Biochemical Pharmacology, Vol. 30, No. 9, pp. 907–913, 1981.
Printed in Great Britain.

0006-2952/81/090907-07 $02.00/0

COMMENTARY

GABA RECEPTOR PHARMACOLOGY

FUNCTIONAL CONSIDERATIONS

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γ-Aminobutyric acid (GABA) appears to be a major inhibitory neurotransmitter in the mammalian central nervous system [1–4]. Among other things, the ubiquitous distribution and high concentration of this amino acid in the neuroaxis attest to the importance of GABA in the control of nervous system function.

While early studies on GABA were chiefly concerned with defining its biochemical and physiological properties, more recent work has focused on understanding the basic pharmacological and functional characteristics of this system as well as the involvement of GABA in neurological and psychiatric disorders [1]. As a result of these investigations it now appears that a dysfunction in GABAergic transmission may contribute to the symptoms of a variety of ailments including Huntington's disease, Parkinson's disease, epilepsy, anxiety, and possibly schizophrenia. While it is unlikely that an alteration in GABAergic function is the primary biochemical abnormality in each of these, it would not be surprising to find that secondary changes in this transmitter system are present in virtually all neuropsychiatric disorders, given the widespread distribution of GABA neurons in brain.

These findings have provided a stimulus for the development of drugs capable of selectively activating the GABA system in man. To this end, three approaches have been taken. One has been to design compounds that will specifically inhibit the metabolism of GABA (GABA transaminase inhibitors), thereby increasing the concentration of this amino acid throughout the brain which, in turn, presumably increases the functional activity of the GABAergic system. Some examples of relatively specific GABA transaminase inhibitors are γ-acetylenic GABA and γ-vinyl GABA [5, 6].

Another strategy has been to synthesize direct-acting GABA receptor agonists, agents that will themselves activate this receptor site. Compounds such as muscimol (3-hydroxy-5-aminomethylisoxozole), THIP (4,5,6,7-tetrahydroisoxazolo (5,4-*c*)pyridone-3-ol], kojic amine (2-aminomethyl-5-hydroxy-4H-pyran-4-one), and SL-76002 [a(chloro-4-phenyl)-fluoro-5-hydroxy-2-benzilidene-amino-4 butyramide] are in this category [7–9].

The third area of drug development has dealt with finding agents capable of inhibiting neuronal high affinity GABA transport, the process thought to be most important for terminating the action of this neurotransmitter [10]. While a number of active compounds have been found, none have been clinically tested because of poor lipid solubility. Recently, however, ester derivatives of some GABA uptake inhibitors have been synthesized in an attempt to facilitate penetration into brain [11, 12].

In addition to their possible clinical utility, these agents are useful as pharmacological tools for investigating the biochemical, physiological, and behavioral consequences of GABA receptor activation in laboratory animals. Accordingly, the development of systemically active GABAmimetics represents a major step in the evolution of GABA pharmacology since their use may yield better insights into the possible therapeutic, and side-effect, potential of GABAergic drugs. The aims of this commentary are to discuss some of the problems encountered with studies of this type and, with these difficulties in mind, to summarize and highlight recent data and theories relating to the functional consequences of GABA receptor activation in an attempt to demonstrate how such information may be useful in predicting the clinical consequences of GABAmimetic therapy.

Experimental procedures

A variety of experimental approaches are used in attempting to define the functional properties of a particular neurotransmitter system. Thus, neurotransmitter receptor agonists or antagonists may be injected directly into, or perfused in and around, specific brain regions. If this treatment induces a significant alteration in a particular biochemical, behavioral or physiological variable, it is hypothesized that this function is normally under the control of this neurotransitter system.

