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ROLE OF GABA IN MEMORY AND ANXIETY

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This review assesses the parallel literature on the role of gamma-aminobutyric acid (GABA) in memory 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 states. By exploring the overlap in these conditions in terms of pharmacology, brain circuitry, and clinical phenomenology, we begin to develop a theory that the two conditions are intrinsically interrelated. The role of GABAergic agents in dissecting out and demonstrating this interrelationship and in pointing the way to future research is discussed. Depression and Anxiety 4:100–110, 1996/1997. *© 1997 Wiley-Liss, Inc.*

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INTRODUCTION

Gamma-aminobutyric acid (GABA) is the primary mediator of inhibitory neurotransmission in the central nervous system. GABA-A receptors are found especially in brain and neural tissue; they represent hetero-oligomeric protein complexes consisting of GABA and benzodiazepine (BDZ) receptors coupled to an integral chloride channel (Mihic et al., 1995). GABA-A receptor activation increases chloride conductance and inhibits neuronal activity by hyperpolarization or depolarization block. Recent findings including data on numerous effects produced by drugs binding to different sites at the receptor are briefly summarised in Table 1 (review in Sieghart, 1992, 1995). Natural ligands for the GABA-A-BDZ receptor include GABA itself, BDZ ligands (beta-carbolines etc.) and steroids of neuronal origin (Izquierdo and Medina, 1991; Klotz, 1990; Majewska, 1992; Lambert et al., 1995). Being a target of action of various natural ligands or exogenous psychotropic drugs, the receptor is believed to be involved in regulation of a number of normal and pathological brain mechanisms including sleep, epilepsy and various emotions (Izquierdo and Medina, 1991; Majewska, 1992).

The important role of GABA-A receptors in modulation of different forms of anxiety, fears, phobias or depression has been reported in many studies (Gray et al., 1984; Haefely, 1992; Coupland and Nutt, 1995; see also Table 2). However, in addition to those effects, there are data indicating that the central GABAergic system may play key role in cognitive processes, including memory formation and consolidation (Gray et al., 1984; Izquierdo and Medina, 1991, 1995; Davis, 1994). A large body of preclinical literature indicates the alteration of memory produced by different effects on GABAergic areas in the brain (Davis, 1994). There are pharmacological findings showing that both anxiety-active endogenous ligands and traditional drugs acting at GABAergic receptors have memory-active properties (Table 2). In addition, there are many consistent clinical observations linking anxiety and cognitive processes (Gray, 1987; Lang, 1986; Cole et al., 1994).

Together, this raises the question of the relationship of GABAergic mechanisms in memory and anxiety (Izquierdo and Medina, 1991), in both animal and human psychopharmacology. It is therefore of importance to take an interdisciplinary approach linking neurochemical manipulations with clinical data and sophisticated tools from cognitive psychology. This review examines the animal and clinical data on the role of GABA in memory and anxiety to help to clarify further directions of the research in this field.

HISTORICAL BACKGROUND

Systemic administration of convulsants such as picrotoxin, pentylenetetrazole or other GABA inhibitors has long been known to enhance behaviour and memory in a variety of tests (Breen and McGaugh, 1961; McGaugh, 1968), although these early studies did not

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TABLE 1. Pharmacology of GABA-A receptors

Major binding sites at GABA-A-BDZ receptor complex	Ligands	Mode of action on the chloride influx	Effects produced by agonists
	Agonists: GABA[a] muscimol		Activation of chloride influx (increase of open channel lifetime and frequency of opening), positive modulation of BDZ site
	Antagonists: Bicuculline	(–)	
Benzodiazepine	Agonists: diazepam	(+)	Modulation of GABA function: increase of the affinity of receptor for GABA, increase of GABA-activated open channel lifetime and channel opening frequency.
	Antagonists: flumazenil	(0)	
	Inverse agonists: beta-carbolines[a]	(–)	
Alcohol	ethanol	(+)	Enhancing of chloride conductance through the receptor channel
Barbiturate	pentobarbital	(+)	Dual dose-dependent action on chloride influx: low doses (positive modulation of GABA site and increase of GABA-activated open channel lifetime); high doses (direct increase of number of open channel)
Steroid	Agonists: Tetra-hydroxyprogesterone[a] pregnenolone[a] progesterone[a]	(+)	Activation of chloride influx (increase of GABA-activated open channel lifetime and frequency of opening), positive modulation of binding sites for GABA, BDZ and barbiturates, modulation of convulsants binding to the ionophore
	Antagonists: pregnenolene-sulfate[a]	(–)	
Convulsant	Picrotoxin Pentylenetetrazole Penicillin Bicyclophosphates	(–)	Physical block of the chloride channel, inhibition of BDZ and Barbiturate sites (Picrotoxin).

