

Appendix A14.11

GABAergic System

Gamma aminobutyric acid (GABA)—the major inhibitory neurotransmitter system in the CNS—is one of the most abundant neurotransmitters, and GABA-containing neurons are located in virtually every area of the brain. Unlike the monoamines, GABA concentrations in the brain are high and in the order of micromoles per milligrams (~1000 fold higher than monoamines) (Nestler et al., 2001). GABA is produced when glucose is converted to α -ketoglutarate which is then transaminated to glutamate by GABA α -oxoglutarate transaminase (GABA-T). Glutamic acid is decarboxylated by glutamic acid decarboxylase (GAD) which leads to the formation of GABA. Indeed, this neurotransmitter and rate-limiting enzyme are localized together in the brain and at approximately the same concentration. Catabolism of GABA occurs via GABA-T, which is also important in the synthesis of this transmitter. The function of this dual role enzyme becomes apparent when placed into the context of its role in the metabolic process. GABA-T converts GABA to succinic acid and subsequent removal of the amino group yields α -ketoglutarate. Thus, α -ketoglutarate is able to be utilized by GABA-T in GABA biosynthesis as mentioned above. This process is called the GABA shunt and maintains a steady GABA supply in the brain. As with the monoamines, the major mechanism by which the effects of GABA are terminated in the synaptic cleft is by reuptake through GABA transporters. The GABA transporters have a high affinity for GABA and mediate their reuptake via a Na^+ and Cl^- gradient.

Table A14.11a
Controlled Baseline Studies of CSF GABA in Depression and Mania

Study Comments	Patients N				CV	D as		M as	
	C	D	M	C		% of C	S	% of C	S
Med-Free at least 1 week									
Gerner & Hare, D < M, p < .01 1981 BP-UP	29	24	6	34	183.2	73	p < .01	102	NS
differences									no
Kasael et al., UP > BP, NS 1982	24	13		41	137.5	70	p < .05		

Gerner et al., D<M, $p<.01$ 1984	36	37	12	14	190	74	$p<.05$	90	NS
Med-Free at least 2 weeks									
Gold et. al., UP<BP, NS 1980	20	15		53	218	56	$p<.01$		
Berrettini et al., only, some 1986	34	15		35	127	102	NS		BPs
lithium treated Joffe et al, 1986 ^a	41	42	8	17	233	88	NS	83	N
Roy et al ,1991	20	25 b		29	140	87	NS		

Control group mean metabolite levels in pmol/ml. Mean levels for depressed and manic patients expressed as a percentage of controls. Three separate assay techniques were used: Kasa et al, Gerner and Hare, and Joffe et al. used only fluorometric chromatography; Gold et al. and Berrenini et al. used only radioreceptor binding; and Gerner et al., used atomic absorption spectrophotometry. Gerner and Hare and JoHe et al. also took samples from the 15-28 ml and neither found D vs C differences.

C = controls, D = depressed, M . manic, CV = coefficient of variation = control group standard deviation divided by control mean, expressed as a percentage, S = significance of difference

^aReanalysis of Post et al.,1980b

b 7 of them were bipolar patients. GABA value levels for patients 123.5+-40.6

GABA Receptors

There are two major types of well-characterized GABA receptors, GABA_A receptors and GABA_B receptors, and most neurons in the CNS possess at least one subtype. The GABA_A receptor is the more prevalent of the two in the mammalian CNS, and as a result has been extensively studied and characterized. The GABA_A receptor contains an integral transmembrane chloride channel, which is opened upon receptor activation, generally resulting in hyperpolarization of the neuron (i.e., suppressing excitability). The GABA receptor is a heteropentameric glycoprotein of approximately 275 kD composed of a combination of multiple polypeptide subunits. The GABA-A receptor displays enormous heterogeneity, being composed of a combination of 5 classes of polypeptide subunits ($\alpha, \beta, \gamma, \delta, \epsilon$), of which there are at least 18 subtypes. The various receptors display variation in functional pharmacology, hinting at the multiple, finely-tuned roles that inhibitory neurotransmission plays in brain function.

It is now well established that benzodiazepines (BDZs) function by binding to a potentiator site on the GABA_A receptor, increasing the amplitude and duration of inhibitory postsynaptic currents in response to GABA binding. The co-expression of additional γ subunits is believed to be necessary for the potentiation of GABA mediated responses by benzodiazepines. In addition to benzodiazepines, barbiturates and ethanol are also believed to exert many of their effects by potentiating the opening of the GABA_A receptor chloride channel. As discussed, the GABA_A receptors have a widespread distribution in the brain, and the majority of GABA_A receptors in the brain are targets of the currently available BDZs. For this reason, there has been considerable interest in determining if the desirable and undesirable effects of BDZs can be differentiated based on the presence of different subunit composition. Much of the work has used gene knockout technology; thus, mutation of the BDZ-binding site of the alpha-1 subunit in mice blocks the sedative, anticonvulsive, and amnesic, but not the anxiolytic, effects of diazepam (see Mohler 2002, Gould et al., 2003). In contrast, the alpha-2 subunit (expressed highly in the cortex and hippocampus) is necessary for diazepam anxiolysis and myorelaxation. Thus, there is now optimism that an alpha-2 selective ligand will soon provide effective, acute treatment of anxiety disorders without the unfavorable side-effects profile of current BDZs. A compound with this preferential affinity has already been demonstrated to exert fewer sedative/depressant effects than diazepam in rat behavioral studies (see Mohler 2002, Gould et al., 2003).

The phosphorylation of GABA_A receptors is another mechanism by which this receptor complex can be regulated in function and expression. In this context, it is noteworthy that recent studies have shown that knockout mice deficient in PKC ϵ isoforms show reduced anxiety and alcohol consumption, and an enhanced response to effects of BDZs (discussed in Gould et al., 2003).

The GABA_B receptors are coupled to Gi and Go, and thereby regulate adenylyl cyclase activity (generally inhibit), K⁺ channels (open) and Ca⁺⁺ channels (close). GABA_B receptors serve the functions of autoreceptors, but are also found abundantly postsynaptically on non-GABAergic neurons. Of interest, there is mounting evidence that receptor dimerization may be required for the activation of GABA_B and *possibly* other G-protein coupled receptors; while receptor dimerization has long been known to occur for growth factor and Jak/Stat receptors, this was not expected for GPCRs. However, recent studies have reported that co-expression of two GABA_B receptor subunits -- the GABA_B receptor subunit 1 (GABA_BR1) and GABA_B receptor subunit 2 (GABA_BR2) -- is necessary to the formation of a functional GABA_B receptor. Some data suggests that GABA_BR2 may be necessary for proper protein folding of the GABA_BR1 (acting as a molecular chaperone) in the endoplasmic reticulum, but this remains to be definitively

established. Support for the physiological relevance of this dimerization comes from studies showing that the GABA_BR1 and GABA_BR2 subunits can be coimmunoprecipitated in rat cortical membrane preparations (Kaupmann et al., 1997) – thus the dimerization is not simply an in vitro phenomenon.

References

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