Theoretical Review

ROLE OF GABA IN ANXIETY AND DEPRESSION

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This review assesses the parallel data on the role of gamma-aminobutyric acid (GABA) in depression and anxiety. We review historical and new data from both animal and human experimentation which have helped define the key role for this transmitter in both these mental pathologies. By exploring the overlap in these conditions in terms of GABAergic neurochemistry, neurogenetics, brain circuitry, and pharmacology, we develop a theory that the two conditions are intrinsically interrelated. The role of GABAergic agents in demonstrating this interrelationship and in pointing the way to future research is discussed. Depression Anxiety 24:495–517, 2007. Published 2006 Wiley-Liss, Inc.[†]

INTRODUCTION

STRESS, ANXIETY, AND DEPRESSION

Stress plays the main role in the pathogenesis of many mental disorders [Lopez et al., 1999], with anxiety and depression being the most common outcomes of stress in humans and animals [Nutt, 2000, 2001]. Anxiety is a psychiatric disorder associated with excessive and pointless worries, motor tension, and fatigue [Nutt, 2005]. Several different subtypes of anxiety include general anxiety disorder, panic disorder, social anxiety, agoraphobia, posttraumatic stress disorder, and obsessive-compulsive disorder [Clement and Chapouthier, 1998; Nutt, 2005]. Depression is a complex heterogeneous disorder with a wide spectrum of anomalies (such as depressed mood, anhedonia, sleep disorders, fatigue and loss of energy, lack of concentration, low self-esteem, negative thinking, and suicidality) and unclear pathogenesis [Cryan et al., 2002; Wong and Licinio, 2004].

Being extremely debilitating, multifaceted psychiatric illnesses, anxiety and depression have a major impact on the quality of life [Rapaport et al., 2005]. In addition, the prevalence of both disorders is on the increase, especially in the young, and they show considerable overlapping and co-occurrence [Freeman et al., 2002; Nutt, 2005]. Many symptoms of anxiety and depression are similar, and mild anxiety can be difficult to distinguish from mild depression. Depression is common in anxiety patients and anxiety is often

reported in depressed patients, both being predictors of poor outcome [Nutt et al., 2002].

Over the past decades there has been intensive study of a variety of neurobiological mechanisms that underlie depression and anxiety [Clement and Chapouthier, 1998; Sundstrom-Poromaa et al., 2003]. Unipolar disorders have been reported to be more frequently comorbid with anxiety than bipolar disorders, suggesting that anxiety and major depression have a common genetic origin [in Nutt, 2001]. Numerous data indicate that generalized anxiety and depression share their genetic determinants but have partly different environmental determinants [Kendler

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et al., 1986, 1987; Roy et al., 1995]. The fact that the symptoms of anxiety and depression may respond to the same treatments support the possibility of a common neurobiological dysfunction, although the exact neurobiological mechanisms behind anxiety and depression have not yet been fully elucidated [Nutt et al., 2002]. It is now becoming recognized that multidisciplinary approaches are necessary to understand the nature of these disorders, and without a knowledge of both clinical and biological aspects of anxiety and depression, it is impossible to offer effective treatment strategies.

Dysfunction of the central gamma-aminobutyric (GABA) system has long been associated with anxiety spectrum disorders [Nutt and Malizia, 2001; Lydiard, 2003; Nemeroff, 2003]. In both human and animal studies, positive modulators of GABA receptors generally possess anxiolytic activity, while negative modulators produce anxiogenic-like effects [Kalueff

and Nutt, 1996; Nutt, 2001]. Consistent with this, various GABA analogs and agents affecting transmitter metabolism to enhance GABAergic tone (e.g., valproate, vigabatrin, and tiagabine) have also been reported to exert anxiolytic effects [Lang and de Angelis, 2003; Nemeroff, 2003; Rosenthal, 2003; Stahl, 2004].

For years, a focus on catecholaminergic mechanisms of depression dominated biological psychiatry. However, a large body of clinical and preclinical literature is now available to support the role of GABA in mood disorders (Tables 1, 2). As such, it is now timely to consider the GABAergic contribution not only to anxiety but also depression disorders [Krystal et al., 2002; Chang et al., 2003; Leung and Xue, 2003]. Here we incorporate recent findings on the GABAergic system in anxiety and depression in order to discuss GABAergic alterations in both psychopathologies and outline possible directions for the search for novel effective medications.

TABLE 1. Effects on depression produced by different GABAergic anxiolytic drugs

| Drugs | Effects on depression | | Depression-like behaviors in animal models (see Table 4) |
	Clinical data	Key references	
GABA analogs and agents affecting transmitter metabolism			
Valproate	↓	Gilmer, 2001; Gajwani et al., 2005[a]	↓
Amino-oxyacetic acid	?		↓
Vigabatrin	↓	Ring et al., 1993; Besag et al., 2001[b]	?
Gabapentin	↓	Ghaemi et al., 1998; Altshuler et al., 1999; Obrocea et al., 2002; Fong et al., 2003	?
Tiagabine	↓	Post et al., 1998; Shelton, 2003	?
Beta-phenyl-GABA	↓	Lapin, 2001	↓
GABA agonists			
GABA, muscimol, progabide[c]	?	Lloyd et al., 1983; Bartholini, 1984	↓
Benzodiazepines	↓	Lemoine et al., 1991; Birkenhager et al., 1995; Petty et al., 1995; Wang and Ketter, 2005	0, ↓
Ethanol	↓	O'Sullivan, 1984; Khisti et al., 2002[d]	↓
Neurosteroid agonists	↓		↓
Allopregnanolone, progesterone[e]		Dubrovsky, 2005; Eser et al., 2006a,b	

↓ means reduction of depression. 0 = no effects, ? = no data.
[a]Also produces mood stabilizing effects [Nestler et al., 2002].
[b]Causes the opposite effect after long-term treatment.
[c]Progabide has agonistic properties at both GABA-A and GABA-B receptors.
[d]Antidepressant action of ethanol in humans is known only for acute mild doses; chronic ethanol consumption (alcoholism) decreases ethanol AD action and is associated with increased depression and anxiety [Enoch, 2003].
[e]Note that progesterone is not a direct modulator of GABA-A receptors, and acts via own progesterone receptors or as an antagonist to brain sigma and nicotinic receptors [reviewed in Bullock et al., 1997; Maurice, 2004]. Recent studies [Reddy et al., 2005] found that anxiolytic effects of progesterone are preserved in mutant mice lacking progesterone receptors due to its conversion to allopregnanolone, suggesting that its behavioral effects are due to allopregnanolone modulation of GABA-A receptors.

TABLE 2. Summary of the effects of depression on GABAergic system

Clinical data	Preclinical data
Reduced level of GABA in plasma [Petty et al., 1990, 1998], CSF and brain [Sundman-Eriksson and Alard, 2002; Sanacora et al., 1999, 2000; Kugaya et al., 2003; Chang et al., 2003]. Reduction in the number of GABA neurons in orbitofrontal cortex of depressed patients [Rajkowska et al., 1999]. Lower cortical GABA in postpartum depression [Epperson et al., 2006].	Reduced GABA-activated chloride influx in LH model in rats [Drugan et al., 1989]. Decreased GABA release in hippocampus in LH model [Petty and Sherman, 1981; Shiah and Yatham, 1998] and in cortex, hippocampus, nucleus accumbens and brainstem in FST in rats and mice [Borsini et al., 1988; Gomez et al., 2003; Briones-Aranda et al., 2005]. Increased brain GABA-A receptor density in OB and LH models in rats [Dennis et al., 1984; Kram et al., 2000].
Reduced plasma and CSF levels of GABA-active steroid agonists; increases concentration of steroid antagonists [George et al., 1994; see also Rupprecht, 2003; Spivak, 2000; and Lydiard, 2003].[a]	Reduced cortex GABA-active steroid allopregnanolone after social isolation in mice [see Rupprecht, 2003 for details]. Region-specific dysregulation of allopregnanolone in OB in rats [Uzunova et al., 2003, 2004].
Reduced benzodiazepine binding in frontal and orbitotemporal cortex in a patient with treatment-resistant depression and anxiety [Kosel et al., 2004]. Increased CSF concentration of DBI [Barbaccia et al., 1986; Roy, 1991; Sandford et al., 2000], including anxiety/depressive patients [Guidotti, 1991; but see George et al., 1994] and suicide depression victims [Rochet et al., 1998].	Decreased benzodiazepine binding after FST in rat hypothalamus and amygdala and in chronic stress model in frontal cortex, hippocampus, and hypothalamus [Medina et al., 1983; Briones-Aranda et al., 2005]. Increased brain DBI expression after long-term stress in mice [Katsura et al., 2002; reversed by antidepressant treatment].[b]
	Increased muscimol binding in rats not susceptible to behavioral despair [Drugan et al., 1993].