However, as opposed to the catecholaminergic and serotoninergic neurons which emanate from a limited number of discrete loci in the brain, GABAergic cell bodies and terminals are found in virtually every area of the central nervous system, making it more difficult to manipulate this system in specific brain regions (Table 1). Thus, for example, high affinity GABA transport, a marker for GABA neurons, and GABA receptor binding are detectable in all gray matter areas. Within the cerebellum GABA is the primary, if not the sole, inhibitory neurotransmitter, and it appears to be the mediator

Table 1. Regional distribution of high affinity GABA transport and receptor binding in monkey brain and GABA-mediated inhibitions

Brain region	[^{3}H]GABA receptor binding* (fmoles/mg protein)	GABA uptake* (fmoles/mg protein)	Types of inhibition†
Olfactory bulb	0.04	232	Granule and periglomerular cell inhibition of mitral cells.
Cerebral cortex			
Frontal cortex	1.53	607	Stellate cell inhibition of pyramidal cells.
Frontal pole	1.82	641	
Occipital pole	2.03	533	
Temporal pole	0.67	739	
Precentral gyrus	0.40	535	
Postcentral gyrus	1.33	563	
Superior temporal gyrus	2.18	815	
Medial temporal gyrus	1.58	746	
Cingulate cortex	1.52	764	
Limbic cortex			
Amygdala	1.40	847	Basket cell inhibition of hippocampal pyramidal cells.
Hippocampus	0.74	390	
Septum	1.21	491	Recurrent inhibition of septal neurons.
Hypothalamus	0.41	787	Intrahypothalamic interneurons.
Thalamus	1.02	224	Recurrent inhibition of thalamocortical relay neurons.
Extrapyramidal areas			
Caudate	2.52	339	Inhibitions by intracaudate, strio-nigral, strio-pallidal, strio-entopeduncular neurons.
Putamen	2.37	299	
Globus pallidus	2.00	852	
Substantia nigra	1.14	587	
Midbrain	0.70	405	Inhibition of red nucleus from cerebral cortex.
Cerebellum			
Cerebellar cortex	1.72	229	Basket cell inhibition of Prukinje cells. Golgi cell inhibition of granule cells. Prukinje cell inhibition of deep nuclei.
Deep cerebellar nuclei	0.30	148	
Pons	0.20	158	
Medulla	0.06	270	Purkinje cell inhibition of vestibular nuclei.
Spinal cord			
Cervical	0.07	154	Prolonged inhibition interneurons, motor neurons and Renshaw cells.
Thoracic	0.09	102	
Lumbar	0.08	196	Depolarization of primary afferent terminals.

* Adapted from Ref. 13.
† Adapted from Ref. 14.

of primary afferent depolarization (pre-synaptic inhibition) in the spinal cord (Table 1). Furthermore, GABA plays a major role in extrapyramidal function, as a transmitter for interneurons and for those projecting from the striatum to the globus pallidus, substantia nigra, and entopeduncular nucleus. In addition to these and other brain regions, GABA also appears to be an important neurotransmitter in regulating pyramidal cell activity in both the cerebral and limbic cortex.

It is also noteworthy that, in addition to the classical post-synaptic GABA receptors, there also appear to be receptors located on GABA terminals (autoreceptors) which, when activated, inhibit GABA release [15]. Indeed, electrophysiological studies have revealed that virtually all central nervous system neurons and glia are responsive to applied GABA, even those that do not receive a GABAergic input [16].

Because of these characteristics, it is extremely difficult to draw definite conclusions about the physiological relevance of an action observed following the administration of a GABAmimetic. For example, if a particular brain region is treated with a GABA receptor agonist, it is conceivable that any resultant effect could be due to the action of the drug on physiologically relevant GABA receptors as well as on those receptors not normally exposed to this neurotransmitter agent. Moreover, a preferential effect on autoreceptors may yield data characteristic of GABAergic antagonism even though an agonist has been administered. Multiphasic or biphasic responses may be observed because of this potential for multiple actions.

Thus, it is not surprising to find that the literature is rife with conflicting results concerning the effects of GABA receptor activation. Because GABA is so widely distributed, a slight difference in the injection

site in brain could lead to activation of a different set of receptors resulting in a dramatic difference in response. Add to this the possibility that there may exist pharmacologically different subsets of GABA receptors and it becomes even more apparent why it is often difficult to reach a consensus about the functional characteristics of the GABAergic system [7, 17].