[a]*Found in the brain.*

TABLE 2. Summary of the effects of GABAergic drugs on anxiety and memory

Drugs	Generally exerted anti-anxiety activity	Effects on memory	Memory tests (animals), see Ref.	References
GABAergic drugs affecting transmitter metabolism:				
sodium valproate	(+)	(–)	conditioned avoidance (rats)	Rayevsky and Kharlamov (1985)
amino-oxyacetic acid	(+)	(–)	active avoidance (rats)	Katz and Liebler (1978)
			habituation, inhibitory avoidance (rats)	Grunewald et al. (1993a)
vigabatrin	(+)	(–)	visual memory test (humans)	Sirvio et al. (1991)
GABA-A site:				
Agonists				
GABA	(+)	(0/?)	pasive avoidance (rats)	Banfi et al. (1982)
muscimol	(+)	(–)	drug-induced amnesia (habituation) (rats)	Rosat et al. (1992)
		(–)	habituation, inhibitory avoidance (rats)	Izquierdo and Medina (1993)
Antagonists				
bicuculline	(–)	(+)	inhibitory avoidance (rats)	Cruz-Morales et al. (1993)[a]
BDZ site:				
Agonists				
diazepam	(+)	(–)	passive avoidance (mice, rats)	Banfi et al. (1982)
		(–)	clinical observations (humans)	Venault et al. (1986)
		(–)	semantic memory study (humans)	Hartley et al. (1982)
lorazepam	(+)	(–)	semantic memory tests (humans)	Saenz-Campos et al. (1995)
alprazolam	(+)	(–)	semantic memory tests (humans)	Saenz-Campos et al. (1995)
Antagonists				
flumazenil	(–/0/+)	(+)	passive avoidance (mice)	Venault et al. (1996)
		(+)	discrimination (mice)	Raffali-Sebille and Chapouthier (1991)
Inverse agonists				
butyl- or methyl-beta-carboline 3-carboxylate	(–)	(+)	habituation, inhibitory avoidance (mice)	Venault et al. (1986)
		(+)	habituation, inhibitory avoidance (rats)	Izquierdo et al. (1991)
FG 7142	(–)	(+)	choice performance (rats)	Smith et al. (1994)
		(+)	lasting defensive behaviour (cats)	Adamec (1991)
Alcohol site:				
ethanol	(+)	(–)	clinical observations (humans)	Nevo[b] and Hamon (1995)
Barbiturate site:				
pentobarbital	(+)	(–)	spatial discrimination (rats)	Tomaz et al. (1982)
		(–)	operant behaviour (monkeys)	Ferguson and Paule (1993)
Steroid site:				
Agonists				
tetra-H-progesterone	(+)	(–)	habituation (rats)	Mayo et al. (1993)
Antagonists				
pregnenolone sulfate	(–)	(+)	active avoidance (mice)	Flood et al. (1992)
		(+)	habituation (rats)	Mayo et al. (1993)
pregnenolone		(+)	active avoidance (mice)	Flood et al. (1992)
Chloride channel blockers:				
picrotoxin	(–)	(+)	habituation (mice)	Venault et al. (1992)
pentylenetetrazole	(–)	(+)	habituation (mice)	Venault et al. (1992)
Ro5-4864	(–)	(+)	habituation, avoidace learning (rats)	Izquierdo et al. (1991)

