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The Potential Use of GABA Agonists in Psychiatric Disorders: Evidence from Studies with Progabide in Animal Models and Clinical Trials[1]

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Animal model Progabide GABA agonists

THE central inhibitory neurotransmitter gamma-aminobutyric acid (GABA) has been found in all areas of human brain examined including different regions of the cortex, limbic system, extrapyramidal system, mid- and hindbrain and spinal cord [55]. A role for GABA neurons in the etiology of neurological disorders is well established, disease states such as epilepsy [44], Parkinson's disease [41] and Huntington's disease [22,38] all having a dysfunction of GABA neurons as shown by post-mortem studies. Furthermore, increasing GABAergic transmission is of therapeutic benefit in epilepsy [38] and dopamine receptor related dyskinesia [2,11].

Thus, the importance of intact GABAergic function is well established for the etiology as well as therapy of certain neurological disorders. However, GABA-mediated functions have not received as much attention in research on psychiatric diseases. A major reason has been the lack of suitable compounds for clinical trials. This situation has recently improved and there are now sufficient data from animal models and clinical trials to assess the potential use of at least one GABA agonist drug (progabide, [31, 41, 82]). THIP (tetrahydroisoxalopyridine-ol [32]) another GABA agonist with clinical potential, is discussed in an accompanying article [13].

Progabide is a GABA agonist (i.e., acting directly at the GABA recognition site) which is metabolized "in vivo" to another GABA agonist, SL 75102, and eventually to GABA itself [82]. The formation of measurable amounts of GABA after progabide administration takes several hours [41]. The evidence that progabide is a GABA agonist resides in its ability to displace ^{3}H-ligands (^{3}H-GABA, ^{3}H-muscimol, ^{3}H-isoguvacine) from the specific GABA recognition site from either rat or human brain membranes [41]. The relative potency of progabide in the binding model is 1/64–1/1000 that of GABA for rat brain membranes and 1/150–1/200 for human cerebellar membranes (ratio of IC 50's, [41]).

SL 75102 (an active metabolite of progabide) has a higher affinity for the GABA receptor than progabide as indicated from binding studies (1/3–1/100 that of GABA [41]). Furthermore, as SL 75102 is water soluble (in contrast to

[1]Portions of these data were presented at the III World Congress of Biological Psychiatry, Stockholm, 1981.

progabide) it has also been assessed neurophysiologically. In the rat dorsal root ganglion, SL 75102 fulfills the criteria for a GABA agonist, showing the same decay time as GABA, a cross desensitization to GABA, a bicuculline- and picrotoxinin-sensitivity and the same reversal potential as GABA [19]. The present article reviews the data on progabide with regard to animal models and clinical trials in psychiatric disorders.

ANXIETY AND ANXIOLYTICS

There are not any findings to date which clearly indicate which neurotransmitters are of consequence for the etiology of anxiety. To the authors' knowledge, only two studies have tried to correlate GABA levels in the CSF with symptoms of anxiety in the same patients. One study reported a significant negative correlation [7] whereas the other study [60] was unable to find a correlation between the two parameters. Thus at the present time it cannot be said that there is any evidence that GABA neurons are dysfunctional in situation leading to anxiety or dominated by anxious state. However, in some animal models, disrupting GABA neuron function has an anxiogenic action [8,72] and GABA turnover is reported to be decreased in limbic areas of brains of rats trained for a conditional emotional response [34].

In contrast to this lack of knowledge in the neurochemistry of anxiety, there is evidence that GABA neurons play an important role in the mechanism of action of anxiolytic drugs [8, 14, 61], and there are data to suggest that some GABA agonists are potential anxiolytics [14,68]. GABA itself has an "anxiolytic" action when injected into either the periaqueductal grey region or dorsal raphe of the rat [8,75].

The present concepts of the mechanism of action of benzodiazepines involve an obligatory role of GABA in the GABA-benzodiazepine macromolecular complex. Thus, the interaction of a benzodiazepine at its recognition site serves to increase the affinity of GABA receptors and the efficacy of GABAergic transmission [14,15]. If this hypothesis is correct, then it should follow that (1) the action of benzodiazepines will be blocked by GABA antagonists, and (2) GABA agonists should show an anxiolytic potential in the appropriate animal models.

Animal Models

To answer these questions, an aversive state was induced in the albino rat by electrical stimulation of the periaqueductal grey matter [77]. Diazepam was used as a typical benzodiazepine and progabide was studied as the GABA agonist RO15-1788 was used as a specific antagonist of benzodiazepine receptors [29].

As can be seen from Table 1, progabide has an effect qualitatively similar to diazepam in the aversive stimulation test, both compounds producing well defined dose-response curves. Furthermore, the actions of diazepam and progabide appear to be synergistic as the combination of an inactive dose of each compound results in a potent antiaversive effect. From Table 1 it is clear that the GABA receptor antagonist bicuculline markedly reduces the antiaversive action of both progabide and diazepam. In contrast, blockade of benzodiazepine recognition sites by RO 15-1788 completely blocks the action of diazepam without altering that of progabide.

These results show that for this model of aversive behaviour, the effect of benzodiazepine receptor occupation is dependent upon a functional GABA-receptor, but that GABA receptor function is not reduced by blockade of benzodiazepine receptors. Thus the two predictions from the GABA hypothesis discussed above are indeed fulfilled by the experimental data.

TABLE 1

EFFECT OF PROGABIDE AND DIAZEPAM ON THE ESCAPE LATENCY IN THE AVERSIVE RESPONSE TO P.A.G. STIMULATION IN THE RAT

Drug	Dose (mg/kg, IP)	Change in Escape Latency (sec)
Saline		+ 5 ± 6
Diazepam	2.5	+ 15 ± 8
	5.0	+ 60 ± 13*
	7.5	+105 ± 10*
Progabide	25	+ 12 ± 3
	50	+ 20 ± 7
	100	+ 78 ± 8*
Diazepam + Progabide	2.5; 50	+ 96 ± 9†
Diazepam + Bicuculline	7.5; 3.0	+ 32 ± 9†
Progabide + Bicuculline	100; 4.0	+ 36 ± 8†
Diazepam + RO 15-1788	7.5; 35	+ 18 ± 5†
Progabide + RO 15-1788	100; 35	+ 71 ± 7*

Electrodes were placed in the periaqueductal grey region and the animals trained in a shuttle-box as previously described [6]. Escape latencies to graded increments (60–80–100–120 μA) of electrical stimuli (one per second, 300 msec trains of 15–0.2 msec pulses, 50 Hz) were measured. The sum of the latencies at the three lowest currents provoking an escape reaction was compared between drug-free and drug-treated sessions and the difference (change in escape latency) was recorded.

All data are expressed as the mean ± S.E.M., 7–10 rats per group. Neither bicuculline nor RO-15-1788 alone decreased the escape latency.

*=$p<0.01$ vs. saline injection.

†=$p<0.01$ vs. diazepam or progabide alone.

