depend as much on dopamine (DA) as 5-HT stimulation in the CNS. Thus a closely related syndrome is induced when L-DOPA is substituted for L-tryptophan and 5-HT and DA antagonists may have similar effects on both syndromes (Jacobs, 1974; Deakin & Green, 1978). Costain & Green (1978), however, found no effect of propranolol on the L-DOPA syndrome.

We have considered the possibility that high precursor doses used in previous hyperactivity studies may preclude a high sensitivity to antagonist drugs quality of effect as well as the sensitivity to antagonist drugs in these syndromes. A central role for propranolol in inhibiting behavioural syndromes which may be 5-HT mediated is confirmed and extended.

References

COSTAIN, D.W. & GREEN, A.R. (1978). β-adrenoceptor antagonists inhibit the behavioural responses of rats to increased brain 5-hydroxytryptamine. *Br. J. Pharmac.*, **64**, 193–200.

DEAKIN, J.F.W. & GREEN, A.R. (1978). The effects of putative 5-hydroxytryptamine antagonists on the behaviour produced by administration of tranylcypromine a l-tryptophan or tranylcypromine and L-DOPA to rats. *Br. J. Pharmac.*, **64**, 201–209.

GREEN, A.R. & G GRAHAME-SMITH, D.G. (1976). (−)-Propranolol inhibits the behavioural responses of rats to increased 5-hydroxytryptamine in the central nervous system. *Nature, Lond.*, **262**, 594–596.

JACOBS, B.L. (1974). Evidence for the functional interaction of two central neurotransmitters. *Psychopharmacologia (Berl).*, **39**, 81–86.

MIDDLEMISS, D.N., BLAKEBOROUGH, L. & LEATHER, S.R. (1977). Direct evidence for an interaction of β-adrenergic blockers with the 5-HT receptor. *Nature, Lond.*, **267**, 289–290.

SCHECHTER, Y. & WEINSTOCK, M. (1974). β-adrenoceptor blocking agents and response to adrenaline and 5-hydroxytryptamine in rat isolated stomach and uterus. *Br. J. Pharmac.*, **52**, 283–287.

WEINSTOCK, M., WEISS, C. & GITTER, S. (1977). Blockade of 5-hydroxy-tryptamine receptors in the central nervous system by β-adrenoceptor antagonists. *Neuropharmac.*, **16**, 273–276.

Intravenous bicuculline in mice facilitates *in vivo* evaluation of drugs affecting GABA like mechanisms

W.R. BUCKETT

Centre de Recherche Merrell International, 16, rue d'Ankara 67084-Strasbourg Cedex, France

It has been established, both by receptor binding (Möhler & Okada, 1977) and neuropharmacologically (Curtis, *et al.*, 1971) that bicuculline antagonizes the action of GABA by competition for postsynaptic action γ-aminobutyric acid (GABA) by competition for postsynaptic receptors. Bicuculline in nonlethal doses in mice produces pronounced myoclonic seizures, a well-defined behavioural end-point, but one which has not been reported in the literature in a systematic way.

This study was designed to examine compounds having diverse modes of action on the GABA system. Groups of ten female CD_1 mice (body wt. 20–25 g) were premedicated with putative GABA-like compounds intravenously at 2 min or intraperitoneally at 30 min or 5 h, prior to intravenous bicuculline (0.55 mg/kg; pH 6.0; 0.2 ml/20 g body weight). The ensuing behavioural syndrome was evaluated for presence or absence of myoclonic seizures, tonic convulsions and mortality, as well as for the time of onset and the duration of seizure activity. The syndrome occurred in 90 ± 4 (±s.e. mean) % of control mice (n = 10 groups) with an onset of 6.5 ± 0.4 s and a duration of 8.2 ± 0.6 seconds. Mortality invariably followed tonic convulsions, but only occurred in 6 ± 3% of control mice. The antagonism of myoclonic seizures by compounds was assessed quantally to determine ED_{50} values.

The results in Table 1 show that at appropriate premedication times GABA transaminase inhibitors, except gabaculine at the doses tested, GABA agonists and the neuronal uptake inhibitors diaminobutyric acid and chlorpromazine, were all active in antagonizing bicuculline-induced myoclonic seizures. In those animals in which seizures were not completely blocked, the time to onset was lengthened and the duration of the behaviour was shortened. Since the benzodiazepines only have low potency in inhibiting bicuculline binding, the high activity of diazepam is interesting. In addition the potency of γ-vinyl GABA was higher than would be expected from a consideration of whole brain GABA levels (Jung *et al.*, 1977) suggesting that regional or subcellular distribution of the generated GABA may play a crucial role. It is concluded that this test allows ready detection of drugs having GABA-like effects *in vivo*.