[a] *See Lister (1990) for details.*
[b] *See also review in Finnigana nd Hammersley, (1992).*

discuss possible involvement of GABAergic mechanisms in cognitive processes (Sarter et al., 1995) because the GABAergic properties of the drugs were discovered some years later (Izquierdo and Medina, 1991). Interestingly, some other convulsants (e.g., strychnine, a glycine receptor antagonist) were reported to have no, or little effect on memory (Venault et al., 1992). In the meantime, some indirect evidence on the role of central GABA in memory processes was obtained by Katz and Liebler (1978) in the shock avoid-

ance test in rats. These authors showed impairment of memory and a lack of consolidation after the inactivation of GABA transaminase produced by aminooxyacetic acid (Katz and Liebler, 1978) presumably due to increase of GABA concentration in the brain. Subsequent evidence on GABAergic involvement in memory and learning was obtained by the demonstration that sodium valproate, an agent facilitating GABAergic function, slowed acquisition (Rayevsky and Kharlamov, 1983).

Another "set" of data to support the concept of GABAergic inhibition of memory and its consolidation came from neurophysiological studies including both lesion and electrophysiological recordings in humans and animals, showing that certain brain areas rich in GABA receptors (e.g., amygdala, septum, hippocampus, entorhinal cortex), played important role in the memory processes (Rawlins, 1987; Davis, 1994). Direct physical effects on these structures or local drug application were reported to affect both memory formation and consolidation (Izquierdo and Medina, 1991), supporting the concept of GABAergic involvement in memory regulation. The brain areas involved in human memory obtained in positron-emission tomography (PET) scan experiments by Grasby et al. (1993a-c), include hippocampus, amygdala and some other "GABA-ergic" regions, traditionally reported to be involved in mechanisms of anxiety.

The neuropharmacology of GABA receptors has moved forward dramatically in the past decade and GABAergic properties of a large number of drugs including positive and negative modulators of GABA-Benzodiazepine receptor complex such as steroids, barbiturates or BDZ have been investigated. These studies support a role for GABA in regulation of memory in that these drugs all have amnestic properties (Table 2).

NEUROPHARMACOLOGY OF GABAERGIC DRUGS AFFECTING MEMORIES

Early experiments aimed to test the specific role of central GABAergic system in memory and used traditional GABA-mimetic and GABA-blocking drugs in relatively simple memory tests (Rayevsky and Kharlamov, 1983). For example, Banfi et al. (1982) tested a large number of substances in a passive avoidance task in mice and rats but failed to demonstrate effects of the GABA per se. However, the GABA-A agonist muscimol administered to entorhinal cortex was reported to induce amnesia (Rosat et al., 1992) or block memory of habituation and inhibitory avoidance in animals (Izquierdo and Medina, 1991). As predicted, opposite to agonists, GABA antagonists like bicuculline were found to be strong memory-activating agents (Cruz-Morales et al., 1993). Indirect GABA modulators such as BDZ agonists have also been studied (see review in Lister, 1990). Diazepam was found to impair memory in passive avoidance tests in animals (Banfi et al., 1982), although reducing the numbers of errors of recall in the running memory test in the high anxiety individuals in experiments of Desai et al. (1983). More recent experimental and clinical data showed that BDZ are generally strong amnestic agents (Thiebot, 1985; Venault et al., 1986; Lister, 1990). Moreover, BDZ antagonists or inverse agonists exert memory-enhancing properties (Venault et al., 1986). For example, administration of BDZ antagonist flumazenil or inverse agonists methyl- and butyl-beta-carboline 3-carboxylate resulted in significant improvement of memory and learning in various tests learning tests (Table 2).

Ethanol is known to stimulate GABAergic transmission through enhancing the effects of GABA, thus, producing both anxiolytic-like effects and deleterious effects on memory and learning (Nevo and Hamon, 1995).

Barbiturates are the other positive modulator of GABAergic receptors that have been tested in various memory tasks. Pentobarbital demonstrated strong memory inhibition in spatial discrimination task in rats (Tomaz et al., 1982) and slowed response rates and decreased the accuracy numerous animal studies (see Volkerts, 1995, for details), including original experiments in monkeys in five different memory tests (Ferguson and Paule, 1993).

Neurosteroids are recently discovered as modulators on GABA-A receptors (Majewska, 1992; Lambert et al., 1995). Although most of those steroids are reported to activate chloride channels at the receptors (Lambert et al., 1995), the pharmacological profile of a few neurosteroids includes potent GABA-inhibiting properties. Interestingly, in recent studies, GABA-inhibiting steroids (such as pregnenolone-sulfate) were able to activate memory (Flood et al., 1992), whereas other steroids that are positive modulators of GABA receptors (for example, tetra-hydroprogesterone) were found to be memory-impairing agents (Flood et al., 1992; Mayo et al., 1993; see also Table 2).