FST, forced swim (Porsolt's) test; TST, tail suspension test; LH, learned helplessness model; OB, olfactory bulbectomy; DBI, diazepam-binding inhibitor; CSF, cerebrospinal fluid.
[a]See also similar data in Daly et al. [2001]; Reddy [2003]; Vaiva et al. [2003] for premenstrual and posttraumatic stress syndromes.
[b]See, however, Dong et al. [1999] reporting reduced DBI mRNA in mouse hypothalamus after social isolation stress.

ANIMAL MODELS OF ANXIETY AND DEPRESSION

The present article aims to present a balanced review where clinical findings will be compared with animal experimentation data. The growing number of experimental models is now extensively used to search for novel therapeutic agents and dissect the neurobiological mechanisms of brain pathogenesis [Geyer and Markou, 1995; McKinney, 2004]. But can we model human anxiety and depression in animals? There are several traditional models of anxiety, including paradigms based on exploration (open field, holeboard, elevated plus maze, light-dark, social interaction, mirror chamber) and conditioned or unconditioned threat responses [reviewed in Rodgers, 1997; Crawley, 1999, 2000; Flint, 2002, 2003; Carobrez and Bertoglio, 2005]. The most popular experimental models of depression include "despair" paradigms (such as Porsolt's forced swim [FST], Steru's tail suspension [TST] tests, and learned helplessness [LH]), as well as olfactory bulbectomy (OB), maternal/social deprivation, and "anhedonic" chronic mild stress (CMS) [see Ho et al., 2002; Nestler et al., 2002; Cryan and Mombereau, 2004; Cryan et al., 2005; Cryan and Holmes, 2005, for details]. There are, however, problems with these models, which have to be critically discussed before claiming parallels between animal and human brain disorders.

First, since many aspects of human anxiety and depression psychopathology are poorly understood today, the important question of what exactly to model remains open [see, e.g., Argyropoulos and Nutt, 1997]. Clearly, there are certain features of human behavior and cognition that cannot be fully reproduced in animals, thus contributing to the problem of objective difficulties with translating human symptoms into animal tests [Crawley, 2000; Wong and Licinio, 2004; Cryan and Holmes, 2005]. In addition, animal paradigms usually fail to reproduce complex multi-syndromal human disorders, may show unwanted selectivity to particular neuromediatory systems, or have questionable ability to detect novel compounds with unknown mechanism(s) of action [see Belzung, 2001; Flint, 2003; Cryan and Mombereau, 2004; Cryan et al., 2005, for discussion]. Other problems include conflicting timecourse results (e.g., acute antidepressant effects in some animal models do not match delayed action of these drugs in humans); model's oversensitivity to external (environmental, epigenetic) or internal (genetic) factors; as well as poor reproducibility (e.g., CMS) even within the same laboratory [see Bai et al., 2001; Cryan et al., 2002; Cryan and Mombereau, 2004, for details]. In addition, some of these models may lack specificity [Schechter and Chance, 1979; e.g., failing to discriminate between anxiolytics and antidepressants: Borsini et al., 2002; Rupniak, 2003], while others, being specific, do not target clinically important comorbidity aspects [Crowley and Lucki, 2005]. Overall, this raises the problem of *mimicking* (at a behavioral phenocopy level) vs. *modeling* a "true" psychiatric state, and the problem of behavioral

vs. physiological vs. cognitive components of pathogenesis [Battaglia and Ogliari, 2005]. Also, there should be, but not always recognized, a clear distinction between a model (simulating the disorder as a syndrome) and a test (relatively simple assay targeting specific features of this disorder) [Rupniak, 2003; Crowley and Lucki, 2005; Urani et al., 2005]. Finally, there is a great need for the creation of a new generation of anxiety and depression tests based principally on new theories and approaches [Cryan et al., 2002; Cryan and Mombereau, 2004; Cryan and Holmes, 2005].

Nevertheless, despite all these caveats, animal tests of anxiety and depression have proven to be crucial for biomedical research, including fast high-throughput testing of anxiolytic and antidepressant drugs [Flint, 2003; Wong and Licinio, 2004], assessment of behavioral phenotypes of mutant or transgenic animals [Crawley, 1999, 2000; Flint, 2002; Urani et al., 2005], testing neurobiological hypotheses [Geyer and Markou, 1995], or finding candidate genes for human behavioral disorders [Crowley and Lucki, 2005]. Thus, understanding the potential benefits and weaknesses of animal models may allow us to obtain valid animal experimentation data to parallel and/or complement the available clinical findings, leading to new, effective therapies for anxiety and depression.

GABAERGIC MECHANISMS IN ANXIETY AND DEPRESSION

GABA AND ITS RECEPTORS

GABA is the primary mediator of inhibitory transmission in the mammalian central nervous system [Sieghart, 1995; Sieghart et al., 1999]. It has complex interactions with other neurotransmitter systems and acts through ionotropic A and metabotropic B type receptors, which play important roles in the brain and are a target for a variety of endogenous and exogenous modulators [Nutt and Malizia, 2001; Korpi et al., 2002; Boehm et al., 2004; Mombereau et al., 2004]. GABA-A receptors inhibit neurons and are crucial to controlling brain excitability [Korpi et al., 2002; Chang et al., 2003]. GABA-A receptors are ligand-gated ion channels composed of five subunits from eight families: α (1–6), β (1–3), γ (1–3), δ, ε, π, θ, and ρ (1–3) [Marowsky et al., 2004; Korpi and Sinkkonen, 2006]. The most abundant composition of GABA-A receptor is $2\alpha,2\beta,1\gamma$ [Sieghart, 1995; Sieghart et al., 1999] such as $\alpha1\beta2\gamma2$ (~40% of all GABA-A receptors throughout the brain) or $\alpha2\beta3\gamma2$ (common in the limbic system, cerebral cortex, and striatum, ~20% of all GABA-A receptors) [Rosahl, 2003; Mohler et al., 2004]. Binding of GABA opens up a Cl^- channel, which is part of the protein structure. GABA-A receptors contain binding sites for many positive modulators including barbiturates, benzodiazepines, steroids, and ethanol [Sieghart et al., 1999; Korpi et al., 2002; Olsen et al., 2004].

In addition, these include GABA-A antagonists, neurosteroid antagonists, benzodiazepine inverse agonists, and chloride channel blockers that are negative modulators of GABA-A receptors [reviewed in Sieghart et al., 1995; Belelli and Lambert, 2005; Dubrovsky, 2005].

Though less well understood, GABA-B receptors are thought to modulate the generation of excitatory postsynaptic potentials and long-term potentiation [Chang et al., 2003]. They are formed from two subunits, B1 and B2, each with seven transmembrane-spanning elements that come together to form heterodimers in which both subunits are necessary for the receptor to be functional [Mombereau et al., 2004, 2005]. The B1 subunit binds ligands within its extracellular N-terminus, while the B2 subunit is responsible for receptor trafficking and its interaction with cognate G-protein [reviewed in Ong and Kerr, 2005]. GABA-B receptors are found both presynaptically and postsynaptically. Both GABA-A and -B receptors are shown to be involved in the regulation of many normal and pathological brain mechanisms including sleep, memory, epilepsy, and various emotions [Kalueff and Nutt, 1996; Kalueff, 1997; Mihalek et al., 1999; Chapouthier and Venault, 2002; Brambilla et al., 2003; Leung and Xue, 2003; Vaiva et al., 2004; Cryan and Kaupmann, 2005].

