cleft or in the striatal neuropil for interaction with dopamine receptor sites. Consequently, they produce a similar response in the rotating animal model. The striatum on the side of the lesion is depleted of dopamine so that the major effect of an uptake inhibitor or of a releasing agent occurs on the intact side. Accordingly, the animal in either case rotates away from the side of greater striatal dopamine activity and towards the lesioned side.

Although the rotating animal model cannot distinguish between these two classes of indirect dopamine agonists, it nevertheless adds a dimension to the study of the 'remote' analogues of amphetamine. The efficacy of the three drugs failed to correlate with their observed potency in inhibiting dopamine uptake *in vitro*. Mazindol is a more potent dopamine uptake inhibitor than nomifensine or dita, the latter two being approximately equivalent. Heikkila & others (1977) found ED50 values (point of 50% inhibition of uptake), for the three drugs of 2·8, 8·5 and 7·8 $\times 10^{-7}$ M respectively. Mazindol was indeed more potent in the rotating rat than dita but nomifensine proved equivalent to mazindol. Possibly the divergent results reflect differences in drug metabolism. For example, several active metabolites of nomifensine are formed *in vivo* (Kruse & others, 1977), one of which is equipotent with nomifensine itself in inhibiting dopamine uptake.

The dopamine uptake inhibitors we have studied also inhibit the uptake of noradrenaline and 5-hydroxytryptamine. Thus the possibility that these monoamines may modulate the circling response in animals with lesions of the dopamine nigrostriatal system cannot be excluded. However, the fact that dopamine uptake inhibitors cause circling in these animals whereas desipramine and amitriptyline, potent inhibitors of noradrenaline and 5-HT uptake, do not (Christie & Crow, 1973; Pycock & others, 1976) is consistent with the growing body of evidence relating rotational behaviour in this animal model primarily to dopamine neural systems.

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GABA involvement in neuroleptic-induced catalepsy

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Neurophysiological (cf. Stevens, Wilson & Foote, 1974; Dray & Straughan, 1976) and biochemical (Kim, Bak & others, 1971; Bartholini & Stadler, 1977; Cheramy, Nieoullon & Glowinski, 1977; Lloyd, Shemen & Hornykiewicz, 1977) evidence indicates that a GABA-mediated mechanism is involved in the regulation of the dopaminergic nigrostriatal tract. Results of behavioural experiments also suggest this regulation, but the data are more difficult to interpret (Stevens & others, 1974; Dray, Fowler & others, 1977; Olpe, Schellenberg & Koella, 1977, Scheel-Kruger, Arnt & Magelund, 1977). However, amongst other parameters, neuroleptic-induced catalepsy has been studied. Thus, benzodiazepines (which have been suggested to act via a GABA-ergic mechanism) as well as aminooxyacetic acid (AOAA), a GABA-transaminase inhibitor, potentiate neuroleptic-induced catalepsy. Furthermore, *p*-chloro-β-phenyl-GABA, which is a structural analogue of GABA (although its mechanism of action is at present unclear), also potentiates this syndrome (Kääriäinen, 1976; Keller, Schafner & Haefely, 1976). The experiments reported here were to study the effects of direct and indirect GABA agonists or antagonists on the catalepsy induced by various neuroleptics.

Male Sprague-Dawley CD COBS rats (180–220 g; Charles River, France) were used. Catalepsy measurements (four-cork test, Worms & Lloyd, 1978) were performed in a quiet laboratory, with the temperature maintained constant at 20° ± 1°. In each experiment 6 rats were used per dose. Dose schedules used were:

* Correspondence.