According to Brioni (1993), the current view of the role of GABAergic system in memory so far is based upon the following principles: (1) the central GABAergic system is involved in memory regulation; (2) modulation of GABAergic system at all stages from the synthesis of GABA to chloride current (including GABA binding site, various sites for binding endogenous and exogenous regulators and drugs affecting the channel) may result in significant alteration of memory; and (3) inhibition of the GABAergic system has memory-facilitating effects, whereas stimulation produces memory impairment.

In conclusion, the concept may be well illustrated by the important observation of Dubrovina and Ilyutchenok (1995) that various GABA inhibitors acting through principally different mechanisms at GABA-A receptors (e.g., bicuculline, picrotoxin and flumazenil) produced similar positive effects on memory (see also Table 2).

INCONSISTENCIES AND CAUTIONS

Despite the facts that the involvement of GABA in memory has received experimental support and GABAergic drugs have definite effects on memory replicated in numerous studies of different laboratories, there is a large number of marked inconsistencies in the reported results (see Table 3, and data on picrotoxin and bicuculline in Cruz-Morales et al., 1993). In line with this, for example, discussing amnestic effects of BDZ, File et al. (1992) and Curran (1994) ask the important questions: How specific such effects are to memory functions? Are BDZ as a group the same in their effects? Importantly, it raises general question as to whether memory-active drugs induce specific effects on memory per se? Weingartner (1994) suggested that such drugs may be on other cognitive domains (e.g., attention, perception or encoding) rather than having specific effects on memory (see also Danion et al., 1993; Gorissen et al., 1995). Cole et al. (1994) indicated that specific effects on memory (e.g., BDZ "tolerance" effects in one-trial passive avoidance) are relatively difficult to study because the drugs may affect a wide range of performance variables, which could reflect either an amnestic effects or, for example, an anxiolytic-like effect.

However, despite these observations, it has been shown in many studies that at least some of these effects appeared to be highly specific (Table 2, see also discussion in File et al., 1992; Danion et al., 1993). In this context it seems therefore that such conflicting findings could be explained in several ways.

1. The differences in experimental protocols, including strain of animals or behavioural methods used (see discussion in Cruz-Morales et al., 1993). For example, Voigt and Morgenstern (1994) reported that diazepam (2–8 mg/kg) altered memory retention in inhibitory avoidance task in mice after the 2.5 A footshock but proved ineffective after the 0.75 A footshock. Moreover, in some studies, the opposite effects of the drugs have been reported in two different strains (see data on the effects of post-training muscimol, picrotoxin or bicuculline on memory retention in an inhibitory avoidance task in C57 and DBA mice; Castellano et al., 1993). In addition, different sensitivities of similar-looking methods to the effects of the drug seem to be a possible source for some other inconsistencies (see data of Ferguson and Paule (1993),

TABLE 3. Data of differential effects of high and low anxiety levels on memory

Experimental conditions	Demonstrated differential (+ or –) effects on memory in low vs. high anxiety groups	Memory tests (subjects)	References
Learning task with a positive or negative reinforcement:			
Flumazenil	No	Reinforced multiple-trial brightness discrimination	Raffalli-Sebille and
Methyl beta-carboline-3-carboxylate	No	task (mice)	Chapouthier (1991)
Ethyl beta-carboline-3-carboxylate	No	Punished and non-punished operant behaviour (squirrel monkey)	Glowa and Insel (1992)
Diazepam	(– vs. +)	Punished and non-punished schedule-induced	Castilla et al. (1994)
Chlordiazepoxide	(– vs. +)	drinking (rats)	
FG 7142	(– vs. +)	Punished and non-punished responding (rats)	Cole and Jones (1994)
Flumazenil in animals with high and low state anxiety	(+ vs. –)	Two-trial swimming test (mice)	Ferre et al. (1994)
Drugs in subjects with high and low state anxiety: Diazepam	(+ vs. –)	Running memory test with variable rate of item presentation and articulatory suppression used (humans)	Desai et al. (1983)
	No	Recall of semantic memory task (humans)	Hartley et al. (1982)
	No	Sensory-motor response (rats)	Orlova et al. (1994)
Subjects with high and low social anxiety	(– vs. +)	Recall of self-relevant information in a self-referent paradigm (humans)	Smith et al. (1983)
	(+ vs. –)	Binary decision, recognition memory and object naming tasks (humans)	Costa and Fozard (1978)
Exposure to stressful and nonstressful stimuli or events	No	Free recall, recognition memory (humans)	Oates and Shrimpson (1991)
	(+ vs. –)	Eyewitness performance (humans)	Dobson and Markham (1992)
	(+ vs. –)	Inhibitory avoidance under high- and low-stimulus condition (mice)	Voigh and Morgenstern (1992)