HISTORICAL BACKGROUND AND RECENT FINDINGS

An important role of GABA in mood disorders was first postulated by Emrich et al. [1980], and over the last decades much data has emerged to support the GABAergic theory of depression [Borsini et al., 1988; Lloyd et al., 1985, 1989; Petty, 1995; Shiah and Yatham, 1998]. There are several good recent articles that discuss clinical and experimental data linking GABA to depression [Tunnicliff and Malatunska, 2003; Brambilla et al., 2003; Leung and Xue, 2003]. Briefly, depression is often associated with decreased GABAergic function, while various antidepressant (AD) manipulations tend to increase it; low GABA function is proposed to be an inherited biological marker of vulnerability for depression; positive modulators of GABA-A receptors can have AD actions, while GABA-A negative modulators often produce depression. There is a large body of evidence to confirm that GABAergic anxiolytic drugs do produce AD effects in patients (Table 1). Unfortunately, there is little clinical data on the effects produced by GABAergic anxiogenic drugs (such as GABA-A antagonists, neurosteroid antagonists, benzodiazepine inverse agonists, as well as the chloride channel blockers pentylenetetrazole and picrotoxin), although some clinical cases with depressed features have been noted where pentylenetetrazole was used to activate epileptic foci [see Rodin, 1958, 1970, for review]. There is more evidence for a role of GABA in depression (see Table 2 for details).

In line with clinical observations, there are animal studies also. The pioneering studies of Petty and Sherman [1981] were first to link the GABAergic system to animal depression. Since this time, in many studies a GABA deficit, paralleled by decreased GABA-A receptor activity, was suggested to be a functional correlate of depression [Belozertseva and Andreev, 1997; Kram et al., 2000] (see also Table 2), while AD treatment activated GABAergic functions both in animals and humans (Table 3). In line with GABAergic hypothesis of depression, GABA mimetics were found to possess AD-like properties, while GABA antagonists increase depression in the above animal models [Raghavendra et al., 2000]. Tables 4 and 5 represent a detailed summary of the effects that different GABAergic drugs demonstrate in currently available animal models of depression. Analysis of data presented in Tables 1, 3, and 4 shows that activation of the GABAergic system has both antianxiety and antidepressant effects in animals and humans. In contrast, decreased GABAergic activity consistently correlates with anxiety and depression (Tables 2, 5). Together, this clearly demonstrates the key role that GABA plays in both psychopathologies and indicates that drugs affecting GABA-A receptors may be useful in the treatment of both anxiety and depression.

In contrast to GABA-A receptors (Tables 1,2,3,4,5), the potential role of GABA-B receptors in anxiety and depression is far less understood [Lloyd et al., 1985;

Nakagawa et al., 1996a; Sand et al., 2000; Mombereau et al., 2004, 2005; Cryan and Kaupmann, 2005; Pilc and Nowak, 2005]. For example, the GABA-B agonist baclofen was found to be ineffective in several animal anxiety tests [Umezu, 1999; Dalvi and Rodgers, 1996; Zarrindast et al., 2001], but revealed anxiolytic-like properties (similar to GABA-A agonists) in several other studies [File et al., 1991, 1992; Shephard et al., 1992; Bueno et al., 2005a]. Baclofen was ineffective in the FST depression test, increased learned helplessness, and attenuated the effects of ADs in rats [Nakagawa et al., 1996a,b], but reduced depressiveness and reversed reserpine effects in the FST in mice [Aley and Kulkarni, 1989; see similar data in rats in Hilakivi et al., 1988]. In humans, baclofen showed no clinical effects in one study [Jamous et al., 1994], but exerted anxiolytic effects in posttraumatic patients [Hinderer, 1990] and was effective in treating patients with posttraumatic stress disorder with comorbid anxiety or depression [Drake et al., 2003]. It was also effective on anxiety and depression in alcoholic patients [Krupitskii et al., 1994] but has been reported to worsen depression in several other clinical cases [Post et al., 1991]. Taken together with recent genetic data, reporting increased anxiety and reduced depression-like behavior in mutant mice lacking GABA-B receptor subunits [Cryan and Kaupmann, 2005; Mombereau et al., 2004, 2005], it seems that (unlike GABA-A receptors) the GABA-B receptor system may differen-

TABLE 3. Summary of the effects of antidepressant treatments on GABAergic system

Clinical data	Preclinical data
Increased cortex GABA [Sanacora et al., 2002] in depressed patients after SSRI treatments [see Rupprecht, 2003; Khisti et al., 2000; Uzunova et al., 2003, for reviews].	Elevated hippocampal GABA release after AD treatments in LH model in rats [Petty and Sherman, 1981; Kram et al., 2000]. Elevated cortical GABA after AD treatment in rats [Yang and Shen, 2005]. Increased brainstem GABA-A $\alpha1$, $\alpha3$, $\beta1$, $\beta2$ and $\gamma2$ subunits mRNA levels [Tanay et al., 1996, 2001] and hippocampal GABA-B1 expression [Sands et al., 2004] after chronic AD treatment in rats. Increased Cl^- uptake in submissive rats after AD treatment [Malatynska et al., 1995, 2000]. Chronic (but not acute) AD antagonized behavioral hyperactivity in rats produced by GABAergic inhibition by picrotoxin [Plaznik et al., 1989].
Increased cortex GABA level after electroconvulsive therapy [Sanacora et al., 2003] and SSRI, but not after cognitive behavioral therapy [Sanacora et al., 2003, 2006; Bhagwagar et al., 2004]. Increased cortex GABA level in drug-resistant depressed patients after electroconvulsive therapy [Mervaala et al., 2001].	Elevated striatal GABA level after AD treatment in rats [Gomez et al., 2003]. Increased GABA synthesis in amygdala, hippocampus, lateral septum after selective NE reuptake inhibitors [Herman et al., 2003]. Reduced pentylenetetrazole-activated hippocampal electroencephalogram power in rats after AD treatment [Matsubara et al., 2000].
Recovery from depression increases plasma level of GABA-active steroid agonists allopregnanolone and pregnanolone but decreases concentration of steroid antagonist 3b-hydroxy-5a-pregnan-20-one [Rupprecht, 2003]. Restored allopregnanolone levels in plasma and cerebrospinal fluid in depressed patients after AD treatment [Uzunova et al., 1998, see Khisti et al., 2000; Rupprecht, 2003; and Uzunova et al., 2003 for details].	Increased level of allopregnanolone in rat brain after SSRIs treatment [Uzunov et al., 1996; also see Rupprecht, 2003, for review]. Restored cortical allopregnanolole levels after chronic AD treatment in olfactobulbectomized rats [Uzunova et al., 2004].

Abbreviations as in Table 2. AD, antidepressant; SSRI, selective serotonin reuptake inhibitors; NE, norepinephrin. See also a detailed discussion in Argyropoulos et al. [2000].