Data from [5, 6, 42].

Clinical Aspects

At the clinical level the possible anxiolytic action of progabide has been tested in an open and a controlled study on patients suffering from neurotic anxiety and also in two open studies run on alcohol and narcotic addicts during the withdrawal period. In all four trials a certain anxiolytic action of progabide was noted. However at the doses used (up to 30 mg/kg) the effect was inferior to that commonly observed with benzodiazepines in such situations.

From this it follows that GABA agonists may have a potential anxiolytic activity, but that more potent compounds are needed. A pertinent question is what advantage GABA agonists might possess as compared to the benzodiazepines, especially if both classes of compounds exert their activities via the same macromolecular receptor complex.

It appears that at least some of the effects of benzodiazepines are not coupled to GABA receptors. Thus, using a simple black-white avoidance task for assessment of the retention of acquisition (memory), seven benzodiazepines disrupted the retention in correlation with their

TABLE 2

EFFECT OF PROGABIDE ON BIOCHEMICAL INDICES OF DOPAMINE NEURON FUNCTION IN STRIATAL AND LIMBIC REGION

Test System	Control Value: Striatum	Control Value: Limbic Areas	Dose of Progabide	Value after Progabide: Striatum	Value after Progabide: Limbic Areas
Dopamine Release (% Control) "in vivo," cat brain (n=5)	100 ± 10%	—	50 mg/kg, IV	1 hr 50 ± 7%†	—
				2 hr 46 ± 5%†	—
				3 hr 59 ± 8%†	
Dopamine Levels after MT, (Rat) (n=12)	2730 ± 160 ng/g	730 ± 30 ng/g	400 mg/kg, IP	3270 ± 170* ng/g	705 ± 68 ng/g
DOPA Levels after NSD—1015 (Rat) (n=10)	1.53 ± 0.10 μg/g	0.98 ± 0.04	400 mg/kg, IP	1.08 ± 0.03† μg/g	0.88 ± 0.05 μg/g

Experimental conditions were previously described in detail [66]. Limbic areas are the nucleus accumbens pooled with the olfactory tubercles and septal regions. α-Methyltyrosine (αMT, 250 mg/kg, IP) was administered 4 hr and progabide 3 hr prior to sacrifice. NSD 1015 (100 mg/kg, IP) was administered 30 min after progabide and the animals sacrificed 30 min thereafter.

Values expressed as means with S.E.M.'s. Number of animals in parentheses. Data from [66].

*$p<0.05$; †$p<0.01$ vs. respective control values.

anticonvulsant activity whereas progabide did not disrupt retention in doses as high as 800 mg/kg, IP (Broekkamp and Lloyd, unpublished observations). Such findings indicate that the anxiolytic potential of GABA agonists may be exploited without provoking some of the adverse secondary effects of the benzodiazepines.

SCHIZOPHRENIA

The most prevalent biological hypothesis for schizophrenia is the dopamine hypothesis, which suggests that a hyperactivity of dopaminergic neurons and/or a supersensitivity of dopamine receptors in the brain (cortex? limbic system? striatum?) are the underlying causes of the schizophrenic condition. In terms of antipsychotic drug action, all presently used neuroleptics block dopamine receptor function [67]. Furthermore diminution of dopamine synaptic function (inhibition of tyrosine hydroxylase by α-methyl-p-tyrosine or inhibition of L-DOPA decarboxylase by α-methyl DOPA) potentiates the clinical effects of neuroleptics (cf, [10,37]). Furthermore reserpine, which depletes dopamine levels in the brain, also has an antipsychotic action [57].

From these findings a logical conclusion is that impairment of central dopamine synaptic function will either have a direct antipsychotic action, or else will potentiate the actions of neuroleptics. A host of studies indicate that nigro-neostriatal dopamine neurones are tonically inhibited by GABA neurons (cf, [20,36]) and that GABA neuron function may be involved in the mechanism of action of neuroleptics [23, 39, 49]. In addition to their interaction with dopamine neurones, GABA synapses have been proposed to be involved directly in psychoses. The basis for the GABA hypothesis being founded both on theoretical considerations [63] and from post-mortem studies (e.g., [4,56]). However the latter are not consistent [16,54] and have been challenged on a methodological basis [30].

Animal Models

As can be seen from Table 2, progabide effectively diminished nigro-striatal dopamine neuron activity as shown by the decrease in endogenous dopamine release from the cat caudate nucleus "in vivo," the decrease in the utilization of striatal dopamine after inhibition of tyrosine hydroxylase by α-MT, and a reduced accumulation of DOPA after DOPA decarboxylase inhibition by NSD-1015. In addition this GABA agonist seems also to reduce the effectiveness of dopamine receptor activation at a site distal to the dopamine receptor. Thus, progabide decreases the stereotyped behaviour provoked by apomorphine (Table 4), an action which cannot be explained by a direct effect on dopamine neurons.

Progabide not only exerts an effect per se on the nigro-striatal dopamine neurons, it also modifies the action of neuroleptics on these neurons. According to the present understanding of the mechanism of action of neuroleptics, these compounds exert a direct dopamine receptor blockade which triggers a feedback mechanism of dopamine neuron activation (cf, [40]). The latter is thought to be a homeostatic adjustment to overcome the dopamine receptor blockade, thus reducing the effect of the neuroleptic by increasing the dopamine-neuroleptic competition at the receptor site. Progabide prevents this activation of dopamine neurons by neuroleptics (Table 3) as demonstrated by the total block of the chlorpromazine-induced enhancement of striatal dopamine release from the cat caudate nucleus, "in vivo." Furthermore, progabide reduces both the increase in dopamine utilization (after α-MT) and DOPA accumulation (after NSD 1015) normally observed after haloperidol administration.

This interaction of progabide with neuroleptics on nigro-striatal dopamine neuron activity has behavioural consequences. Thus, the antistereotypic effect of haloperidol is

TABLE 3

EFFECT OF PROGABIDE ON NEUROLEPTIC-INDUCED ALTERATIONS IN BIOCHEMICAL INDICES OF DOPAMINE NEURON FUNCTION

Test System	Value for Neuroleptic		Dose of Progabide	Value after Neuroleptic + Progabide	
	Striatum	Limbic		Striatum	Limbic
Dopamine Release	(n=11)			(n=5)	
(% Control) "in vivo", cat brain, chlorpromazine, 1 mg/kg, IV	1 hr 252 ± 30%	—	50 mg/kg, IV	1 hr 93 ± 20%‡	—
	2 hr 246 ± 55%	—		2 hr 97 ± 22%‡	—
Dopamine Levels* in the brain after α-MT and Haloperidol (0.5 mg/kg, IP) (n=20)	2.30 ± 0.08 μg/g	1.45 ± 0.09 μg/g	400 mg/kg, IP	2.68 ± 0.10‡	1.48 ± 0.08
DOPA Levels† in the brain after NSD 1015 and Haloperidol (0.5 mg/kg, IP) (n=10)	5.07 ± 0.20 μg/g		1000 mg/kg, IP	2.80 ± 0.40‡	—

Experimental conditions were previously described in detail [66]. Limbic areas consist of nucleus accumbens pooled with olfactory tubercles septal areas. α-MT (250 mg/kg, IP) was administered 2.5 hr, progabide 2 hr and haloperidol 1.5 hr before sacrifice. NSD 1015 (100 mg/kg, IP) was administered 60 min, haloperidol 35 min and progabide 30 min prior to sacrifice.