Another experimental approach used is to study the biochemical, behavioral, and physiological responses following systemic administration of GABAergic agonists or antagonists. Although it has been argued that this procedure is more physiologically relevant than studies using isolated tissue or after direct injection into discrete brain regions, there are a number of reasons why confusion may also result from data obtained using this route of administration. Among the more obvious are factors such as drug specificity, the rates of drug absorption, metabolism and excretion, the pharmacological effects of metabolites [18], and the possibility that changes in central nervous system function may be secondary to a peripheral effect of the drug. Furthermore, the effects of direct-acting GABA receptor agonists may, to some extent, not accurately represent normal GABAergic activity since these drugs are capable of activating GABA receptors not associated with GABAergic synapses. In addition, if pharmacologically different GABA receptors do exist, it is conceivable that any given drug may activate only a certain subclass of receptors, making it difficult to generalize about the overall relationship between GABA and a particular action. With regard to GABA transaminase inhibitors, functional responses to these agents might also be misleading since they increase the GABA content throughout the central nervous system including tissue, such as glia, where the GABA concentration is normally quite low. This lack of neuronal selectivity makes it possible that the response measured may be due, at least in part, to the activation of "nonspecific" GABA receptors in brain.

Theoretically then, drugs capable of selectively inhibiting neuronal high affinity GABA transport would be the best tools for defining the functional properties of this system since these agents would potentiate transmission only at GABA synapses. To date, however, all GABA uptake inhibitors appear to be co-transported by this uptake process making it possible that, even if they could penetrate the blood–brain barrier, they may ultimately act as false transmitters if administered for a sufficient period of time [6, 19]. What is needed then are potent, neuron selective inhibitors of GABA transport that cannot be accumulated and stored by these cells.

Pharmacological analysis of GABA receptor function

From the foregoing it is apparent that much of the confusion relating to the functional activity of the GABAergic system is generated by the difficulty in determining which effects observed after drug treatment are a reflection of normal GABAergic activity *per se* as opposed to those effects which are peculiar for that particular pharmacological agent. While both are important issues, to address the former it is necessary to assume a high degree of selectivity and specificity on the part of the drug being administered, an assumption which is difficult to make given the issues discussed above. In contrast, the latter question is much easier to address since no hard assumptions need be made about drug specificity in that the aim is to understand the effect of a given agent regardless of the precise mechanism of action. Thus, in the absence of a specific pharmacological tool, the only way to gain insights into the functional activity of the GABA system using a pharmacological approach is to study the effects of a variety of putative GABAergic agents having different mechanisms of action on the theory that those effects common to these diverse compounds are likely to be a reflection of normal GABAergic activity, whereas effects observed with only select agents represent actions unrelated to the synaptic GABA receptor. In the past this approach was limited due to the paucity of GABAergic compounds. With the development of a variety of GABAmimetics, however, such a research strategy is now more feasible.

Using this type of pharmacological analysis, certain generalizations can be made about GABA receptor function. For example, inhibition of GABAergic activity by drugs which either decrease GABA synthesis or block GABA receptors always results in convulsions, indicating that the GABA system is important in maintaining a normal seizure threshold. All GABAmimetics, whether GABA transaminase inhibitors or direct-acting receptor agonists, cause central nervous system depression, a decrease in spontaneous activity, and an increase in threshold for some types of seizures. While information such as this is important, it reveals little about the functional activity, or the relative contributions, of any particular GABAergic pathway in brain. This latter information is also important for gaining insights into the possible role of GABA in neuropsychiatric disorders and for more precisely predicting the therapeutic utility of GABAergic drugs.

Recent studies aimed at examining the effects of GABAmimetics on the extrapyramidal system are useful for illustrating the value of multiple drug studies for examining the functional activity of the GABAergic system in discrete brain regions. For these studies [20–24], a variety of GABAmimetics were employed and, among other things, their effects on striatal dopamine receptor binding and function were measured. Drugs used were aminooxyacetic acid (AOAA) and isonicotinic acid hydrazide, nonspecific inhibitors of GABA transaminase, and γ-acetylenic GABA (GAG), a more selective and irreversible inhibitor of this enzyme. In addition, two direct-acting GABA receptor agonists, kojic amine and THIP, were also studied and compared. As shown in Table 2, chronic treatment (2 weeks) with any one of these agents caused a significant increase in dopamine receptor binding in the rat corpus striatum. In all cases these changes in binding were due to an increase in the maximum number of binding sites with no significant change in receptor affinity. Drug-induced increases in receptor binding are normally interpreted to be indicative of the development of receptor supersensitivity. To test