Muscimol and THIP were a generous gift of Dr Povl Krogsgaard-Larsen, Copenhagen.

Table 1 ED_{50} values of standard GABA-like compounds for antagonism of myoclonic seizures induced by (+)-bicuculline (0.55 mg/kg intravenously) in female CF_1 mice (20–25 g)

Compound	*Route of administration*	*Premedication time*	*ED_{50} mg/kg*	*95% Limits*
γ-Vinyl GABA	i.p.	5 h	54	(47–63)
γ-Vinyl GABA	i.v.	2 min	Not active up to 200 mg/kg	
γ-Acetylenic GABA	i.p.	5 h	26	(17–36)
γ-Acetylenic GABA	i.v.	2 min	Not active up to 200 mg/kg	
Gabaculine HCl	i.p.	5 h	Not active up to 25 mg/kg	
Isogabaculine trifluoro-methane-sulphonate	i.p.	5 h	17	(14–22)
Aminooxyacetic acid	i.p.	5 h	19	(15–23)
Sodium valproate	i.p.	30 min	120	(110–130)
Muscimol HBr	i.v.	2 min	1.8	(0.62–3.4)
THIP	i.v.	2 min	2.3	(2.2–2.4)
Diazepam	i.v.	2 min	0.038	(0.029–0.049)
Baclofen	i.v.	2 min	Not active up to 10 mg/kg	
Diaminobutyric acid	i.p.	6 h	320	(260–370)
Chlorpromazine	i.p.	30 min	0.51	(0.45–0.58)
β-Alanine	i.p.	3 h	Not active up to 500 mg/kg	

References

CURTIS, D.R., DUGGAN, A.W., FELIX, D., & JOHNSTON, G.A.R. (1971). Bicuculline, an antagonist of GABA and synaptic inhibition in the spinal cord. *Brain Res.*, **32**, 69–96.

MÖHLER, H. & OKADA, T. (1977). GABA receptor binding with [H^3](+) bicuculline-methiodide in rat CNS. *Nature, Lond.*, **267**, 65–67.

JUNG, M.J., LIPPERT, B., METCALF, B.W., BÖHLEN, P. & SCHECHTER, P.J. (1977). γ-Vinyl GABA (4-amino-hex-5-enoic acid), a new selective irreversible inhibitior of GABA-T: effects on brain GABA metabolism in mice. *J. Neurochem.*, **29**, 797–802.

The isolated anococcygeus muscle of the mouse

A. GIBSON & C.V. WEDMORE

Department of Pharmacology, Chelsea College, Manresa Road, London, SW3 6LX

The responses of the anococcygeus muscles of rat, cat, rabbit, and dog to drugs and nerve stimulation have already been described (Gillespie, 1972; Gillespie & McGrath, 1974; Creed, Gillespie & McCaffery, 1977; Dehpour, Khoyi, Koutcheki & Zarrindast, 1978), and marked species variations have been observed. In the present study we report initial observations on the pharmacology of the isolated anococcygeus muscle of the mouse.

Male mice (LACA; 25–35 g) were killed by stunning and exsanguination, and the anococcygeus muscles dissected as described by Gillespie (1972). The muscles were set up in series, joined at the ventral bar, in Krebs'-bicarbonate solution (37°C). A resting tension of 100 mg was placed on the tissue and changes in tension recorded isometrically. Field stimulation was applied by ring electrodes attached to a square wave pulse generator (1 ms supramaximal voltage).

The resting muscle had neither tone nor spontaneous activity and responded with slow, maintained contractions (peak rise within 3 min) to noradrenaline ($pD_2 = 6.01 \pm 0.25$; max. 564 ± 53 mg; $n = 15$) and to carbachol ($pD_2 = 5.93 \pm 0.17$; max. 417 ± 38 mg; $n = 15$). The contractions were inhibited by phentolamine ($pA_2 = 6.9$) and atropine ($pA_2 = 9.5$) respectively. Cocaine (1 μM) produced a selective leftward shift of the dose-response curve to noradrenaline ($pD_2 = 7.26 \pm 0.16$; $n = 6$). High concentrations of isoprenaline (>10 μM) produced contractions which were unaffected by propranolol but were completely blocked by phentolamine (300 nM). 5-Hydroxytryptamine (1 μM) contracted the tissue, the response being blocked by methysergide (1 μM). Histamine (1 mM)