Values expressed as means with S.E.M.'s. Number of animals in parentheses.

*Data from [3].

†Data from [66].

‡$p<0.01$ vs. neuroleptic alone.

potentiated by progabide (Table 4). However the progabide-neuroleptic interaction is more complex than it appears initially, as although moderate doses (100 mg/kg, IP) of this GABA agonist potentiate haloperidol induced catalepsy (probably via action on GABA receptors both presynaptic and postsynaptic to the striatal DA nerve terminal), very low doses reduce the cataleptic effect of the neuroleptic. This is unlikely a result of an action of progabide on dopamine neurons as these doses are completely inactive on biochemical indices of dopamine neuron function. Rather, it would seem that this anticataleptic action is subsequent to a very sensitive GABA receptor-mediated inhibition of striatal cholinergic neuron activity [64].

Although the final effect of progabide is similar to that of neuroleptics in that it blocks nigro-striatal dopamine neuron activity, the sensitivity of the limbic system to these compounds is very different. Thus, in limbic areas (septum + olfactory tubercle + n. accumbens) dopamine utilization after α-MT, or DOPA accumulation after NSD 1015 (Table 2) are unaltered by doses which markedly diminish nigro-striatal dopamine neuron activity. Furthermore in these limbic regions, the haloperidol-induced increase in dopamine utilization (after α-MT) (Table 3) is unaltered by doses of progabide which markedly decrease the activation of nigro-striatal neurons by neuroleptics (see above). This is in contrast to the sensitivity of the limbic system to neuroleptic compounds, most of which have an equal, or more pronounced, effect on limbic as compared to striatal dopamine neurons [65].

This low sensitivity of the biochemical indices of limbic dopamine neuron activity is reflected in the behavioural profile of progabide. Thus, the anti-apormorphine-induced climbing activity of haloperidol is not altered by this GABA agonist (Worms and Lloyd, unpublished observations).

Clinical Studies

There are data reported to date on 26 schizophrenic patients who have undergone clinical trials with progabide [51], 16 received progabide as monotherapy and 10 received the GABA agonist in combination with standard neuroleptic treatment. Progabide was administered for 3–64 days at doses of 1500–2400 mg per day.

Either as monotherapy or in combination with neuroleptic drugs, progabide was devoid of any evident anti-psychotic action. In fact, a few patients suffering from paranoid schizophrenia presented an aggravation of the clinical picture with increased hallucinations and delirium. In contrast a certain improvement in responsiveness to the environment and in social interactions was noticed in hebephrenic and schizoaffective syndromes under progabide.

These clinical studies confirm previous observations with other GABA agonists (e.g., muscimol [11]) that these compounds are ineffective as antipsychotic agents. This is possibly a reflection of the weak activity of GABA agonists on limbic dopamine neurons. This is consistent with most reports that GABA levels in CSF are not abnormal in schizophrenia [7, 16, 25, 35, 50, 78].

Nonetheless, the effectiveness of GABA agonists on striatal dopamine neurons may be apparent at the clinical level. Thus, although devoid of antipsychotic activity, these compounds (e.g., progabide, muscimol) diminish tardive dyskinesia [11,51]. This activity is reproduced in animal

TABLE 4

EFFECT OF PROGABIDE ON DOPAMINE-MEDIATED BEHAVIOUR: INTERACTION WITH HALOPERIDOL

Test System	Control Value	Progabide Dose (mg/kg, IP)	Progabide Value	Haloperidol Dose (mg/kg, IP)	Haloperidol Effect	Progabide + Haloperidol
Apomorphine (0.25 mg/kg, SC) stereotypies in mice mean score	13 ± 1.0 (n=30)	100	10.8 ± 0.6 (n=12)	0.05	10.0 ± 0.5* (n=12)	6.0 ± 1.0‡ (n=12)
		400	5.5 ± 0.5† (n=16)		—	—
Catalepsy in rats % of animal cataleptic		12.5	0	0.6	60 ± 4% (n=6)	31 ± 7%‡ (n=6)
		100	0	0.6	60 ± 4% (n=6)	83 ± 4%‡ (n=6)

Catalepsy (10 sec minimum in 4-cork test) and stereotypies (0–4 point rating scale) were measured as previously described [81]. The behaviour of the rats were rates for 1 hr after administration of either apomorphine plus progabide or haloperidol progabide.

Values expressed as means with S.E.M.'s.

†Data taken from [45].

*$p<0.05$; †$p<0.01$ vs. apomorphine alone.

‡$p<0.001$ vs. haloperidol alone.

models for either dopaminomimetic or neuroleptic dyskinesia [43].

DEPRESSION

Until recently there was no reason to implicate GABA synapses in either the etiology of depression or in the mechanism of action of antidepressant drugs. This is likely due to the concentration of research efforts on the "classical" anti-depressant drug actions. Recently interest has taken hold on the possibility that GABA systems may play a role in affective disorders. The major impetus for this effort has been the demonstration that one GABA agonist (progabide) has antidepressant qualities (see below) and that another GABA agonist (THIP) is mood elevating (Krogsgaard-Larsen, personal communication). Supporting evidence is the observation that GABA levels are low in the CSF [25,26 but not 60] and plasma [57] of depressed patients, that GABA agonists and mimetics are effective in certain animal models for depression (see below) and that some antidepressant drugs alter GABA uptake and release (although at concentrations greater than those effective on monoamines [28, 55, 71]). With this in mind we have investigated the effect of progabide on behavioural and biochemical indices used to predict antidepressant drug action.