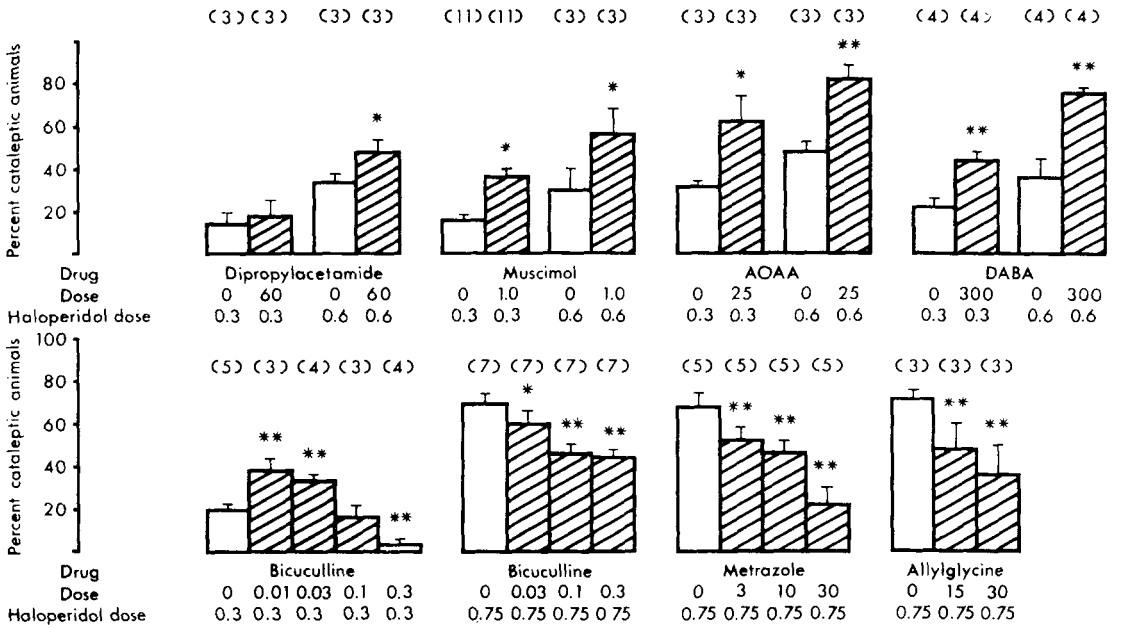

FIG. 1. Effects of GABA agonists and antagonists on haloperidol-induced catalepsy. Catalepsy is measured every 30 min, for 2 h after haloperidol injection, and noted as (+) or (−). Data are presented as mean percentages of cataleptic animals (±s.e.m.). All doses are expressed as mg kg^{-1}, intraperitoneally. Number of experiments within parentheses. * $P < 0.05$. ** $P < 0.01$ *vs* haloperidol controls (Non parametric analysis of variance: Kruskall-Wallis test). Ordinate: % cataleptic animals. Hal: haloperidol.

muscimol and dipropylacetamide simultaneously with the neuroleptic (haloperidol, chlorpromazine or thioridazine); bicuculline, picrotoxinin, metrazole (leptazol) or allylglycine, 30 min after the neuroleptic; diaminobutyric acid (DABA) 2 h before the neuroleptic; AOAA, 2 and 4 h before the neuroleptic.

Muscimol (0·1), dipropylacetamide (60), AOAA (25) and DABA (300 mg kg^{-1}) all markedly potentiated the catalepsy induced by haloperidol (0·3 or 0·6 mg kg^{-1}) in rats (Fig. 1). Furthermore, AOAA (25 mg kg^{-1}) and muscimol (1 mg kg^{-1}) potentiated the catalepsy induced by chlorpromazine (6·0 or 9·0 mg kg^{-1}) or thioridazine (10 or 30 mg kg^{-1}) (Fig. 2). By themselves, at these doses, muscimol, AOAA or DABA did not elicit any catalepsy.

In contrast to these results, in sub-convulsant doses, bicuculline, metrazole and allylglycine significantly decreased in a dose-dependent manner the catalepsy induced by haloperidol (0·75 mg kg^{-1}, i.p.) (Fig. 1). However, when a lower dose of haloperidol (0·3 mg kg^{-1}, i.p.) was used, which induced catalepsy only in a few animals (less than 20%), bicuculline (Fig. 1) or picrotoxinin (results not shown) exhibited a biphasic effect: thus, these compounds at low doses significantly increased and at higher doses decreased the neuroleptic-induced catalepsy.