whether the increase in striatal dopamine receptor binding was of any functional consequence, mice that had been treated chronically with AOAA were given various doses of apomorphine, a dopamine receptor agonist, and their responses in the form of apomorphine-induced gnawing behavior, purported to be an index of striatal dopamine receptor activity [25], were measured and compared to control animals given apomorphine alone [22]. The animals treated chronically with AOAA displayed a significant increase in sensitivity to apomorphine, indicating that the increase in dopamine receptor binding observed after all GABAmimetics was probably related to a functional alteration in this system.

This increase in dopamine receptor binding and function is reminiscent of that observed following chronic treatment with neuroleptics [26, 27]. In the case of neuroleptics, this effect is thought to be due to the prolonged blockade of dopamine receptors by these drugs. It has also been proposed that the neuroleptic-induced increase in dopamine receptor binding and function may be responsible for some of the extrapyramidal side-effects, such as tardive dyskinesia, which accompany the use of these drugs.

It is unlikely that the striatal dopamine receptor alteration observed after chronic treatment with GABA agonists is a result of a direct blockade of these receptors since, as a class, these drugs have little or no affinity for dopamine receptors in brain. Rather, a more likely explanation is that chronic GABAmimetic therapy causes a decrease in the activity of the nigrostriatal dopamine pathway, a decrease which ultimately results in the development of striatal dopamine receptor supersensitivity. Accordingly, the results of this study would seem to indicate that activation of GABA receptors within the basal ganglia leads to a decrease in dopaminergic activity and that prolonged therapy with GABAmimetics may result in the development of extrapyramidal symptoms due to this change in dopamine receptor function.

Using this approach it was also possible to study the relationships between the cholinergic, dopaminergic and GABAergic systems in the basal ganglia. For this, animals were treated chronically with atropine, a cholinergic muscarinic receptor antagonist, with either the GABA transaminase inhibitor GAG, or the direct-acting receptor agonist THIP. Co-administration of atropine completely prevented the development of dopamine receptor supersensitivity in the GAG-treated animals, but it had no effect on animals treated with THIP (Table 2). This finding suggested that the GABAergic neurons that regulate the activity of the nigrostriatal dopamine system are under cholinergic control since an anticholinergic agent is capable of blocking the effect of the GABA transaminase inhibitor, the action of which is dependent upon the firing rate of the GABA neuron. In contrast, the anticholinergic agent has no effect on the response to THIP since the action of this drug is not dependent upon the activity of GABA cells.

Systematic studies such as these can provide some insight into the functional properties of GABA receptors which may be of value in predicting clinical response as well as in understanding the fundamental relationships between various neurotransmitter systems in brain. For example, since it appears that chronic GABAmimetic treatment decreases the activity of the nigrostriatal dopamine system, it could be predicted that these drugs will be of value in treating disorders such as Huntington's disease and tardive dyskinesia, symptoms of which appear to be related to an overabundance of striatal dopaminergic activity. In contrast, GABAmimetic drugs would appear to be contraindicated in a disorder such as Parkinson's disease since this disability appears to be related, at least in part, to a deficiency in nigrostriatal dopaminergic tone. Furthermore, the results with atropine suggest that if the GABA-mediated changes in dopaminergic activity induce extrapyramidal symptoms, it may be possible to prevent or attenuate this side-effect of GABA transaminase inhibitors by the co-administration of an anticholinergic agent.