Animal Models

In the two behavioural models studied (olfactory bulbectomy and learned helplessness) progabide exerted an antidepressant-like activity, similar to that of imipramine (Fig. 1). Furthermore, in the olfactory bulbectomized rat, progabide had a faster onset of action than did imipramine. In this regard, the acute action of progabide in this model was qualitatively similar to that of the serotonin-uptake inhibitors (e.g., fluoxetine, [9]). This action of progabide, in at least the olfactory bulbectomy model, was apparently related to its GABA agonist activity as the action of the compound was completely blocked by bicuculline (Fig. 1) at doses of bicuculline which are inactive per se (unpublished data). Furthermore muscimol, at a dose of 1.0 mg/kg, IP, also reversed the passive avoidance deficit in the olfactory

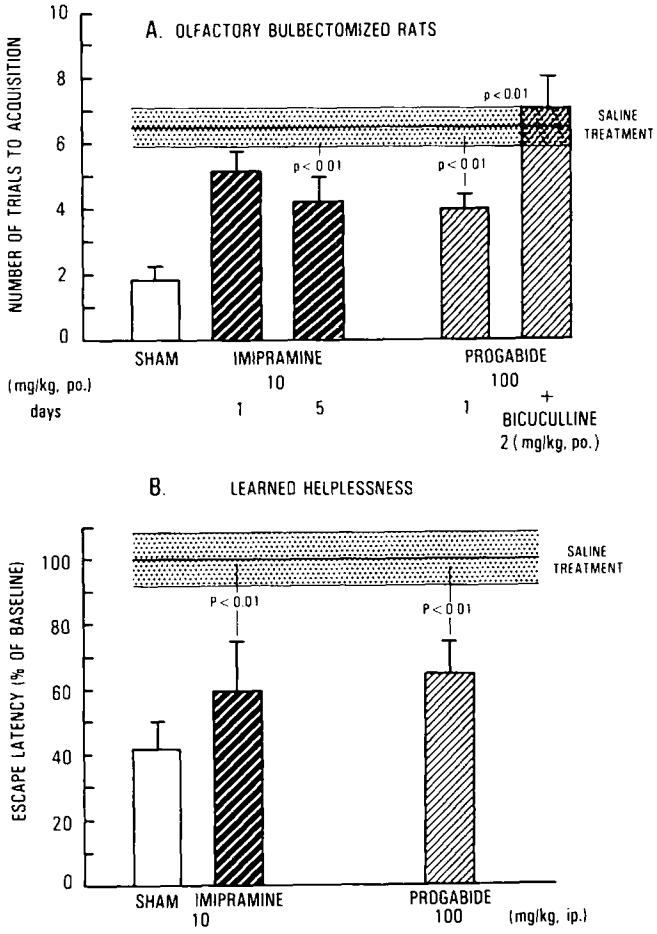

FIG. 1. Rats were previously subjected to either olfactory bulb removal (A) or unavoidable shock (B) before being trained for passive (A) or active (B) avoidance. Values expressed as means with SEMs for 5–7 rats per group.

TABLE 5

EFFECT OF PROGABIDE ON BEHAVIOURAL INDICES OF NORADRENERGIC AND SEROTONINERGIC NEURON FUNCTION

Test System	Progabide	Imipramine	Mianserine
Reserpine-Induced Ptosis in the mouse ED 50 mg/kg, IP	200	1.0	>20
Reserpine-Induced PGO waves in the cat % decrease, dose mg/kg, IV	−35% at 16 mg/kg, IV	0.13	>10
Reversal of 5-hydroxy-tryptophan Head Twitches in the mouse, ED 50 mg/kg, IP	25	>10	0.2

For the reversal of reserpine ptosis in the mouse [27] reserpine (4 mg/kg, IP) and progabide or imipramine were injected simultaneously. For the reversal of the 5-HTP (250 mg/kg, IP) induced head-twitches [80], the test substances were administered, simultaneously with 5-HTP. The reversal of the reserpine (0.75 mg/kg, IV, 3 hr previous) induced phasic PGO waves in the cat was studied as previously described [17].

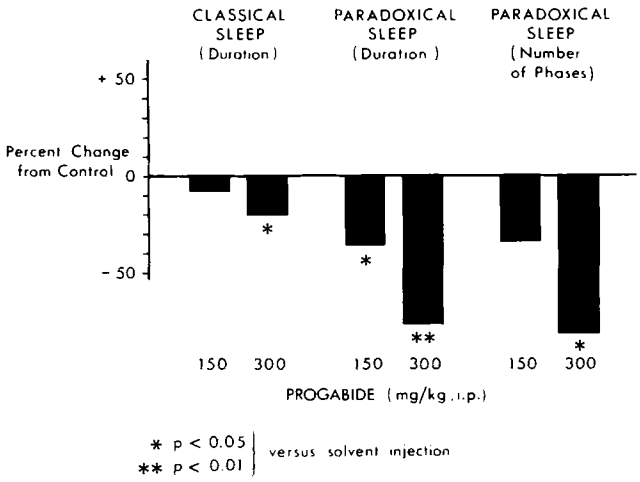

FIG. 2. Electrode implantation, EEG recording and analysis and drug administration schedules (day 1=vehicle control; day 2=progabide, 150 mg/kg, IP and day 3=progabide, 300 mg/kg, IP; day 4=vehicle control) were carried out as described in detail in the text.

bulbectomized rat (4.1±0.5 trials for muscimol vs 6.5±0.6 for saline, $p<0.02$).

The observation that progabide reverses the passive avoidance deficit in olfactory bulbectomized rats is consistent with the existence of GABA neurons in this region [1, 47, 62] some of which terminate in the amygdala [47], a site of action for antidepressant drug action in this model [24]. There is also supportive evidence that GABA neurons are involved in the action of antidepressant drugs in the learned helplessness model of depression and that intracerebral instillation of GABA itself will reverse the learned helplessness situation [58,69].

Progabide alters the normal rhythm of the sleep-wakefulness cycle in that it preferentially diminishes paradoxical sleep in the rat at doses which have little, or minimal, effect on classical slow-wave sleep (Fig. 2). This action of preferentially blocking paradoxical sleep is typical for compounds exerting an antidepressant action in man [18,33].

Most of the presently recognized antidepressant drugs exert an action on NE and/or 5-HT neurons. Although progabide exerts its action in a bicuculline-sensitive manner in the olfactory bulbectomized rats, and is without a direct action on noradrenaline or serotonin receptors or uptake systems ([41] and Scatton *et al.*, unpublished data), it was of interest to determine if progabide would alter other parameters of noradrenergic and serotonergic neuron activity. In behavioural tests closely related to NE neuron function (reserpine induced ptosis or PGO waves), progabide was at most weakly active (Table 5). However in tests indicative of an action on 5-HT neurons (or 5-HT receptor mediated events), progabide showed a potent activity. In this manner the spectrum of progabide activity resembles much more that of mianserine than imipramine (Table 5).

In terms of neurochemistry, progabide altered indices of both NE and 5-HT neuron function (Table 6). After acute administration of progabide, NE neuron activity appeared to be increased as indicated by enhanced MOPEG-SO_4 levels and a more rapid disappearance of NE after inhibition of tyrosine hydroxylase. On the other hand, 5-HT neuronal activity appeared to be decreased by acute progabide, as shown by a decreased disappearance of 5-HT after inhibition of tryptophan hydroxylase, and a slower accumulation of 5-HTP after decarboxylase inhibition.

After subacute (14 day) administration of progabide, NE turnover was no longer modified; however the decrease in 5-HT neuron activity is increased [83]. The effects of progabide on the biochemical indices of noradrenergic transmission are in contrast to those observed with classical tricyclic antidepressants which acutely diminish MOPEG-SO_4 levels and which on repeated treatment increase the concentrations of this NE metabolite [73].