TABLE 4. Summary of antidepressant effects produced by GABAergic anxiolytic drugs in animal experimental models

Drugs	Models
Valproate	FST in mice [Fernandez Teruel et al., 1988; Aley and Kulkarni, 1989; Raghavendra et al., 2000]
	Potentiated effects of other ADs in the FST in mice [Szymczyk and Zebrowska-Lupina, 2000]
Amino-oxyacetic acid	FST in rats [Borsini et al., 1986, 1988]
Vigabatrin	Potentiated ADs' effects in the FST in mice [Szymczyk and Zebrowska-Lupina, 2000]
	OB in rats [Kelly et al., 1997]
Beta-phenyl-GABA	Eliminated increase in benzodiazepine receptors produced by the FST in rats [Rago et al., 1990]
GABA	FST in mice, LH in rats [Aley and Kulkarni, 1989; see Kram et al., 2000 for details]
	Potentiated effects of ADs, reversed depressant effects of reserpine in FST in mice [Aley and Kulkarni, 1989]
Muscimol	FST in mice/rats [Aley and Kulkarni, 1989; Borsini et al., 1986; Nakagawa et al., 1996a; Raghavendra et al., 2000]
	Reversed depressant effects of reserpine in FST in mice [Aley and Kulkarni, 1989]
	Potentiated AD effects of ethanol and allopregnanolone in the FST in mice [Hirani et al., 2002; Khisti et al., 2000]
Progabide[a]	AD-like effects in animal tests [Bartholini, 1984]
Diazepam	FST in rats [Nishimura et al., 1989, 1992; but Bourin et al., 1991]
	Reduced muricide in OB in rats [Shibata et al., 1984]
Carbamazepine and oxcarbazepine	FST and LH in rats [Beijamini et al., 1998, Joka et al., 2000]
	Potentiated ADs' effects in the FST in mice [Szymczyk and Zebrowska-Lupina, 2000]
Alprazolam, adinazolam	OB, FST in rats [O'Connor et al., 1985; Flugy et al., 1992]
Pentobarbital	FST in mice [Schechter and Chance, 1979]
Ethanol	FST in mice, acute administration [Hirani et al., 2002][b]
	Attenuated depressant action of cocaine in the FST in rats [Hayase et al., 2002]
Allopregnanolone and progesterone[a]	FST in mice/rats [Khisti et al., 2000; Estrada-Camarena et al., 2002; Rupprecht, 2003]
	Enhanced effects of other ADs in the FST in mice/rats [Estrada-Camarena et al., 2002; Rupprecht, 2003]
	Potentiated AD effects of ethanol in FST in mice [Hirani et al., 2002]
	Sub-antidepressant doses of steroid agonists in the FST in mice reversed depression associated with ethanol withdrawal [Hirani et al., 2002]

Abbreviations as in Tables 2, 3.
[a]See legend to Table 1 for details on progabide and progesterone mechanisms of action.
[b]Note that antidepressant action of ethanol in the FST is reported only for its acute administration; its prolonged consumption produced tolerance to this effect and its withdrawal enhanced behavioral despair and elicited tolerance to antidepressant-like action of acute ethanol [Hirani et al., 2002].

tially affect anxiety and depression, so is most likely not involved in synergetic anxiety–depression pathogenesis [Pilc and Nowak, 2005]. The GABA-B receptor system will therefore not be discussed here in much detail.

GENETIC DATA: GABAERGIC RECEPTORS

It has long been known that genetic factors play a role in the etiology of both anxiety and depression [Kendler et al., 1986, 1987; Finn et al., 2003; Villafuerte and Burmeister, 2003; Gillespie et al., 2004]. A recent study found lowered plasma GABA in depressed patients and their first-degree relatives [Bjork et al., 2001], confirming that GABAergic tone also may be under genetic control. Not surprisingly, neurogenetic approaches (such as genetic polymorphism, quantitative trait loci, microarray, and mutagenesis studies) provide us with new insights into biological psychiatry of GABA-related aspects of these disorders.

GABA-A receptor genes form clusters ([ρ1, ρ2, δ]; [α2, α4, β1, γ1]; [α5, β3, γ3]; [α1, α6, β2, γ2], [α3, θ, ε]) on several chromosomes, whereas two GABA-B receptor (B1, B2) genes have been mapped to two different chromosomes [Hisama et al., 2001; Martin et al., 2001; Boehm et al., 2004; MGI, 2006]. While genes encoding α2, α3, α4, α6, β1, γ1, and γ2 subunits have been associated with anxiety-like behaviors in animals [Vekovisheva, 2003; Rosahl, 2003; Marowsky et al., 2004; Chandra et al., 2005; Gill and Boyle, 2005; Korpi and Sinkkonen, 2006], the association has also been established in animals between α1, α3, α6 genes and depressiveness, and α5 gene and cognitive functions [Crestani et al., 1999; Collinson et al., 2002; Atack et al., 2005]. Multiple genetic loci studies in mice [Yoshikawa et al., 2002] linked animal depressive-like behavior in the FST and TST to GABAergic loci on chromosomes 8 and 11, encoding α1, α6, and γ2 subunits of GABA-A receptors. Recent gene expression studies in rats showed downregulation of both GABA-A and GABA-B genes (encoding α1, α4, α5, α6, γ1, δ, and B1 subunits) in highly anxious PVG hooded (vs. Sprague-Dawley) strains following cat exposure [Wang et al., 2003], as well as reduced expression of α2, γ1, or δ subunits after fear conditioning [Mei et al., 2005], chronic unpredictable stress [Verkuyl et al., 2004], or depression evoked by social confrontation [Kroes et al.,

TABLE 5. Summary of prodepressant effects produced by GABAergic anxiogenic drugs in animal experimental models (all these drugs reduce GABA-A function in one way or another[a])

Drugs	Models
Bicuculline (GABA-A-antagonist)	FST and LH in rats/mice [Petty and Sherman, 1981; Aley and Kulkarni, 1989; Hayase et al., 2002]
	Reversed effects of several AD in the FST in rats [Nakagawa et al., 1996a]
	Reversed AD effects of valproate, ethanol, fengabine and melatonin in the FST and OB in rats/mice [Lloyd et al., 1987; Fernandez Teruel et al., 1988; Raghavendra et al., 2000; Hirani et al., 2002]
FG 7142 (benzodiazepine inverse agonist)	FST in mice [Chopra et al., 1988]
	LH in rats [Drugan et al., 1985; Tunnicliff and Malatynska, 2003]
Ro 15-3505 (benzodiazepine inverse agonist)	FST in rats [Skrebuhhova et al., 1999]
Beta-carboline-3-carboxylic acid methyl (CCM) ester (benzodiazepine inverse agonists)	FST in rats [Nishimura et al., 1989]
	Mice bred for increased sensitivity for CCM show increased depression in the FST and TST [Do-Rego et al., 2002].
Pregnanolone sulphate (Cl⁻ channel closer)	No effects were found in the FST in mice [Urani et al., 2001, but see Reddy, 2003].
Finasteride, trilostane, and indomethazine (inhibitors of the endogenous neurosteroid biosynthesis)	Attenuated AD effects of ethanol in the FST in mice [Hirani et al., 2002].
Picrotoxin (Cl⁻ channel blocker)	FST in mice/rats [Aley and Kulkarni, 1989; Skrebuhhova et al., 1999]
	Reversed effects of muscimol, valproate, and other ADs in the FST and LH in rats [Borsini et al., 1986; Fernandez Teruel et al., 1988; Cannizzaro et al., 1993; see also Tunnicliff and Malatynska, 2003]
	Reversed AD effects of progesterone in FST in rats [Estrada-Camarena et al., 2002]
Pentylenetetrazole (Cl⁻ channel blocker)	FST in rats [Cannizzaro et al., 1993; Skrebuhhova et al., 1999]

Abbreviations as in Tables 2, 3.
[a]See also interesting data on GABA-A receptor antisense nucleotides that attenuate AD-induced Cl⁻ uptake in rats [Malatynska et al., 2000].

2005]. In contrast, chronic antidepressants upregulated α1, α3, β1, β2, and γ2 genes in rat brainstem [Tanay et al., 1996, 2001], while altered anxiety and depression-related behavior was found in mutant mice lacking B1 and B2 receptors [Mombereau et al., 2004, 2005].

A recent human study showed that severe treatment-resistant depression with anxiety was linked to a mutation in the β1 subunit of GABA-A receptor [Kosel et al., 2004]. Positive genetic associations were found between polymorphism in human GABA-A receptor subunits genes and unipolar (α3, α5), bipolar (α1, α3, α5, α6) depression or neuroticism (α6) [Bell et al., 1989; Buckle et al., 1989; Oruc et al., 1997; Papadimitriou et al., 1998; Massat et al., 2002; Yamada et al., 2003; Henkel et al., 2004; Horiuchi et al., 2004; Sen et al., 2004; Korpi and Sinkkonen, 2006] as well as posttraumatic stress disorder with anxiety and depression (β3) or hormonal and autonomic stress response (α6) [Feusner et al., 2001; Uhart et al., 2004]. In line with this, comprehensive genetic linkage studies reported the 5q34 locus (containing a cluster of α, β, and γ GABA-A genes) to be associated with mood disorders [Edenberg et al., 1997], and exonic variants of the B1 receptor gene with panic disorder [Sand et al., 2000]. Recent

microarray study also revealed altered expression of GABA-A (α5, β3, γ2, δ) and GABA-B (B1) receptor genes in cortex of depressed patients [Choudary et al., 2005].