on different effects produced by barbiturates in five operant tests in monkeys).

2. Significant difference in experimental procedures may also contribute to the "pool" of inconsistent data. For example, results of studies involving local injection of the drugs to certain brain areas are critically dependent on the type of memory these areas are involved in. Thus, employment of different memory tasks may result in opposite results. It is well known that different brain structures control different types of memory; for example, habituation is controlled mostly by the hippocampus, whereas memory of inhibitory avoidance is controlled by amygdala, hippocampus and medial septum (Izquierdo and Medina, 1993). Moreover, "fine" specialisation was found even within such structures; for example, Tomaz et al. (1994) showed that retention-impairing effects of diazepam injected prior to acquisition were affected by lesions of central and lateral amygdala but not of the basolateral nuclei. However, anterograde amnesia in animals was produced by diazepam injected in lateral and basolateral but not central amygdala nuclei (Tomaz et al., 1994). Thus, some drugs injected into some certain areas theoretically may have no effects when tested in "wrong" memory tasks (see data on picrotoxin in medial septum in Rosat et al., 1992) due to some "specialisation" of the brain regions related to different memories (Potier et al., 1988; Rosat et al., 1992; Tomaz et al., 1994).

3. It seems that the differences in pharmacological properties of the drugs themselves may cause misinterpretation due to the fact that certain brain regions may be targeted in a different way by substances having different levels of tissue absorbtion or permeability through the blood-brain barrier. Interestingly, recent data on BDZ of Saenz-Campos et al. (1995) showed that similarly acting anxiolytic BDZ drugs (e.g., lorazepam and alprazolam) may have differential amnestic effects on certain types of cognitive processes. For example, in healthy subjects, equivalent doses of lorazepam produced higher psychomotor and semantic memory function disruptions, whereas alprazolam produced larger subjective impact (self-grading of performance, mood states). In addition, the drugs demonstrated different time course of action and recovery profiles (Saenz-Campos et al., 1995).

4. Together with pharmacokinetic aspects, pharmacodynamic properties are also of importance. Thus, the use of different doses of the drug may be the reason for the inconsistent results (Cruz-Morales et al., 1993; Venault et al., 1992). For example, at low doses of 50–200 mg/kg, vigabatrin was reported to have no effects on the choice accuracy in displayed nonmatching task in rats, but repeated administration with 300 mg/kg or a single dose of 1,000 mg/kg decreased behaviour activity of the animals in that working memory task (Mazurkiewicz et al., 1993) probably as greater inhibition of GABA-transaminase was produced. Generally, neuropsychopharmacological studies often demonstrate bell-shaped or polyphasic dose-dependent modes of the drugs action. So far, in order to be able to compare the results obtained in different experiments it is therefore critical that the drug used was tested over a wide and similar dose range.

5. Finally, some studies reported the alteration of memory produced by drugs in unusual experimental conditions. For example, postseizure memory-improving effects of some of antiepileptic drugs exerting GABA-activating properties were reported in epileptic patients (see data on vigabatrin in Thompson, 1992; and data in Grunewald et al., 1993a,b; Del Pesce et al., 1993). It is difficult to interpret such data because strong antiepileptic action may mask other psychopharmacological effects, including effects on memory.