Although progabide and the classical tricyclic antidepressants appear to act differently at the presynaptic level of noradrenergic neurons, they seem to act synergisti-

TABLE 6

EFFECT OF PROGABIDE ON BIOCHEMICAL INDICES OF NORADRENERGIC AND SEROTONINERGIC NEURON FUNCTION IN THE RAT BRAIN*

Parameter Measured	Control Value	Progabide dose (mg/kg, IP)	Value after Progabide
MOPEG-SO_4 in	100 ± 8%	400	136 ± 9%†
Whole Brain (n=10)		1000	141 ± 12%†
% Control			
Noradrenaline Levels	677 ± 40	400	461 ± 33†
after α-MT	ng/g		ng/g
Septal areas (n=8)			
5-HT Levels			
Limbic areas	630 ± 25 ng/g	600	674 ± 34 ng/g
Striatum	388 ± 11 ng/g	600	386 ± 10 ng/g
5-HIAA Levels			
(n=10–40)			
Limbic Areas	336 ± 22 ng/g	600	399 ± 33 ng/g
Striatum	430 ± 9 ng/g	600	602 ± 21† ng/g
5-HT Levels after			
α-propyldopacetamide			
(500 mg/kg, IP) % control			
(n=21)			
Limbic areas	72 ± 6%	600	74 ± 7%
Striatum	60 ± 4%	600	85 ± 4†%
5-HTP Levels after			
NSD-1015 (100 mg/kg, IP)			
(n=15)			
Limbic areas	205 ± 13 ng/g	600	200 ± 11 ng/g
Striatum	187 ± 6 ng/g	600	150 ± 5† ng/g

Experimental conditions were previously described in detail [66]. Septal areas refers to the septum pooled with the nucleus accumbens septi whereas limbic areas refers to the nucleus accumbens pooled with the olfactory tubercles and septum. α-MT was administered 4 hr, 2-propyldopacetamide 3 hr and NSD 0.5 hr prior to sacrifice. Progabide was injected 1 hr post α-MT, 0.5 hr post α-propyldopacetamide and 0.5 hr prior to NSD 1015. For the determination of MOPEG-SO_4 progabide was injected 2 hr before sacrifice, for 5-HT and 5-HIAA determinations progabide was administered 1.5 hr prior to sacrifice.

Data expressed as means with S.E.M.'s, number of animals in parentheses.

*Data from [66].

†$p<0.01$ vs. control value.

cally at the postsynaptic level. Thus at doses of progabide and imipramine which alone are inactive, repeated administration of the two drugs together induces a subsensitivity in β-adrenoceptor coupled adenylate cyclase activity [83], an effect which has been proposed to be a reliable predictor for antidepressant action [74].

It would appear that, from the neurochemical and pharmacological evidence available, progabide exerts its acute effects in antidepressant tests by an agonistic action on GABA receptors modifying, inter-alia, 5-HT neuron activity. Thus, in behavioural experiments progabide is active upon single administration in the olfactory bulbectomy model; this is in common with antidepressant drugs with a predominant 5-HT effect whereas noradrenergic compounds must be administrated repeatedly to show activity [9]. Furthermore progabide is at most weakly active against reserpine-induced ptosis and PGO waves, tests most sensitive to noradrenergic compounds, whereas this GABA agonist is markedly active in altering the activity of 5-HTP, similarly to mianserin and amitriptyline [48].

Clinical Studies

Data in man support the hypothesis that GABA-agonists have a therapeutic action in depressive syndromes. In a preliminary open study run on 15 depressive patients suffering from either endogenous (11 cases) or reactive (4) depressive states, progabide administered at the dose of 2–30 mg/kg/day led within 8–10 days to a significant improvement in 7 cases (6 endogenous and 1 reactive). The amelioration was characterized by a mobilization of defenses, disappearance of culpability and death thought, reappearance of critical judgement and mood elevation [51].

In a second more recent double blind study run against imipramine (1.6–3.3 mg/kg) in patients suffering from major depressive episodes (DSM III) or depressive reactions [52], the antidepressant action of progabide was found to be similar to that of imipramine both for the global clinical rating and the Hamilton Rating Scale of Depression. A significant reduction or disappearance of depressive symptoms was observed in 8 out of 11 cases with progabide and 9 out of 11

cases with imipramine. As during the first study the antidepressant action was manifest within 8–10 days of treatment.

To the authors' knowledge, the results of clinical trials using the GABA agonist compounds have not been published.

GENERAL DISCUSSION AND CONCLUSIONS

The availability of a GABA agonist with a pharmacological and toxicological profile acceptable for human studies has allowed the testing of several hypotheses for the biological basis of neuropsychiatric disease. Until the advent of progabide the compounds available for testing GABA hypotheses were either too toxic (e.g., muscimol, [11]), did not cross the blood-brain barrier [12,76] or were indirectly acting compounds with other actions in addition to those on GABA synapses (e.g., sodium valproate). Progabide and its metabolite SL 75102 are specific GABA receptor agonists [41] and progabide is well tolerated in man [51,52]. This compound has already provided strong experimental [82] and clinical [46, 51, 79] support for the GABA hypothesis of epilepsy and anticonvulsant drug action.

The present studies have focussed upon the activity of a GABA agonist in animal models and clinical studies of common psychiatric disorders: anxiety, schizophrenia and depression. Of these, the present results appear to question the "GABA" hypothesis of schizophrenia and indicate that GABA agonists (at the classical GABA receptor) are unlikely candidates as antipsychotic agents. This conclusion is supported by earlier studies with muscimol [11]. The likely basis for this inactivity is that the doses necessary to inhibit meso-limbic or meso-cortical dopamine neurons by GABA agonists cannot be reached in the clinic, although nigrostriatal dopamine neurons activity is readily diminished. This is in contrast to most neuroleptics which may even preferentially inhibit mesocortical or mesolimbic dopamine neuron function, and this activity has been proposed to be related to their antipsychotic action [65].

The studies in animal models for anxiety support the hypothesis of a GABA-benzodiazepine macromolecular receptor complex and show that GABA receptor activity is necessary for the action of both benzodiazepine and GABA agonists; however GABA receptors may function independently of benzodiazepine receptors. The clinical situation does not completely reflect the findings in the animal models for anxiety, for although progabide exerts a measurable anxiolytic action, this is more moderate than that observed with the benzodazepines.

The clinical antidepressant activity of progabide opens the question of GABA synaptic function in affective disorders. These observations find support in the neurochemistry [74] and pharmacology (this paper) of animal models for depression and is consistent with the observations that CSF GABA levels are below normal in depressed patients. Furthermore, the accompanying paper by Emrich and collaborators [21] strongly suggests that GABA synaptic function plays a role in mania as well as in depression. These studies indicate the importance not only of GABA neurons in psychiatric disorders, they also underscore the necessity to develop new specific drugs for the treatment and understanding of such disorders.

