, choline acetyltransferase (CAT), tyrosine hydroxylase (TOH), glutamate decarboxylase (GAD) in striatal homogenates and (b) assessment of neurotransmitter receptors by specific binding of tritiated quinuclidinyl benzylate ([^{3}H]-QNB), [^{3}H]-KA and [^{3}H]-GABA to striatal membrane preparations. Results expressed as percentage changes were all statistically significant.

The effectiveness of 6-OHDA lesions was confirmed by a 90% reduction in TOH activity in lesioned striata. GAD activity was increased by 25% with no change in CAT activity. Specific [^{3}H]-GABA and [^{3}H]-QNB binding were reduced by 18% and 15% respectively with no change in [^{3}H]-KA binding. It has previously been demonstrated that specific binding of [^{3}H]-spiperone to the dopamine receptor is elevated by 44% in rat striatum after 6-OHDA lesions (Cross, Longden, Owen, Poulter & Waddington, 1978).

The effective destruction of striatal cell bodies by KA was confirmed by reductions of 52% and 30% in GAD and CAT activities, respectively. This lesion resulted in a 23% increase in TOH in lesioned striata. Specific [^{3}H]-QNB and [^{3}H]-KA were reduced by 61% and 40% respectively whereas [^{3}H]-GABA binding was increased by 78%. Analysis of saturation data indicated that the increase in [^{3}H]-GABA binding was characterized by a decrease in the dissociation constant for high affinity [^{3}H]-GABA binding with no change in receptor numbers. This contrasts with the effects of striatal KA lesions on nigral [^{3}H]-GABA binding where increased binding (Cross & Waddington, 1978) is characterised by an 81% increase in high affinity receptor numbers with no change in dissociation constant. In both studies the characteristics of low affinity GABA binding were unchanged.

These results suggest that (i) a proportion of [^{3}H]-GABA binding sites may be located on non-dopaminergic striatal afferents and (ii) [^{3}H]-KA

binding sites may be located on striatal perikarya.

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References

COYLE, J.T. & SCHWARCZ, R. (1977). Lesion of striatal neurons with kainic acid provides a model for Huntington's chorea. *Nature Lond.*, **263**, 244–246.

CROSS, A.J. & WADDINGTON, J.L. (1978). Evidence suggesting denervation supersensitivity of nigral GABA receptors following destruction of the striatonigral GABA pathway. *J. Physiol. Lond.*, (in press).

CROSS, A.J., LONGDEN, A., OWEN, F., POULTER, M. & WADDINGTON, J.L. (1978). Inter-relationships between behavioural and neurochemical indices of supersensitivity in dopaminergic neurons. *Br. J. Pharmac.*, **63**, 383P.

DUVOISIN, R.C. (1976). Parkinsonism: animal analogues of the human disorder. In *The Basal Ganglia*, ed. Yahr, M.D., pp. 293–303, New York: Raven Press.

WADDINGTON, J.L. & CROSS, A.J. (1978). Neurochemical changes following kainic acid lesions of the nucleus accumbens. *Life Sci.*, **22**, 1011–1014.

WADDINGTON, J.L. & CROW, T.J. (1978). Methodological problems in the measurement of drug-induced rotational behaviour. *Psychopharmac.*, **58**, 153–155.

Excitation of CA1 neurones of the rat hippocampus by the octacosapeptide, vasoactive intestinal polypeptide (VIP)

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Recently a number of authors have drawn attention to a number of peptides which not only have a hormonal role in the intestine but may have a neurotransmitter role at that site and in the brain (Bryant, Polak, Modlin, Bloom, Albuquerque & Pearse, 1976). Earlier in keeping with this hypothesis we were able to show that somatostatin applied to the cell bodies of CA1 and CA2 region of the rat hippocampus *in vitro* resulted in a strong excitation which was fast in onset and thus resembled that evoked by glutamate (Dodd & Kelly, 1978). Using the same preparation we now report that vasoactive intestinal polypeptide (VIP) also excites these neurones when applied in their vicinity by pressure injection from a small tipped micropipette. As shown in Figure 1 the excitation was accompanied by a large and abrupt depolarization. The depolarization was of sufficient intensity to cause inactivation of the spike generating mechanism. The associated fall in membrane resistance was large enough to completely suppress the smaller of the hyperpolarizing pulses used to test the membrane resistance and completely unbalanced the larger pulses.

These results confirm the earlier work of (Phillis, Kirkpatrick & Said, 1978) who showed iontophoretic applied VIP to excite spontaneously active cerebral neurones in rats and depolarize motoneurones in the toad spinal cord.

References

BRYANT, M.G., POLAK, J.M., MODLIN, I., BLOOM, S.R., ALBUQUERQUE, R.H., & PEARSE, A.G.E. (1976). Possible dual role for vasoactive intestinal peptide as gastro-intestinal hormone and neurotransmitter substance. *Lancet*, **i**, 991–993.

DODD, J. & KELLY, J.S. (1978). Is somatostatin an excitatory transmitter in the hippocampus? *Nature Lond.*, **273**, 674–675.

PHILLIS, J.W., KIRKPATRICK, J.R. & SAID, S.I. (1978). Vasoactive intestinal polypeptide excitation of central neurons. *Can. J. Physiol. Pharmac*, **56**, 337–340.

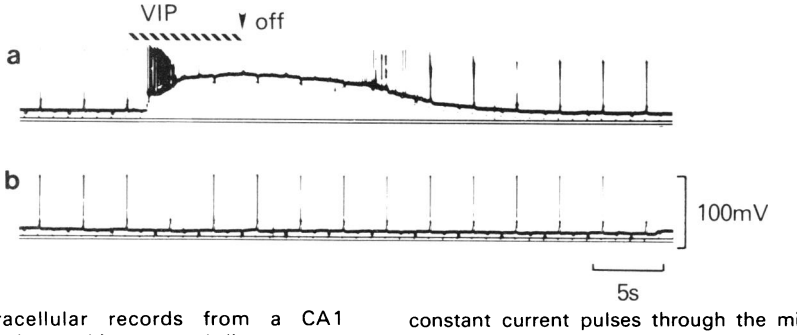

Figure 1 Intracellular records from a CA1 pyramidal neurone in a rat hippocampal slice preparation to show the depolarizing action of VIP. VIP was pressure injected into the vicinity of the dendrites with a pressure of 20 lbs/sq in from a fine micropipette with a tip diameter of 2 μm, containing a 0.3 mM solution of VIP dissolved in 100 mM sodium acetate. By repeatedly passing the same series of constant current pulses through the microelectrode into the cell, the excitability was tested by a depolarizing ramp every 3 s and the membrane resistance by means of both a large and a small hyperpolarizing square wave. Note the decrease in membrane resistance indicated by changes in the size and polarity of all three pulses during the depolarizing action of VIP.