Collectively, these data indicate that both GABA-A and GABA-B genes may be involved in the regulation of anxiety and depression. Despite the fact that we still lack a complete understanding of genes that increase the risk of depression and anxiety [Nestler et al., 2002; Finn et al., 2003; Villafuerte and Burmeister, 2003], these striking data coming from behavioral neurogenetics and clinical studies provide substantial support for the key role that GABA may play in depression and anxiety pathogenesis. This also suggests that manipulations with GABAergic genes in both animals and humans, as well as the use of subunit-specific GABAergic drugs with selective pharmacological profiles [see Atack, 2003, 2005; Whiting, 2003; Atack et al., 2005; Rudolph and Mohler, 2006], may allow us to find new possibilities to cure anxiety and depression.

GABA METABOLISM

In addition to receptor actions, a role in anxiety and depression pathogenesis belongs to factors affecting

GABA metabolism and uptake [Goddard et al., 2004]. For example, glutamic acid decarboxylase (GAD) is a key enzyme of GABA biosynthesis from glutamic acid. Both unipolar and bipolar mood disorders have been found to be associated with polymorphism in the GAD67 gene encoding a 67-kDa isoform of GAD [Lappalainen et al., 2004; Lundorf et al., 2005] responsible for 90% of GABA synthesis from glutamate in the brain. Reduced GABA levels and increased anxiety were found in mice lacking a small 65-kDa isoform of GAD (GAD65) responsible for fine-tuning of GABAergic neurotransmission [Kash et al., 1999; Stork et al., 2000], whereas GAD65 expression was increased by AD reboxetine in septum of stressed rats [Herman et al., 2003]. Recent studies found the link between polymorphism in the GAD65 gene and anxiety-related behavioral inhibition in children [Smoller et al., 2001], while prefrontal cortex and cerebellar GAD65 and GAD67 levels were decreased in depressed patients [Guidotti et al., 2000; Fatemi et al., 2005],

GABA transaminase (GABA-T) is another key enzyme in GABA turnover, which catabolizes GABA. Its inhibitors (such as valproate and vigabatrin) elevate GABA levels, show pronounced anxiolytic effects in various experimental models [Sherif and Oreland, 1995; Lang and de Angelis, 2003], and are able to exert (valproate) consistent AD effects in humans [reviewed in Post, 2004; Rogawski and Loscher, 2004; Gajwani et al., 2005, Zwanzger and Rupprecht, 2005].

Several known GABA transporter proteins (GAT 1–4) and their subtype-specific modulators have also been shown to influence GABAergic signaling [Sundman et al., 1997; Keros and Hablitz, 2005], thus opening the possibility of novel psychotropic GAT-related drugs [Schousboe et al., 2004]. Indeed, GAT-1 inhibitors (such as NO-711 and tiagabine) increase GABA tone and exert predictable anxiolytic effects in animals [Dalvi and Rodgers, 1996; Schmitt and Hiemke, 1999; chronic treatment: Schmitt et al., 2002] and humans [Crane, 2003; Schaller et al., 2004; Connor et al., 2006]. For example, tiagabine was useful to treat treatment-resistant anxiety as well as various anxiety disorders combined with anxiety [reviewed in Zwanzger and Rupprecht, 2005]. Although in a recent study suicidal depression did not correlate with altered GAT-1 binding in frontal cortex and cingulated gyrus [Sundman-Eriksson and Allard, 2002], several clinical studies indicate that GAT inhibitors such as tiagabine may be used as mood stabilizers, indicating their utility in therapy for depression [Kaufman, 1998; Schaffer et al., 2002; Schwartz, 2002] via modulation of central GABAergic system [but see Post, 2004]. Collectively, these findings indicate that both anxiety and depression depend on GABA metabolism, whose imbalance may play a role in their overlapping pathogenesis. Therefore, novel drugs targeting both the activity and expression of enzymes of GABA synthesis and metabolism, as well as GAT [Sarup et al., 2003], may

represent potential interest for antianxiety/antidepressant therapy.

Notably, drugs affecting GABA metabolism may also have additional mechanisms of action, which have to be taken into account. For example, valproate modulates metabolism of γ-hydroxybutyric acid (GHB), a weak agonist at GABA-B receptors [reviewed in Crunelli et al., 2005]. In line with this, the AD phenelzine (effective in therapy of social anxiety and panic disorders in humans) inhibits GABA-T, elevates brain GABA levels, produces anxiolytic-like effects in animals, and also modulates glutamate and catecholamine neurotransmission [reviewed in Yang and Shen, 2005]. Taken together, these data contribute to the complexity of GABAergic and other mechanisms in anxiety and depression, prompting new strategies of therapy targeting simultaneously GABA and other mediator systems (see below).

GABA AND OTHER SUBSTANCES INVOLVED IN ANXIETY AND DEPRESSION

The well-established endocrine abnormalities of depression and anxiety [Erickson et al., 2003] are another important aspect to consider in relation to GABA. For example, neurosteroids modulating GABAergic/benzodiazepine functions may have a potential for the development of new AD drugs [Strohle et al., 1999; Khisti et al., 2000] which at the same time should have an anxiolytic profile [Ungard et al., 2000; Reddy, 2003]. Interestingly, the well-known acute anxiolytic and mood lifting–euphoric action of ethanol may be produced by its direct effects on GABA-A receptors as well as due to modulation of the neurosteroid system [Khisti et al., 2002]. As such, the search for novel drugs binding to ethanol site on GABA-A receptors may be a promising multitarget approach.

On a related point, anxiety and depression have long been associated with alterations in secretion of many hormones including adrenocorticotropic hormone (ACTH), cortisol/corticosterone, corticotropin-releasing hormone (CRH), adrenal catecholamines, oxytocin, prolactin, and rennin [Arborelius et al., 1999; Carrasco and Van de Kar, 2003; Finn et al., 2003]. As summarized by these authors, endogenous and exogenous GABAergic drugs may affect the secretion of some of these hormones. Several benzodiazepine agonist ligands decrease ACTH/corticosterone as well as oxytocin and prolactin responses to stressors [Carrasco and Van de Kar, 2003]. Also, the GABAergic system inhibits stress-induced cortisol secretion as well as CRH liberation into the portal vein [Lopez et al., 1999]. It is therefore possible that in depression a deficiency of endogenous GABA/benzodiazepine ligands (see Table 2) could lead to neuroendocrinological disregulation that contributes to pathogenesis. It also seems possible that correction of stress-induced neuroendocrinological mechanisms by GABAergic

drugs may be a potential therapeutic approach to treat depression and anxiety targeting both "low GABA → high stress" and "high stress → low GABA" pathogenic mechanisms. Perhaps affecting one disorder (e.g., anxiety) through direct anxiolytic action on GABA receptors, some GABAergic drugs may in parallel correct stress-induced neuroendocrine mechanisms. This may not only target the "endocrine" component of the existing anxiety but also aim at the endocrine mechanisms underlying depression. The latter may lead to additional very useful therapeutic effects targeting anxiety/depression disorders and/or their comorbidity caused by neuroendocrine disregulations.

A possible interplay between aversive memories and stress neuroendocrinology outlines a further possibility where GABAergic intervention may be useful to treat anxiety and depression. Treating one disorder (e.g., anxiety) through direct anxiolytic action on GABA receptors, GABAergic drugs may in parallel block recurrent negative memories that not only complicate the existing disorder [Kalueff and Nutt, 1996] but also provoke the other disorder (e.g., depression). The role of negative memories in both anxiety and depression has been reported extensively in the literature [Davidson, 2002]. In addition to the above positive effects, GABAergic drugs may further improve the situation by correcting neuroendocrine mechanisms produced by negative memories. In line with this, the amnestic action of GABA-positive modulators has been shown to block conditioned vasopressin, oxytocin, and ACTH stress responses [Carrasco and Van de Kar, 2003]. The latter may lead to the additional (third) useful therapeutic effect of GABAergic-positive modulators targeting the disorders within a complex treatment approach we are presenting here.