REFERENCES

1. Austin, L., M. Recasens and P. Mandel. GABA in the olfactory bulb and olfactory nucleus of the rat: The distribution of gamma-aminobutyric acid, glutamic acid decarboxylase, gaba transaminase and succine semialdehyde dehydrogenase. *J Neurochem* **32:** 1473–1477, 1979.
2. Bartholini, G., K. G. Lloyd, P. Worms, J. Constandinidis and R. Tissot. GABA and GABAergic medication: Relation to striatal dopamine function and Parkinsonism. In: *Advances in Neurology*, vol 24, edited by L. J. Piorier, T. L. Sourkes and P. J. Bedard. New York: Raven Press, 1979, pp. 253–257.
3. Bartholini, G., B. Scatton, B. Zivkovic and K. G. Lloyd. On the mode of action of SL 76002, a new GABA receptor agonist. In: *GABA-Neurotransmission*, edited by P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod. Copenhagen: Munksgaard, 1979, pp. 326–339.
4. Bird, E. D., E. G. Spokes, J. Barnes, A. V. P. Mackay, L. L. Iversen and M. Shepherd. Increased brain dopamine and reduced glutamic acid decarboxylase and choline acetyltransferase activity in schizophrenia and related psychoses. *Lancet* **2:** 1247–1249, 1977.
5. Bovier, P., C. L. E. Broekkamp and K. G. Lloyd. Anxiolytic potential of GABAergic agents. In: *Biological Psychiatry, 1981*, edited by C. Perris, G. Struwe and B. Jansson. Amsterdam: Elsevier, 1981, pp. 425–428.
6. Bovier, P., C. L. E. Broekkamp and K. G. Lloyd. Enhancing GABAergic transmission reverses the aversive state in rats induced by electrical stimulation of the peraqueductal grey region. *Brain Res* **248:** 313–320, 1982.
7. Bowers, M. B., B. I. Gold and R. H. Roth. CSF GABA in psychotic disorders. *Psychopharmacology (Berlin)* **70:** 279–282, 1980.
8. Brandão, M. L., J. C. de Aguiar and F. G. Graeff. GABA mediation of the anti-aversive action of minor tranquilizers. *Pharmacol Biochem Behav* **16:** 397–402, 1982.
9. Broekkamp, C. L. E, D. Garrigou and K. G. Lloyd. Serotonin-mimetic and antidepressant drugs on passive avoidance learning by olfactory bulbectomized rats. *Pharmacol Biochem Behav* **13:** 643–646, 1980.
10. Brogden, R. N., R. C. Heed, T. M. Speight and G. S. Avery. Alpha-methyl-tyrosine: A review of its pharmacology and clinical use. *Drugs* **21:** 81–89, 1981.
11. Chase, T. N. and C. Taminga. GABA system participation in human motor. Cognitive and endocrine function. In: *GABA-Neurotransmitters*, edited by P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod. Copenhagen: Munskgaard, 1979, pp. 283–294.
12. Chase, T. N. and J. R. Walters. Pharmacologic approaches to the manipulation of GABA mediated synaptic function in man. In: *GABA in Nervous System Function*, edited by E. Roberts, T. N. Chase and D. B. Tower. New York: Raven Press, 1976, pp. 497–513.
13. Christensen, A. V. and O. Svendesen. Behavioural effects of THIP after systemic administration. *Brain Res Bull*, in press.
14. Costa, E. Benzodiazepine and neurotransmitters. *Arzneimittelforsch* **30:** 858–861, 1980.
15. Costa, E. and A. Guidotti. Molecular mechanisms in the receptor action of benzodiazepines. *Annu Rev Pharmacol Toxicol* **119:** 531–545, 1979.
16. Crow, T. J., F. Owen, A. J. Cross, R. Lofthouse and A. Longden. Brain biochemistry in schizophrenia. *Lancet* **1:** 36–37, 1978.

