direct methods have been employed for causing its elevation in the brain. Notable among these methods is the use of aminooxyacetic acid, AOAA, a potent GABA-transaminase enzyme inhibitor but this compound possesses convulsant properties at high doses (Wallach, 1961; Osuide, 1972). In this experiment, we have therefore investigated an analogue of AOAA namely ethyl-*N*-phthalimidoxy acetate (ENPA) for anticonvulsant properties among other studies.

Experiments were performed on young male Warren chicks weighing 35–50 g and adult male albino rats weighing between 150–230 g. Maximal electroshock was delivered, via steel electrodes, using the Ugo Basile ECT unit model 7801. Chemical convulsions were induced with strychnine, and leptazol, injected intraperitoneally. Results from electroshock experiments were compared with phenytoin while troxidone was used as our standard drug for comparing results from strychnine- and leptazol-induced seizure experiments.

ENPA (100 mg/kg) offered a complete protection against ECT in chicks when administered i.p. 5–6 h before electroshock. It thus proved more potent than phenytoin which was able to offer approximately 60% protection under similar conditions. It was equipotent with troxidone in offering total protection against doses of strychnine and leptazol which produced 60% convulsions and 10–20% lethality in chicks. ENPA was inferior to AOAA in its anticonvulsant effects but was completely devoid of convulsant properties even at doses many times higher than convulsant doses of AOAA. It is thought that the blocking of the amino group in such a way as to make hydrolysis, *in vivo*, difficult was to a large extent accountable for the elimination of convulsant actions of AOAA. Measurement of brain GABA levels following ENPA administration showed that GABA levels were greatly elevated during the period of peak anticonvulsant activity. This probably contributed immensely to the observed anticonvulsant property.

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Biphasic effect of direct GABA mimetic drugs on haloperidol-induced catalepsy

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γ-Aminobutyric acid (GABA) is involved in the regulation of dopaminergic neuron activity within the forebrain. This includes direct inhibitory and indirect excitatory effects of GABA on the nigrostriatal DAergic pathway and also regulation of DA transmission by striatal GABA interneurons (Bartholini & Stadler, 1977; Lloyd, 1978). We have recently reported that GABA-mimetic drugs potentiate neuroleptic-induced catalepsy (Worms, Willigens & Lloyd, 1978). Such an effect was interpreted as evidence for the inhibitory action of GABA on nigro-striatal DA neurons. However, low doses of GABA antagonists potentiated and high doses antagonized haloperidol-catalepsy supporting the interaction of two GABA receptors with the DA neurons.

In the study reported here, male Sprague Dawley rats (CD COBS, Charles River, France) weighing 200 to 250 g were used. Catalepsy measurements (4-cork test) were performed as described previously (Worms *et al.*, 1978). Drugs were injected i.p. simultaneously with- (SL 76 002, muscimol) or 2 h prior to- (AOAA, γ-acetylenic GABA: GAG) halopéridol (0.6 mg/kg i.p.).

Muscimol and SL 76002 ([α-(chloro-4'-phenyl) fluoro-5-hydroxy-2-benzylidene amino]-4-butyramide) caused a biphasic effect, first decreasing at low doses and then potentiating at higher doses the haloperidol-mediated catalepsy (Muscimol: 42% and 137% of haloperidol treated animals at 0.25 and 2 mg/kg, respectively; SL 76002; 50% and 138% of haloperidol treated animals at 12.5 and 100 mg/kg, respectively. $P < 0.01$ vs haloperidol alone in all cases). In contrast, administration

of AOAA or GAG resulted only in a potentiation of haloperidol catalepsy (AOAA: 0.3 to 12.5 mg/kg: 98% to 150%* of haloperidol treated rat; GAG: 1.0 to 50 mg/kg: 94% to 138%* of haloperidol treated animals (*$P < 0.05$ versus haloperidol alone). These data indicate that the direct GABA mimetic drugs SL 76002 (DiChiara, Porceddu, Morelli, Mulas & Gessa, 1979; Lloyd, Worms, Depoortere & Bartholini, 1979) and muscimol exert a biphasic action on neuroleptic-induced catalepsy, with an inverse dose-response curve as compared with the direct GABA antagonists, bicuculline and picrotoxinin (Worms *et al*, 1978). At least three mechanisms may play a role in these interactions: low doses of directly acting GABA drugs (i) may selectively affect GABA 'autoreceptors' within the substantia nigra (Mitchell & Martin, 1978) thus decreasing GABA release and increasing DA neuron activity, (ii) may exert a preferential inhibitory effect on a nigral non-dopaminergic out-put pathway which may be an inhibitor for DA-mediated events (DiChiara *et al*, 1979), and/or (iii) may act selectively at the level of striatal GABAergic interneurons thus inhibiting cholinergic neurons.

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Leptazol antagonises the post-synaptic actions of γ-aminobutyric acid

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Neurones in the olfactory cortex show sensitivity towards γ-aminobutyric acid (GABA) and GABA might mediate post-synaptic inhibition on to these neurones (Brown & Scholfield, 1979). This report demonstrates that leptazol can antagonise post-synaptic GABA action in a similar manner to the antagonism of the presynaptic actions which occur in the cuneate nucleus (Simmonds, 1978).

Neurones in the guinea-pig olfactory cortex *in vivo* slice preparation were impaled with single barrelled microelectrodes (Scholfield, 1978*a*). Such slices were maintained in Krebs solution at 25°C and various concentrations of GABA added to the perfusate for 1–3 min alone and in the presence of leptazol. GABA action was measured from the voltage deflections produced by constant current pulses injected into the neurones and calculated as the change in input conductance of that neurone.

GABA alone increased the membrane conductance by up to 20-fold or more at bath concentrations of 0.01–0.5 mM. The maximum GABA conductance was beyond the resolution of the measurement. GABA sensitivity was reduced with leptazol and the amount of GABA antagonism was dependent on the leptazol concentration 0.1–30 mM (6 slices). Thus in leptazol (1 mM) the GABA dose-conductance curve was shifted by 2.00 ± 0.18 to the right and by 5.4 ± 0.04 in leptazol (10 mM, mean ± s.e. mean).

When the lateral ofactory tract is stimulated an inhibitory post-synaptic conductance (i.p.s.c.) is generated (Scholfield, 1978b). During this inhibitory phase the conductance is normally immeasurably high. In the presence of leptazol (10 mM) the conductance at the same latency was reduced to a value between 2-fold and 20-fold of the resting (unstimulated) conductance. Leptazol (0.1–30 mM) increased the duration of the excitatory post-synaptic potential resulting in the generation of a train of action potentials (a seizure-like discharge) compared to the single action potential normal solution.

These experiments show that leptazol antagonises GABA action post-synaptically and probably blocks GABA mediated inhibition in the same way. This consequently releases excitatory activity normally shunted out by the i.p.s.c. and together with the antagonism of the presynaptic actions of GABA contributes to the convulsant action of leptazol.