With regard to fundamental neurobiology, these studies have provided further evidence to support the notion of a functional link between the GABA, dopamine and cholinergic systems in the basal ganglia [28, 29], indicating that GABA is inhibitory on the nigrostriatal dopamine system and that the GABA neurons which influence dopaminergic activity are regulated, at least in part, by the cholinergic system. The indication of a functional relationship between the cholinergic and GABAergic systems in this brain area may also be important for understanding the mechanism of action of anticholinergics in the treatment of Parkinson's disease. That is, prior to the development of *l*-dopa, anticholinergics were the most widely used drugs for the treatment of this disorder, and their salutary effect was attributed to their ability to correct an imbalance between the cholinergic and dopaminergic systems in the basal ganglia. From the preceding data it could be speculated that this therapeutic effect of anticholinergics may be related to the interaction of this

Table 2. Effect of GABAmimetics and atropine on dopamine receptor binding in the rat corpus striatum*†

Treatment	Dose (mg/kg)	[^{3}H]Spiroperidol binding in the corpus striatum (% of control)
Aminooxyacetic acid	10	128‡
Isonicotinic acid hydrazide	20	170‡
γ-Acetylenic GABA	10	123‡
THIP	8	164‡
Kojic amine	18	188‡
γ-Acetylenic GABA	10	110
+atropine	5	
THIP + atropine	8 + 5	173‡
Atropine	5	104

* Male Sprague–Dawley rats were injected i.p. twice daily at the doses indicated, except for aminooxyacetic acid which was injected once daily. On day 15, 24 hr after the last dose, the animals were killed, and striatal dopamine receptor binding was analyzed using [^{3}H]spiroperidol as a ligand [22]. Each value is the mean of ten to fifteen separate experiments. [^{3}H]Spiroperidol binding in the control animals was 157 ± 7 fmoles/mg protein.

† Adapted from Refs. 20, 22 and 24.

‡ $P < 0.05$, two-tailed Student's *t*-test.

system with the GABA pathways in this brain area. Since the GABAergic neurons that exert an inhibitory influence on the nigrostriatal dopamine pathway appear to be under cholinergic control, blockade of this cholinergic system reduces the GABAergic activity which, in turn, disinhibits the dopaminergic system. In this way the dopaminergic pathway is activated, relieving some of the symptoms of this disorder.

Another area that has been the subject of systematic investigation has been the regulation of prolactin release by the GABAergic system [30–33]. Various types of *in vivo* and *in vitro* experiments have been performed using a variety of GABA receptor agonists and antagonists to characterize this interaction. As a result of these studies, it now seems apparent that prolactin secretion is regulated by both central and peripheral GABA receptors, with activation of the central nervous system receptors inducing an increase in prolactin release and stimulation of receptors on the anterior pituitary inhibiting the release of this hormone. From a clinical standpoint these results are intriguing since they indicate that activation of anterior pituitary GABA receptors may counteract the prolactin elevation induced by neuroleptic drugs. Accordingly, administration of a GABA receptor agonist that does not penetrate the blood–brain barrier may be useful for blocking the prolactin elevating effect of neuroleptics.

There also appears to be strong evidence for a functional link between GABA receptors and the pharmacological actions of the benzodiazepines [34, 35]. Thus, based on earlier electrophysiological studies, it has been suspected for some time that the benzodiazepines may act, at least in part, by facilitating GABAergic transmission, since these drugs are known to enhance pre-synaptic inhibition in the spinal cord and dorsal column nuclei and post-synaptic inhibition in a variety of brain areas including the cerebral and cerebellar cortex and hippocampus [36]. Furthermore, benzodiazepines have been shown to facilitate behavioral responses thought to be mediated by GABA [37]. It has only been recently, however, that biochemical evidence has been obtained to support this hypothesis.

Thus, receptor binding studies have revealed that GABA receptor affinity is regulated, to some extent, by the presence of an endogenous substance, termed "GABA-modulin", which is located on or near the recognition site for this neurotransmitter [34]. Reports have indicated that the benzodiazepines may act by removing or displacing this endogenous substance which, when absent, leaves a GABA receptor with a substantially higher affinity for the neurotransmitter, thereby facilitating GABAergic transmission. Because of these findings it has been proposed that some, if not all, of the pharmacological actions of the benzodiazepines may be mediated by an activation of GABAergic transmission. If this hypothesis is correct, it would be further proof for the functional importance of GABA in controlling seizure activity and anxiety.

