An Overview

LIGAND-BINDING STUDIES ON GABA RECEPTORS—RELATION TO PHYSIOLOGY AND BEHAVIOR*

F. V. DEFEOUDIS**

Université Louis Pasteur
67085 Strasbourg Cedex
France

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Some studies that have been conducted with ligand-binding methods support the contention that activation of cerebral GABA-receptors is involved in the control of certain behaviors. Further study of the changes in GABA-receptors that are associated with altered physiology and behavior in experimental animals and in man might lead to the development of new therapies for certain neuropsychiatric, cardiovascular, and endocrinological disorders.

INTRODUCTION

The initial studies of "GABA-binding" were conducted by Elliott and van Gelder (14) and by Sano and Roberts (27). This binding of GABA was shown to occur by a Na+-dependent, non-enzymatic mechanism and was considered to be involved in GABA uptake by brain tissue. More recently, Na+-independent GABA binding processes have been demonstrated (16, 38). Such Na+-independent GABA binding might represent interactions of GABA and some of its membrane receptors. Some recent studies which indicate that data obtained with the ligand-binding technique might be related to certain animal behaviors, or to certain neuropsychiatric disorders of man, will be discussed here. Na+-independent GABA (or

* Dedicated to K. A. C. Elliott on his 80th birthday.
** Director of Scientific Projects, Institut Henri Beaufour, 17 Avenue Descartes, 92350 Le Plessis Robinson, France.
GABA-agonist) binding, which occurs exclusively in neuronal elements (12), was determined, except where otherwise indicated.

**Convulsions and Epilepsy**

In vivo studies with GABA-agonists and GABA-antagonists have revealed that GABA-receptors and associated Cl−-ionophores might be involved in some convulsive states. In support of this notion, recent in vitro studies have revealed that several anticonvulsant agents (e.g., benzodiazepines and barbiturates) might act by enhancing GABA binding to its receptors (9). Furthermore, electroshock-induced seizures in the rat have been shown to enhance [3H]GABA binding to synaptic membranes prepared from cerebral cortex (26), and the density (maximal binding capacity; $B_{\text{max}}$) of high-affinity [3H]GABA binding sites is decreased, but their affinity is increased (decreased binding or dissociation constant; $K_B$) in audiogenic mice, as compared to seizure-resistant mice (34).

Studies performed on membranes prepared from cerebral cortex tissue from patients who had undergone surgical resection for temporal lobe epilepsy have indicated that when the epilepsy was associated with the presence of a tumor the affinity of [3H]GABA binding was decreased (21).

**Extrapyramidal Functions**

Unilateral injections of the rigid glutamate-analogue kainate (about 2 μg) into the striata of rats produced a degeneration of "GABA-ergic" interneurones while not affecting axons (30). From 2–3 weeks after such injections, high-affinity [3H]GABA binding in particles prepared from the injected striatum was about 3-fold greater than in the contralateral striatum, and this effect was related to an increase in binding affinity (29). Also, as ablation of the dopaminergic nigrostriatal pathway (by intranigral injection of 6-hydroxydopamine) prior to sacrifice or kainate lesion produced a decrease in [3H]GABA binding in the ipsilateral striatum and attenuated the increase in [3H]GABA binding that was produced by kainate lesion, denervation supersensitivity might exist for rat striatal GABA-receptors that are involved in the inhibitory strionigral GABA-ergic pathway (29). [3H]GABA binding was also increased in the substantia nigra of the rat after unilateral injection of 2.5 μg of kainate into the striatum (37). $B_{\text{max}}$ values for both high- and low-affinity [3H]GABA binding sites were increased in particles prepared from the lesioned side, but no changes occurred in $K_B$. Receptor supersensitivity, detected by rotational responses following unilateral intranigral injections of muscimol, was correlated with such increases in [3H]GABA binding.