17. Depoortere, H. and K. G. Lloyd. Ponto-geniculo-occipital spikes: a model for ths study of the central action of noradrenergic compounds. In: *Presynaptic Receptors*, edited by S. Z. Langer, K. Starke and M. L. Dubocovitch. Oxford: Pergamon Press, 1979, pp. 173–178.
18. Depoortere, H. and V. Santucci. The influence of antidepressant drugs on the rebound phenomenon following paradoxical sleep deprivation and in the PGO activity induced by reserpine. In: *Sleep 1978*. Basel: Karger, 1978, pp. 475–477.
19. Desarmenien, M., P. Feltz, P. M. Headley and F. Santangelo. SL 75102 as a GABA agonist: Experiments on dorsal root ganglion neurones in vitro. *Br J Pharmacol* **72:** 355–364, 1981.
20. Dray, A. The striatum and substantia nigra: A commentary on their relationships. *Neuroscience* **4:** 1407–1439, 1979.
21. Emrich, H. M., H. Altmann and D. V. Zerssen. Therapeutic effects of GABAergic drugs in affective disorders. *Brain Res Bull*, in press.
22. Enna, S. J., L. Z. Stern, G. J. Wastek and H. I. Yamamura. Neurobiology and neuropharmacology of Huntington's disease. *Life Sci* **20:** 205–212, 1977.
23. Fuxe, K., T. Hokfelt, A. Ljungdahl, L. Agnati, O. Johansson and M. Perez de la Mora. Evidence for an inhibitory GABAergic control of the meso-limbic dopamine neurons: Possibility of improving treatment of schizophrenia by combined treatment with neuroleptics and GABAergic drugs. *Med Biol* **53:** 177–183, 1975.
24. Garrigou, D., C. L. Broekkamp and K. G. Lloyd. Involvement of the amygdala in the effect of antidepressants on the passive avoidance deficit in bulbectomized rats. *Psychopharmacology (Berlin)* **74:** 66–70, 1981.
25. Gerner, R. H. and T. A. Hare. CSF GABA in normal subjects and patients with depression, schizophrenia, mania and anorexia nervosa. *Am J Psychiatry* **138:** 1098–1101, 1981.
26. Gold, B. I., M. B. Bower, R. H. Roth and D. W. Sweeney. GABA levels in CSF of patients with psychiatric disorders. *Am J Psychiatry* **137:** 362–364, 1980.
27. Garret, C., G. Mocquet, A. Costeau and G. Raynaud. Interaction des divers psychotropes avec cinq effets de la reserpine chez la souris et chez le chat: ptose palpebrale, hypothermie, hypomotilité, catalepsie et pointes PGO. *J Pharmacol* **8:** 333–350, 1977.
28. Harris, M., M. Hopkins and M. J. Neal. Effects of centrally acting drugs on the uptake of γ-aminobutyric acid by the brain. *Br J Pharmacol* **44:** 339P–340P, 1972.
29. Hunkeler, W., H. Möhler, L. Pieri, P. Polc, E. P. Boretti, R. Cumin, R. Schaffner and W. Haefely. Selective antagonists of benzodiazepines. *Nature* **290:** 514–516, 1981.
30. Iversen, L. L., E. Bird, E. Spokes, S. H. Nicholson and C. J. Suckling. Agonist specificity of GABA binding sites in human brain and GABA in Huntington's disease and schizophrenia. In: *GABA-Neurotransmitters*, edited by P. Krogsgaard-Larsen, J. Scheel-Kruger and H. Kofod. Copenhagen: Munksgaard, 1979, pp. 179–190.
31. Kaplan, J. P., B. Raizon, M. Desarmenien, P. Feltz, P. M. Headley, P. Worms, K. G. Lloyd and G. Bartholini. New anticonvulsants: Schiff bases of GABA and GABAmide. *J Med Chem* **23:** 702–704, 1980.
32. Krogsgaard-Larsen, P., H. Hjeds, D. Curtis, D. Lodge and G. A. R. Johnston. Dihydromuscimol, thiomuscimol and related heterocyclic compounds as GABA analogues. *J Neurochem* **32:** 1717–1724, 1979.
33. Kupfer, D. J., I. Hanin, D. G. Spiker, J. Neil and P. Coble. EEG sleep and tricyclic plasma levels in primary depression. *Commun Psychopharmacology* **3:** 73–80, 1979.
34. Lane, J. D., M. P. Sands, M. E. Freeman, D. R. Cherek and J. E. Smith. Amino acid neurotransmitter utilization in discrete rat brain regions is correlated with conditioned emotional response. *Pharmacol Biochem Behav* **16:** 329–340, 1982.
35. Lichtshtein, D., J. Dobkin, R. P. Ebstein, J. Biederman, R. Rimon and R. H. Belmaker. Gamma-aminobutyric acid (GABA) in the CSF of schizophrenic patients before and after neuroleptic treatment. *Br J Psychiatry* **132:** 145–148, 1978.
36. Lloyd, K. G. Neurotransmitter interactions related to central dopamine neurons. In: *Essays in Neurochemistry and Neuropharmacology*, vol 3, edited by M. B. H. Youdin, W. Lovenberg, D. F. Sharman and J. R. Lagnado. Chichester: Wiley, 1978, pp. 131–207.
37. Lloyd, K. G. Observations concerning neurotransmitter interaction in schizophrenia. In: *Cholinergic-Monoaminergic Interactions in the Brain*, edited by L. L. Butcher. New York: Raven Press, 1981, pp. 135–140.
38. Lloyd, K. G. Indications for GABA neuron dysfunction in mental disease. In: *Enzymes and Neurotransmitters in Mental Disease*, edited by E. Usdin, T. L. Sourkes and M. B. H. Youdim. New York: Wiley, 1980, pp. 329–344.
39. Lloyd, K. G. and O. Hornykiewicz. Effect of chronic neuroleptic or L-DOPA administration on GABA levels in rat substantia nigra. *Life Sci* **21:** 1489–1496, 1977.
40. Lloyd, K. G. and P. Worms. Sustained GABA receptor stimulation and chronic neuroleptic effects. In: *Long-term Effects of Neuroleptics*, edited by F. Cattabeni, G. Racagni and P. F. Spano. New York: Raven Press, 1979, pp. 253–258.
41. Lloyd, K. G., S. Arbilla, K. Beaumont, M. Briley, G. M. DeMontis, B. Scatton, S. Z. Langer and G. Bartholini. Gamma-aminobutyric acid (GABA) receptor-stimulation. II. Specificity of progabide (SL 76002) and SL 75102 for the GABA receptor. *J Pharmacol Exp Ther* **220:** 672–677, 1972.
42. Lloyd, K. G., P. Bovier, C. L. Broekkamp and P. Worms. Reversal of the antiaversive and anticonvulsant actions of diazepam, but not of progabide, by a selective antagonist of benzodiazepine receptors. *Eur J Pharmacol* **75:** 77–78, 1981.
43. Lloyd, K. G., C. L. Broekkamp and P. Worms. Involvement of GABA neurons in the induction and reversal of dopamine receptor related dyskinesia. In: *Behavioral Pharmacology in Toxicology*, edited by R. Paoletti, B. Weiss, G. Zbinden, V. Cuomo and G. Racagni. New York: Raven Press, 1983, in press.
44. Lloyd, K. G., C. Munari, L. Bossi, C. Stoeffels, J. Talairach and P. L. Morselli. Biochemical evidence for the alterations of GABA-mediated synaptic transmission in pathological brain issue (stereo EEG or morphological definition) from epileptic patients. In: *Neurotransmitters, Seizures, and Epilepsy*, edited by P. L. Morselli, K. G. Lloyd, W. Löscher, B. Meldrum and E. H. Reynolds. New York: Raven Press, 1981, pp. 325–338.
45. Lloyd, K. G., P. Worms, B. Zivkovic, B. Scatton and G. Bartholini. Interaction of GABA mimetics with nigro-striatal dopamine neurons. *Brain Res Bull* **5:** Suppl 2, 439–445, 1980.
46. Loiseau, P., B. Cenraud, L. Bossi and P. L. Morselli. A double blind controlled study versus placebo with progabide (SL 76002) in severe epilepsy. In: *Proceedings of the 12th Epilepsy International Symposium*, edited by M. Dam, L. Gram and J. K. Penry. New York: Raven Press, 1981, pp. 135–140.
47. Mack, G. and P. Mandel. Inhibition du comportement muricide du rat par la taurine, le GABA et ses analogues. *Comptes-Rendus Acad Sci D (Paris)* **283:** 361–362, 1976.
48. Maj, J. Studies on the action of antidepressant drugs of second generation. *Pol J Pharmacol* **32:** 437–449, 1980
49. Mao, C. C., E. Marco, A. Revuelta and E. Costa. Antipsychotics and GABA turnover in mammalian brain nuclei. In: *Interactions between Putative Neurotransmitters in the Brain*, edited by S. Garattini, J. R. Pujol and R. Samarin. New York: Raven Press, 1978, pp. 151–160.
50. McCarthy, B. W., U. R. Gomes, A. C. Neethling, B. C. Shanley, J. J. F. Taljaard, L. Potgieter and J. T. Roux. Gamma-aminobutyric acid concentration in cerebrospinal fluid in schizophrenia. *J Neurochem* **36:** 1406–1408, 1981.
51. Morselli, P. L., L. Bossi, J. F. Henry, E. Zarifian and G. Bartholini. On the therapeutic action of SL 76002, a new GABA-mimetic agent: Preliminary observations in neuropsychiatric disorders. *Brain Res Bull* **5:** Suppl 2, 411–414, 1980.
52. Morselli, P. L., J. F. Henry, J. P. Macher, P. Bottin, J. P. Huber and V. H. Van Landeghem. Progabide and mood. In: *Biological Psychiatry, 1981*, edited by C. Perris, G. Struwe and B. Jansson. Amsterdam: Elsevier, 1981, pp. 440–443.