The critical role of neuropeptides in modulation of GABAergic function and anxiety/depression interplay also has to be considered. For example, melatonin, which is known to modulate the GABAergic system, was shown to have both anxiolytic and AD properties in animals [Raghavendra et al., 2000]. Similar properties have been found for antagonists of cholecystokinin—the neuropeptide that modulates the GABAergic system and is suggested to be involved in both anxiety and depression pathogenesis [see Lofberg et al., 1998, for details]. Finally, the interaction of GABA with other brain neurotransmitter systems shall be mentioned. For example, the potential for norepinephrine (NE) interaction with GABA in the limbic region [recently suggested by Herman et al., 2003] may be critical since both mediators are largely involved in anxiety and depression pathogenesis [Coplan and Lydiard, 1998]. As such, multiple vs. specific neurotransmitter system dysfunctions shall be considered for possible therapeutic purposes. Perhaps improving anxiety by GABAergic drugs we may at the same time improve depression through the interaction of GABA with NE, and vice versa.

BRAIN CIRCUITS OF ANXIETY AND DEPRESSION

The GABAergic system is now rapidly emerging as a target for development of medications of anxiety and mood disorders [Krystal et al., 2002; Nutt et al., 2002]. It therefore seems important to consider the possible neural anatomical underpinnings of both anxiety and depression relating to GABA [Davidson et al., 2002; Chang et al., 2003]. Chronic stress exposure— the most common cause of depression—has been shown to activate GABAergic forebrain areas, including dorsomedial hypothalamus and hippocampus [Herman et al., 2003]—important parts of depression circuits. Several studies have found significant reductions in hippocampal volume in depressed subjects [see review in Sheline, 2003], indicating the role the hippocampus may play in depression pathogenesis (see Table 6 for details). The hippocampus is particularly rich in GABAergic neurons [Banks et al., 2000]. The well-known role the hippocampus plays in memory, and the role memory plays in anxiety and depression, may link depression and anxiety pathogenesis to memory-related GABAergic processes in the hippocampus.

Brain morphological and metabolic changes associated with major depression have been found in the amygdala [Drevets, 1999; Sheline, 2003]—the GABAergic structure that has long been associated with anxiety and also involved in storage of aversive memories [Davis and Whalen, 2001; Chhatwal et al., 2005]. Proving this putative amygdala–anxiety– depression–memory link, Jasnow and Huhman [2001] reported GABAergic involvement in a conditioned social defeat model in hamsters. In line with these preclinical findings, recent functional MRI studies established marked amygdala activation in response to fearful facial affect in depressed patients vs. normal controls [Yurgelun-Todd et al., 2000]. Interestingly, Strakowski et al. [2002] found that amygdalar changes are specific to the type of depression—with amygdalar volume increased in bipolar disorders and decreased in unipolar depression. The latter raises the possibility that the amygdala plays different roles in various depression disorders and might explain why the drugs affecting GABAergic neurons would differently treat unipolar and bipolar depression.

Recently, the important role of the midbrain tectum was suggested for anxiety and depression pathogenesis [Graeff et al., 1993; Brandao et al., 2003]. The midbrain tectum is rich in GABAergic neurons [Pandossio et al., 2000; Bueno et al., 2005a] and a number of animal studies have shown GABAergic drugs affect the midbrain tectum and alter stress-related anxiety-like behavioral responses, while certain neurochemical or morphological alterations in this brain area have been found in animal depression-like states (Table 6). As such, although clinical studies are still needed to confirm this notion, it seems possible

TABLE 6. Clinical and preclinical data linking common GABAergic brain areas to pathogenesis of anxiety and depression

Anxiety	Depression

Clinical data

Amygdala[a]

Activation in patients with posttraumatic stress disorder [Rauch et al., 1996], during anticipatory anxiety [Phelps et al., 2001], in adults and adolescents viewing fearful faces; also positive correlation of amygdalar activation and social anxiety scores [Morris et al., 1998; Killgore and Yurgelun-Todd, 2005].

Reduced volume in depressed patients [Caetano et al., 2004] and children [Rosso et al., 2005]. Correlation of amygdalar activation in response to emotional faces with symptom improvement in major depression [Canli et al., 2005]. Activation in adults viewing sad vs. happy faces [Killgore and Yurgelun-Todd, 2005].

Hippocampus

Reduced blood flow in anxious volunteers during phobogenic (vs. neutral) visual stimulation [Wik et al., 1993]. Decreased blood flow in right hippocampus in women with post-traumatic stress disorder [Bremner et al., 1999].

Reduced volumes in depressed (including drug-free) patients; negative correlation between hippocampal volumes and length of depression [Caetano et al., 2004; Hickie et al., 2005; Neumeister et al., 2005; Saylam et al., 2006], also see [Sheline et al., 2002] for a detailed review.

Hypothalamus

Activation in patients with panic disorder [Boshuisen et al., 2002].

Activation in depressed patients viewing negative vs. reference images [Malhi et al., 2004].

Prefrontal cortex

Reduced blood flow in anxious volunteers during phobogenic (vs. neutral) visual stimulation [Wik et al., 1993]. Reduced blood flow in women with posttraumatic stress disorder [Bremner et al., 1999].

Altered magnetoencephalographic activity in depressed patients vs. healthy controls [Mainhofner et al., 2005]. Altered metabolism in depressed patients, its correction after electroconvulsive therapy [Michael et al., 2003]. AD effects of repetitive transcranial magnetic stimulation in drug-resistant depressed patients [Rossini et al., 2005].

Midbrain tectum

Activation in patients with panic disorder [Boshuisen et al., 2002]. Panic-like effects following stimulation in humans [Nashold et al., 1969; Amano et al., 1978].

Preclinical data

Amygdala

Reduced anxiety in rats following muscimol injection to basolateral amygdala [Bueno et al., 2005b]. Reduced amygdalar expression of GABA-A receptor associated protein[b] 6 h after fear conditioning in rats [Mei et al., 2005]. Increased c-fos expression[c] in rats following administration of several anxiogenic drugs [Singewald et al., 2003]. Increased lactate-evoked anxiety by bicuculline injected into basolateral amygdala in rats [Sajdyk and Shekhar, 2005]. Correlation between anxiety phenotype in several inbred mouse strains and reduced GABA-A receptor densities, benzodiazepine binding and γ 2 subunit mRNA levels in central, lateral and medial amygdalar nuclei [Yilmazer-Hanke et al., 2003; Caldji et al., 2004]. Reduced extracellular GABA in amygdala in mice exposed to conditioned fear stimulus [Stork et al., 2002].

ADs reduce muricide and amygdaloid after-discharge in rats induced by amygdalar stimulation [Kamei et al., 1975]. Reduced benzodiazepine binding in amygdala 24 h after FST in mice [Briones-Aranda et al., 2005]. Reduced allopregnanolone levels in amygdala in the olfactobulbectomy model of depression in rats [Uzunova et al., 2003]. Altered neurotransmitter turnover in amygdala following FST in Wistar–Kyoto vs. non-stressed or Wistar rats [De La Garza and Mahoney, 2004]. Reduced allopregnanolone levels in amygdala of depressed olfactobulbectomized rats [Uzunova et al., 2003].

Hippocampus

Reduced expression of α 2 GABA-A receptor subunit 6 h after fear conditioning in rats [Mei et al., 2005]. Reduced hippocampal expression of α 1 and α 2 subunits mRNA in punished rats [Zhang et al., 1998]. Altered volume in anxious HAB (vs. low-anxiety LAB) rats [Kalisch et al., 2005]. Increased c-fos expression[c] in rats following administration of several classical anxiogenic drugs [Singewald et al., 2003]. Reduced hippocampal allopregnanolone levels in anxious high-vocalizing rats [Zimmerberg et al., 2005].