Thus, there is a substantial amount of evidence suggesting that the GABAergic system is important in controlling seizure activity, extrapyramidal function, prolactin release, and possibly anxiety. Other functions have been proposed for the GABA receptor system, though the biological and clinical importance of these findings are as yet uncertain. Included among these are the indications that GABA receptor activation may modify aggression, feeding behavior, satiety, and pain [38–40]. GABAergic drugs also appear to modify blood pressure and heart rate in a variety of species [41–43]. GABA agonists have also been reported to increase the release of growth hormone and gonadotrophin and to decrease plasma levels of thyrotropin [30, 44]. These data, coupled with what is known about the relationship between GABA and prolactin secretion, indicate that the GABA system may be important in controlling various aspects of adenohypophyseal hormone secretion. Furthermore, as in the basal ganglia, the GABA system has been reported to regulate dopaminergic activity in limbic areas, suggesting that alterations in GABAergic transmission may play some role in the etiology of schizophrenia [45].

Clinical correlations

Clinical trials with GABAergic compounds are another means to assess the functional characteristics of this system. In addition to providing practical information about the therapeutic utility of GABA-mimetic drugs, such studies are also useful for testing hypotheses derived from animal data. Unfortunately, however, few double-blind studies have been performed. Thus, although positive clinical findings have been reported, more extensive examination will be necessary to firmly establish a role for GABA-mimetic drugs in the treatment of neuropsychiatric disorders. Nevertheless, it is of interest to comment briefly on some of the reports concerning the effects of GABAmimetics in man in an attempt to determine whether the results obtained in laboratory studies have any relevance to the clinical situation.

As described above, laboratory studies have suggested that GABAmimetics may be of value in treating Huntington's disease and tardive dyskinesia. Indeed, clinical reports have indicated that muscimol is effective in the treatment of tardive dyskinesia, and SL-76002 appears to be of value in Huntington's disease [9, 46], suggesting that in man, as well as in the experimental animal, the GABAergic system may exert an inhibitory influence on the nigrostriatal dopamine system.

Similarly, the proposition that activation of GABA receptors may be of benefit in treating seizure disorders appears to be substantiated by recent clinical studies with SL-76002. That is, a preliminary study indicated that this GABAmimetic substantially reduced the number of epileptic attacks in patients suffering from complex partial or generalized seizures. Of significance is the fact that these positive results were obtained in individuals found to be resistant to standard antiepileptic medication [9]. There have also been anecdotal reports that this compound elevates mood and reduces hyperactivity and aggressive behavior.

With regard to the endocrine system, administration of muscimol to patients resulted in a significant, dose-dependent, elevation in the circulating levels of prolactin and growth hormone, supporting the

contention that GABA functions as a regulator of hormone release [47].

Less positive results have been found in studies with schizophrenic patients. No significant improvement was observed after treatment with SL-76002, and muscimol has also been reported to be ineffective in this disorder [9, 48]. No clinical studies have yet been reported on the anxiolytic or analgesic activity of GABAmimetics in man.

At the present time clinical trials are continuing with SL-76002 and have been initiated with THIP and GAG. Because of this, it seems likely that more definitive information about the functional activity of the GABAergic system in man will be forthcoming in the near future.

Conclusions

The recent development of a number of GABA-mimetic compounds has made it possible to undertake a series of systematic studies aimed at defining the functional consequences of GABA receptor activation. However, the ubiquitous distribution of the GABA system, the existence of nonspecific as well as specific GABA receptors, and the possibility of pharmacologically distinct subtypes of receptors make it difficult to determine which responses are a reflection of normal GABAergic activity. Even with these limitations, however, sufficient data have been obtained to make it appear likely that the GABAergic system plays an important role in regulating seizure threshold, the extrapyramidal system, and adenohypophyseal hormone secretion. Furthermore, GABA may also be an important mediator of the anxiolytic action of benzodiazepines. Preliminary clinical trials with GABAmimetics have indicated that these drugs may be useful in treating epilepsy, tardive dyskinesia, and Huntington's disease, findings which support hypotheses made on the basis of functional studies conducted with laboratory animals. More specific compounds for manipulating this system are needed, however, to better define the biological function of the GABA system and to more firmly establish its importance in the etiology and treatment of clinical disorders.

Acknowledgements—Preparation of this manuscript was made possible, in part, by grants from Merck, Sharp & Dohme, Mead Johnson, and the United States Public Health Service (NS-13803 and NS-00335).

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