53. Olsen, R. W., M. K. Ticku, P. C. Van Ness and D. Greenlee. Effects of drugs on gamma-aminobutyric acid receptors, uptake, release and synthesis in vitro. *Brain Res* **139:** 277–294, 1978.
54. Perry, E. K., G. Blessed, R. H. Perry and B. E. Tomlinson. Brain biochemistry in schizophrenia. *Lancet* **1:** 35–36, 1978.
55. Perry, T. L., K. Berry, S. Hansen, S. Diamond and C. Mok. Regional distribution of amino acids in human brain obtained at autopsy. *J Neurochem* **18:** 513–519, 1971.
56. Perry, T. L., J. Buchenan, S. J. Kish and S. Hansen. Gamma-aminobutyric acid deficiency in brain of schizophrenic patients. *Lancet* **1:** 237–239, 1979.
57. Petty, F. and M. A. Schlesser. Plasma GABA in affective illness. *J Affective Disord* **3:** 339–343, 1981.
58. Petty, F. and A. D. Sherman. GABAergic modulation of learned helplessness. *Pharmacol Biochem Behav* **15:** 567–570, 1981.
59. Poldinger, W. *Compendium of Psychopharmacotherapy*. Basel: Roche, 1972.
60. Post, R. M., J. C. Ballenger, T. A. Hare, F. K. Goodwin, C. R. Lake, D. C. Jemerson and W. E. Bunney. Cerebrospinal fluid GABA in normals and patients with affective disorders. *Brain Res Bull* **5:** Suppl 2, 755–759, 1980.
61. Preziosi, P. and G. Nistico. Psychotropic drugs: Mechanism of action of the neurotransmitter level. *Int J Clin Pharmacol* **15:** 497–518, 1977.
62. Riback, C. W., J. E. Vaughan, K. Saito, R. Barber and E. Roberts. Glutamate decarboxylase localization in neurons of the olfactory bulbs. *Brain Res* **126:** 1–8, 1977.
63. Roberts, E. An hypothesis suggesting that there is a defect in the GABA system in schizophrenia. *Neurosci Res Program Bull* **10:** 468–482, 1976.
64. Scatton, B. and G. Bartholini. Gamma-Aminobutyric acid (GABA) receptor stimulation. IV. Effect of progabide (SL 76002) and other GABAergic agents on acetylcholine turnover in rat brain areas. *J Pharmacol Exp Ther* **220:** 689–695, 1982.
65. Scatton, B., J. Glowinski and L. Julou. Neuroleptics: effects on dopamine synthesis in the nigro-neostriatal, mesolimbic and meso-cortical dopaminergic systems. In: *Antipsychotic Drugs: Pharmacodynamics and Pharmacokinetics*, edited by G. Sedwall, B. Uvnas and Y. Zotterman. Oxford: Pergamon Press, 1976, pp. 243–256.
66. Scatton, B., B. Zivkovic, J. Dedek, K. G. Lloyd, J.Constantidinidis, R. Tissot and G. Bartholini. Gamma-Aminobutyric acid (GABA) receptor stimulation. III. Effect of Progabide (SL 76002) on norepinephrine, dopamine and 5-hdyroxytryptamine turnover in rat brain areas. *J Pharmacol Exp Ther* **220:** 678–688, 1982.
67. Seeman, P. Brain dopamine receptors. *Pharmacol Rev* **32:** 229–313, 1980.
68. Sepinwall, J. and L. Cook. Relationship of gamma-aminobutyric acid (GABA) to anti-anxiety effects of benzodiazepines. *Brain Res Bull* **5:** Suppl 2, 839–848, 1980.
69. Sherman, A. D. and F. Petty. Neurochemical basis of the action of antidepressants on learned helplessness. *Behav Neurol Biol* **30:** 119–134, 1980.
70. Sherman, A. D., G. L. Allers, F. Petty and F. A. Henn. A neuropharmacologically relevant animal model of depression. *Neuropharmacology* **18:** 891–893, 1979.
71. Snodgrass, S. R., E. T. Hedley-White and A. V. Lorenzo. GABA transport by nerve ending fractions of cat brain. *J Neurochem* **20:** 771–782, 1973.
72. Soubrié, P., M. H. Thiebot and P. Simon. Enhanced suppressive effects of aversive events induced in rats by picrotoxinin: Possibility of GABA control on behavioural inhibition. *Pharmacol Biochem Behav* **10:** 463–469, 1979.
73. Sugrue, M. Effects of acutely and chronically administered antidepressants on learned helplessness. *Life Sci* **28:** 377–384, 1981.
74. Sulser, F., J. Vetulani and P. L. Mobley. Mode of action of antidepressant drugs. *Biochem Pharmacol* **27:** 257–261, 1978.
75. Thiébot, M. H., A. Jobert and P. Soubrié. Conditioned suppression of behaviour: Its reversal by intra raphe microinjection of chlordiazepoxide and GABA. *Neurosci Lett* **16:** 213–217, 1980.
76. Tower, D. B. GABA and seizures: clinical correlates in man. In: *GABA in Nervous System Function*, edited by E. Roberts, T. N. Chase and D. B. Tower. New York: Raven Press, 1976, pp. 461–478.
77. Valenstein, E. S. Independence of approach and escape reactions to electrical stimulation of the brain. *J Comp Physiol Psychol* **60:** 20–30, 1965.
78. Van Kammen, D. P., D. E. Sternberg, T. A. Hare, J. G. Ballenger, S. R. Marder, R. M. Post and W. E. Banney. Schizophrenia: Low spinal fluid GABA levels? *Brain Res Bull* **5:** Suppl 2, 731–735, 1980.
79. Van der Linden, G. J., H. Meinardi, J. W. A. Meijer, L. Bossi and C. Gomeni. A double-blind cross-over trial with SL 76002 against placebo in patients with secondary generalized epilepsy. In: *Proceedings of the 12th Epilepsy International Symposium*, edited by M. Dam, L. Gram and J. K. Penry. New York: Raven Press, 1981, pp. 141–144.
80. Van Riezen, H. Different central effects of the 5-HT antagonists mianserine and cyproheptadine. *Arch Int Pharmacodyn Ther* **198:** 256–269, 1972.
81. Worms, P. and K. G. Lloyd. Predictability and specificity of behavioural screening tests for neuroleptics. *Pharmacol Ther* **5:** 445–450, 1979.
82. Worms, P., H. Depoortere, A. Durand, P. L. Morselli, K. G. Lloyd and G. Bartholini. Gamma-aminobuytric acid (GABA) receptor stimulation. I. Neuropharmacological profiles of progabide (SL 76002) and SL 75102, with emphasis on their anticonvulsant spectra. *J Pharmacol Exp Ther* **220:** 660–671, 1982.
83. Zivkovic, B., B. Scatton, J. Dedek and G. Bartholini. GABA influence on noradrenergic and serotonergic transmissions: Implications in mood regulation. In: *New Vistas in Depression*, edited by S. Z. Langer, R. Takahashi, T. Segawa and M. Briley. Oxford: Pergamon Press, 1982, pp. 195–201.