Reduced GABA levels 24 h after FST in mice [Briones-Aranda et al., 2005]. Altered cDNA gene expression profile in rats after chronic ADs [Drigues et al., 2003]. Altered hippocampal neurotransmission after FST in rats [Linthorst et al., 2002]. Altered volume in rats with higher depressiveness in FST [Kalisch et al., 2005]. Reduced benzodiazepine binding and GABA-A α 1 subunit mRNA in mice and rats exposed to repeated FST [Medina et al., 1983; Weizman et al., 1989; Montpied et al., 1993].

Hypothalamus

Increased sensitivity to chemically evoked anxiety in rats with experimentally reduced GABA synthesis in hypothalamus [Shekhar et al., 1996]. Increased c-fos expression[c] in rats following administration of several anxiogenic drugs [Singewald et al., 2003]. Reduced anxiety in rats following intra-

Reduced benzodiazepine binding in mice exposed to repeated FST [Weizman et al., 1989]. Reduced GABA levels and benzodiazepine binding 24 h after FST in mice [Briones-Aranda et al., 2005]. Reduced GABAergic transmission and altered GABA-A α 5, γ 1[d] and δ subunits gene expression following

TABLE 6. Continued

Anxiety	Depression
hypothalamic administration of GABAergic anxiolytic drugs [Jardim and Guimaraes, 2001].	3-week chronic unpredictable stress in rats [Verkuyl et al., 2004].
Prefrontal cortex	
Increased c-fos expression[c] in rat prelimbic cortex following administration of several anxiogenic drugs [Singewald et al., 2003]. Reduced anxiety in rats following muscimol infusion into prefrontal cortex [Shah et al., 2004]. Increased anxiety and reduced activity in anxious HAB vs. non-anxious LAB rat strains [Kalisch et al., 2004].	Altered neurotransmitter turnover following FST in Wistar–Kyoto vs. non-stressed or Wistar rats [De La Garza and Mahoney, 2004].
Midbrain tectum	
Panic-like escape behavior in rats evoked by electrical stimulation or microinjections of GABA-A antagonists [Schenberg and Graeff, 1978; Graeff et al., 1986; Brandao et al., 2003], and reduced by GABA-A agonists and benzodiazepines [Bovier et al., 1982; Audi and Graeff, 1984, 1987; Graeff et al., 1986]. Reduced panic-like behavior in rats by intra-DPAG injection of muscimol and baclofen, and increased panic by benzodiazepine inverse agonist FG 7142 [Bueno et al., 2005a]. Increased anxiety by prior electrical stimulation of the inferior colliculus in rats [Pandossio et al., 2000]. Reduced vocalization and freezing in rats following muscimol or midazolam injection into the inferior colliculus [Nobre and Brandao, 2004].	Reduced benzodiazepine binding in mice exposed to repeated FST [Weizman et al., 1989]. Neurochemical changes in mouse inferior colliculus following AD treatment [Williams et al., 2005]. Reduced blood flow in inferior colliculus in several different models of depression in rats [Caldecott-Hazard et al., 1988]. Pronounced neuromorphological changes in inferior colliculus in rats following chronic immobilization stress [Dagnino-Subiabre et al., 2005].

DPAG, dorsal periaqueductal gray; FST, forced swim test of depression; AD, antidepressant.
[a]Also see Quirk and Gehlert [2003] for a detailed review.
[b]Modulates channel kinetics and neurotransmission by promoting GABA-A receptor clustering.
[c]Genetic marker of neuronal activation.
[d]Robust trend ($P = .06$) for this subunit.

that GABAergic influences on the midbrain tectum may play a role in anxiety and depression.

The prefrontal cortex has been reported to be activated by a provocation test across several anxiety disorders [Davidson, 2002; Nestler et al., 2002] and is also an important part of the brain depression circuits (Fig. 1) [Sheline, 2003]. Morphological and metabolic changes associated with depression have been found in the prefrontal cortex in many studies [Yurgelun-Todd et al., 2000; Sheline, 2003]. It is worth mentioning that GABAergic neurons represent the highest population in the cortex and play a crucial role in regulation of inputs and outputs of the cortex. The prefrontal cortex has also been traditionally linked to memory and higher cognitive functions—ones that that are extremely relevant to linking anxiety and depression (see, for example, data on reduced benzodiazepine binding in prefrontal cortex in combat-related posttraumatic stress disorder [Bremner et al., 2000b]). Recent postmortem studies have established that depressive disorders are characterized by alterations in the density and size of neuronal and glial cells in frontolimbic brain regions [Rajkowska, 2003]. Importantly, these regions, rich in GABAergic neurons, are also reported to be involved in anxiety spectrum disorders [Mindus et al., 1986; Wu et al., 1991]. For example, infusion of the GABA agonist muscimol in prefrontal cortex produced clear anxiolytic effects in rats [Shah et al., 2005]. Taken together, the available neuroanatomical

data indicate clear overlapping of several GABAergic neural circuits (Table 6) that may be considered as one integral anxiety/depression circuit (Fig. 1) consisting of three interplaying domains—anxiety, memory, and depression.

GABA NEUROIMAGING DATA

Recent sophisticated neuroimaging methods, such as positron emission (PET) and single photon emission computed (SPECT) tomography and proton magnetic resonance spectroscopy (MRS), enable further neurobiological underpinning of anxiety and depression [Kaschka et al., 1995; Bremner et al., 1997; Malizia et al., 1998; Ketter and Wang, 2002; Chang et al., 2003; Epperson et al., 2005]. Despite certain limitations in spatial and temporal resolution, these methods enable an in vivo real-time assessment of specific areas in these disorders with direct measurement of GABA neurochemistry and comparison of therapeutic effects of different therapies [Bremner et al., 2000a,b; Grachev and Apkarian, 2000; Kosel et al., 2004; Sanacora et al., 2006].

Obtained using different techniques, neuroimaging data firmly confirm the involvement of central GABA in anxiety and depression. In patients with panic disorder, a reduction in benzodiazepine binding in the brain was found by PET [Malizia et al., 1998] and SPECT [Kaschka et al., 1995; Bremner et al., 2000a].

While a similar phenomenon has been revealed by SPECT in patients with posttraumatic stress disorder [Bremner et al., 2000b] or severe treatment-resistant anxiety and depression [Kosel et al., 2004], numerous neuroimaging studies [MRS: Kugaya et al., 2003; Epperson et al., 2006; Sanacora et al., 2006; SPECT: Kosel et al., 2004; Mervaala et al., 2001] consistently show reduced central GABAergic function in depression and its correction by AD therapy (see Tables 2, 3 for details). Strikingly paralleling other clinical and experimental data (reviewed above), these findings further support the notion that impaired GABAergic function is directly involved in anxiety, depression, and their interplay.

CONCLUSION

Summarizing, it seems likely that there are overlapping GABAergic mechanisms of anxiety and depression due to: 1) common neurochemical mechanisms; 2) similar brain structures involved in the regulation of anxiety and depression; 3) common genetic origins of anxiety and depression; and 4) overlapping or correlation in neuropsychopharmacological effects of drugs (Tables 1–6). Consistent overlapping of clinical efficacy as well as activity in animal tests across all classes of GABAergic anxiolytics and antidepressants further strengthens the idea that such effects are not the result of a "lack of specificity," but rather represent a fundamental anxiolytico-antidepressant potential of GABA-A-positive modulators. It is also clear that since GABA, as a part of both anxiety and depression pathogenesis, is responsible for many symptoms of these disorders, drugs that affect GABA-A receptors may be especially useful in selective treatment of symptoms that are common for anxiety and depression (Fig. 2). Here we will make a further step and outline several possible directions for future progress in this field.

1. Since anxiety and depression have many common emotionality features, it may be suggested that GABA-active agents are particularly effective in treating the "emotional" component of both anxiety and depression. The frontolimbic network and especially prefrontal cortex is a key substrate for voluntary suppression of sadness, while chronic incapacity to suppress negative emotions was suggested to be a key factor in the genesis of depression and anxiety [Levesque et al., 2003]. Because GABAergic drugs have been shown to act on this brain structure, it is possible to expect that they may lead to antianxiety and antidepressant effects by improving the patient's ability to control her/his own negative emotions.