Of the compounds used, muscimol (Johnston, 1976) is considered to be direct acting agonist of GABA; DABA (Schon & Kelly, 1974) is an inhibitor of GABA uptake whereas AOAA (at the doses used) is an inhibitor of GABA transaminase (Wu, 1976). Dipropylacetamide is a derivative of sodium dipropylacetate (valproate) which inhibits the metabolism of GABA; however the enzymatic step involved is still open to debate (for review, see Pinder, Brogden & others, 1977). Thus, both direct and indirect GABA mimetic compounds potentiated the catalepsy induced by neuroleptics in agreement with similar observations for AOAA (Kääriäinen, 1976; Keller & others, 1976). These data indicate that increased GABA-receptor activity results in a behavioural action similar to that observed by either augmenting dopamine receptor blockade (e.g. by increasing the dose of neuroleptic) or by diminishing the amount of dopamine available at the synaptic level (by γ-hydroxybutyrate or α-methyl-*p*-tyrosine). It is likely that in the present situation increasing GABA receptor activity decreases the firing rate of dopaminergic neurons and thus the release of dopamine into the synaptic cleft. This effect may be exerted at the level of the substantia nigra as both neurophysiological (cf. Dray & Straughan, 1976) and biochemical evidence (Lloyd & others, 1977) indicate the presence of a GABA receptor on cell bodies, or their dendrites. Striatal GABA neurons may also play a role in the release of dopamine from its terminals (Bartholini & Stadler, 1977).

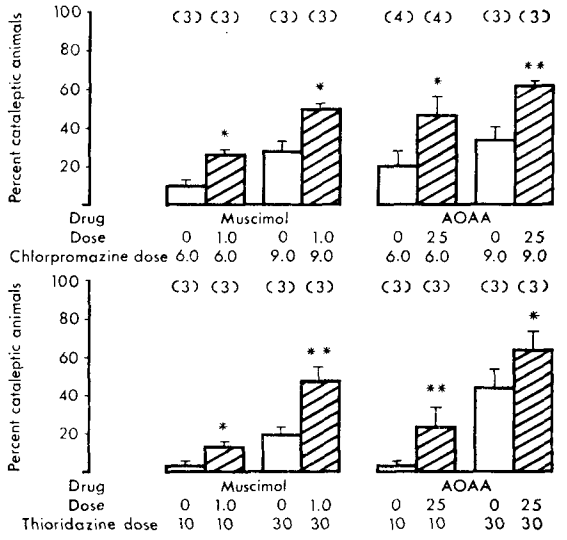

FIG. 2. Effects of muscimol and AOAA on chlorpromazine and thioridazine-induced catalepsy. For methodology, see Fig. 1. * $P < 0.05$. ** $P < 0.01$ *vs* neuroleptic controls (non parametric analysis of variance: Kruskall-Wallis test). Ordinate: % cataleptic animals.

The inhibitory GABA action on dopamine neurons is supported also by the findings that GABA antagonists such as bicuculline or picrotoxinin (cf. Johnston, 1976) and inhibitors of GABA synthesis such as allylglycine (Orlowski, Reingold & Stanley, 1977) at non-convulsant doses antagonized the catalepsy induced by haloperidol (0·75 mg kg^{-1}, i.p.) (Fig. 1). Moreover, strychnine, a preferential glycine antagonist (cf. Johnston, 1976) was completely inactive (catalepsy = 99–106% of controls at doses of 0·01–0·3 mg kg^{-1}, i.p., mean of 3 experiments) towards haloperidol (0·75 mg kg^{-1}, i.p.) catalepsy.

The reason why bicuculline and picrotoxinin exert a biphasic action on the catalepsy induced by lower doses of haloperidol is not clear. It may depend on possible partial agonist properties of these compounds, or, that at low doses these compounds preferentially block a presynaptic GABA receptor, thus enhancing GABA neuron activity. The latter possibility receives some support from the experiments of Johnston & Mitchell (1971) in which bicuculline (but not picrotoxin) was found to release GABA from brain slices. A more likely situation is the existence of opposite effects of different GABA-mediated synapses on dopamine neuron activity. This latter possibility is supported by the observations that intrastriatally applied GABA diminishes whereas picrotoxin enhances striatal dopamine release (Bartholini & Stadler, 1977; Cheramy & others, 1977); in contrast, intranigrally applied GABA has apparently opposite effects (as interpreted from behavioural experiments) on dopaminergic neurons (Scheel-Kruger & others, 1977).

In conclusion, the present results support the view that GABA neurons participate in the feed-back regulation of dopamine neurons following dopamine receptor blockade.

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