2. These drugs may be used as a specific medication of choice for anxiety (and, perhaps, panic) and depression comorbidity states.

3. The fine-tuning and homeostatic balance of the GABAergic inhibitory tone in the brain is a prerequisite for controlling excitatory neurotransmission [Sarup et al., 2003]. Several drugs that affect GABA transport and metabolism also possess effects on anxiety and depression. Further studies on modulation of GABA transport and metabolism are of therapeutical interest in GABA-related disorders, including anxiety and depression.

4. GABAergic drugs may be effective in psychopathologies with mixed or unclear symptoms, and also in some urgent clinical cases of severe anxiety and/or depression. It is especially critical in situations when the previous history of the patient is unknown and/or
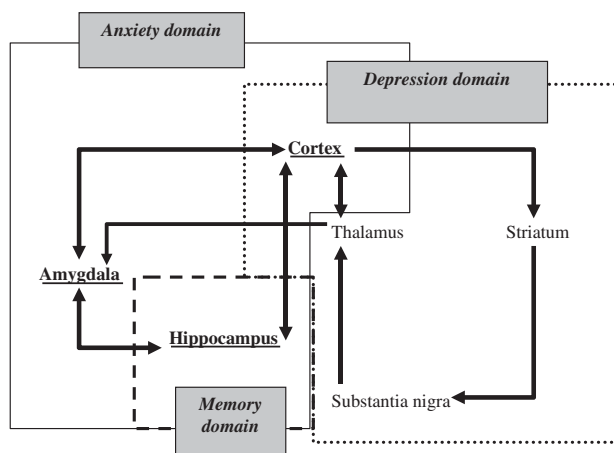

Figure 1. Overlapping anxiety and depression circuits (GABAergic areas are in bold).
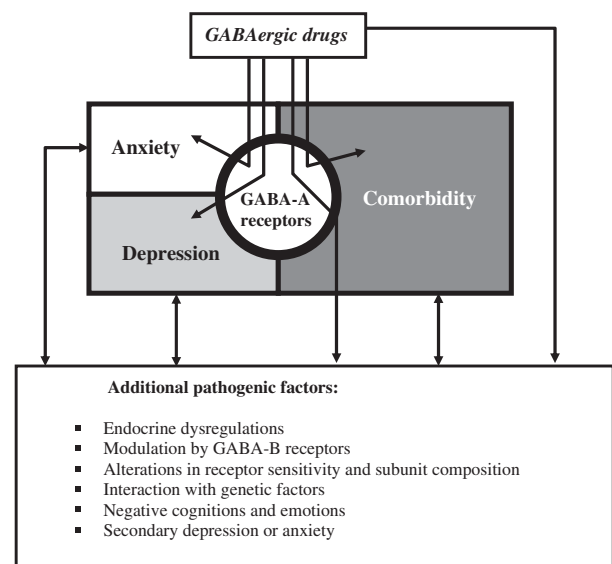

Figure 2. Multiple targets for GABAergic drugs in a complex treatment of stress-related disorders.

there is no time for proper diagnostics. We therefore speculate that some highly effective potential mood-stabilizing, antipanic, antimanic, and antisuicide drugs may be designed on the basis of selective exogenous or endogenous modulators of the central GABAergic system [see also Shelton, 2003].

5. Since GABA-active neurosteroids play an important role in the pathogenesis of anxiety and depression [Strohle et al., 1999; Guidotti et al., 2001; Reddy, 2003], it is possible to expect that novel GABAergic steroid agents will be a useful tool in the treatment of steroid-dependent disorders including premenstrual and menopausal syndromes [Barbaccia et al., 2000; Sundstrom et al., 1997; Sundstrom-Poromaa et al., 2003] characterized by increased anxiety and depression. In addition, steroids may play a unique modulatory role in tuning sensitivity of GABAergic receptors to GABA and other GABA-active substances [Turner et al., 1989; Olsen et al., 1991; also see Olsen and Sapp, 1995, for review]. The genomic mechanism of neurosteroid action may include effects of expression of genes encoding subunits of GABAergic receptors [Gulinello et al., 2001]. As such, alterations in endogenous steroids during anxiety or depression may largely affect brain GABAergic processes [reviewed in Dubrovsky, 2005; Eser et al., 2006a,b]. This, in turn, may lead to i) further acceleration of the existing anxiety or depression pathogenesis and/or ii) provoke new, secondary (e.g., anxiety, comorbidity, etc.) emotional disorders. Importantly, based on the nature of neurosteroid actions on the nervous system [Reddy, 2003], it is possible to expect that steroid-based GABAergic modulators may in fact create the grounds for the fast-acting AD drugs—the need for which has been so widely recognized.

6. GABA-A receptors appear to occupy a central role in mediating the effects of ethanol in the brain [Davies, 2003]. Alcoholism is often associated with low GABAergic function and increased anxiety and depression [Roy et al., 1991; Enoch, 2003]. A GABAergic genetic component is established for human anxiety, depression, and alcoholism [Nutt et al., 2002; Davies, 2003] as well as alcohol-related phenotypes in animals [Boehm et al., 2004]. Given this and the role of GABA-A receptors in ethanol's behavioral actions [Boehm et al., 2004], the involvement of GABAergic genes in a complex interplay between these three disorders may be postulated. In addition, GABA-active neurosteroids play a pivotal role in the actions of ethanol and in depression associated with chronic ethanol consumption [Hirani et al., 2002, 2005]. Therefore, multitarget complex treatment of anxiety/depression complicated with alcohol abuse [Enoch, 2003] by positive modulators of GABA-A receptors may be a promising therapeutic approach to treat these specific conditions.

7. The important role of cognitive factors in both anxiety and depression pathogenesis [Kalueff and Nutt, 1996] outlines further possibilities where GABAergic drugs may theoretically have extraordinary effectiveness. It is well known that several subtypes of anxiety and depression are characterized by recurrent unpleasant cognitions that complicate therapy and, in fact, are a key part of pathogenesis per se (Fig. 2). Since GABAergic drugs are traditionally known to possess robust effects on memory [reviewed in Kalueff and Nutt, 1996; Chapouthier and Venault, 2002], we suggest that their use may be especially effective in targeting anxiety and/or depression associated with negative memories [also see good recent reviews in Quirk and Gehlert, 2003; Barad, 2005]. Importantly, the same approach may be used for a complex treatment of patients with posttraumatic stress disorder. Inhibition of such memories by GABAergic-positive modulators in some cases could be an important part of rational antidepressant and anxiolytic therapy.

8. Stress as well as many GABAergic psychotropic drugs have been reported to change GABA receptor subunits expression, while the composition of GABA receptors is known to dramatically affect its functions [Zhang et al., 1998; Vekovisheva, 2003]. As such, "programming" of GABAergic receptors by stress (including anxiety and depression) may not only facilitate the existing disorder but provoke a new illness or induce comorbidity states. However, modulation of the GABA receptor composition by GABAergic drugs may provide us with an additional therapeutic tool to fight anxiety and depression disorders. For example, while affecting one disorder (e.g., anxiety) through direct anxiolytic action, certain GABAergic drugs may influence type- and region-specific expression of the receptor subunits. The latter may lead to additional therapeutic effects of the drug targeting the second (e.g., depression) disorder due to changes in the GABA receptor properties.

9. Finally, since all currently available medications for mood disorders exert their therapeutic effects in weeks or months, there is a widely recognized need to find novel drugs that will affect depression much faster [Freeman, 1997; Nestler et al., 2002]. GABAergic drugs, acting both pharmacologically and genomically, might represent a particularly promising area of research in this field. Indeed, upregulation of GABA-A receptor subunits expression by benzodiazepines occurred within several days vs. several weeks needed for similar effects produced by traditional antidepressants [Tanay et al., 2001].

Together, it is now clear that, accompanied by intensive studies in the field of pharmacological and neurogenetical regulation of memory, anxiety, and depression, the "anxiety-depression" GABAergic concept that we develop here may significantly improve our understanding of the general mechanisms underlying stress-induced brain disorders. It may also point to new directions for a rational search for novel agents and even classes of stress-protecting psychotropic drugs.

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