INTERRELATIONSHIPS BETWEEN MEMORY AND ANXIETY: PRECLINICAL AND CLINICAL ASPECTS

Involvement of the GABAergic system in the regulation of certain key processes in brain has been long known (see Sieghart, 1995). However, its major role in regulation of anxiety and fear was accepted much later (Gray et al., 1984; Haefely, 1992), leading to a number of different theories (see Coupland and Nutt, 1995). Thus, like the memory-regulating effects of this system, its anxiety-modulating role underwent some evolution before it was generally accepted. Significant evidence to support the view of GABAergic modulation of anxiety-related behaviours came from intensive studies of brain "anxiety" topography: it has been shown that areas rich in GABA-A receptors such as amygdala, hippocampus and medial septum are major areas for perception of, and reaction to, anxiety (Gray et al., 1984; Davis, 1994). Moreover, GABAergic drugs exert strong anxiety-affecting properties. Briefly, the inhibition of GABAergic system by BDZ inverse agonists was reported to produce severe anxiety in various tests both in humans and animals, whereas activation of that system generally results in the reduction of anxiety (Haefely, 1992; Sieghart, 1992). A summary of the recent data on behavioural pharmacological effects of different principal GABAergic drugs is given in Table 2. Interestingly, these findings showed a close correlation between the effects on anxiety and those on memory, produced by these drugs.

Cognitive neuroscience methods have also been useful for defining anxiety-active drug-induced changes in a number of well-developed models of human memory (see review on memory-impairing properties of BDZ in Danion et al., 1993). Importantly, much clinical data also give support to the concept. For example, substantial evidence suggests that stimulants such as pentylenetetrazole can enhance learning and memory as well as attenuate some forms of amnesia (Altman et al., 1987). The early clinical studies of von Meduna and Friedman (1939) and Good (1940) showed some interesting psychological aspects of pentylenetetrazole

therapy then used to treat depression. For example, patients who received pentylenetetrazole treatment not only felt acute anxiety, but intensively tried to avoid further injections (von Meduna and Friedman, 1939; Good, 1940; Rodin, 1958). This shows clearly that pentylenetetrazole has provoked a state of conditioned fear with avoidance (i.e., "learned fear" or "learned anxiety"). However, not surprisingly, there are no recent clinical results because of the side effects associated with the use of such compounds, which are now not approved for clinical use as cognitive enhancers in any clinical population (Altman et al., 1987).

In those early studies, the mechanism of pentylenetetrazole action was unknown, and therefore the role of GABAergic system in such complex psychopharmacological effects was not discussed. An initial clue to the "cognitive" functions discharged by this neural system was the idea of common neuropsychology of anxiety and memory proposed by Gray et al. (1984) and Gray (1987). These authors indicated that anxiety-active drugs have some effects on memory: for example, anxiolytics had mostly negative effects on memory in a number of tasks (i.e., passive avoidance, on-the-baseline conditioned suppression, emergence time, partial reinforcement extinction and acquisition, differential reinforcement, successive discrimination and reversal learning).

A latter development of the concept of "GABAergic" role in memory and anxiety has been suggested by Davis et al. (1994). They pointed to data on amygdala and GABA neurotransmission in fear and anxiety, and suggested that amygdala and its efferent projections act as a central fear system involved both in expression and acquisition of conditioned fear. Anxiety produced decrease of GABA transmission in these areas and improvement of aversive conditioning, whereas anxiolytics increased GABAergic transmission and retarded aversive conditioning (see Table 2).

Summarising, it seems likely that there are overlapping GABAergic mechanisms of memory and anxiety due to: (1) common neurochemical mechanisms are involved in regulation of both memory and anxiety; (2) similar brain structures are involved; and (3) overlapping or correlation in neuropsychopharmacological effects of drugs compare mode of effects on memory and anxiety in Table 2).

In addition, a fourth association is that both memory and anxiety occur on a regular basis as a part of life in the real world. Interestingly, this raises the question of the existence of some "endogenous" molecules both producing anxiety and regulating memories. An analysis of possible candidates for such substances present in living organisms (Table 1) points to a limited number of GABAergic ligands substances which includes GABA, BDZ and steroids (Klotz, 1990; Izquierdo and Medina, 1991; Lambert et al., 1995). Not surprising, they all can play important roles in regulating both memory and anxiety (Table 2). More important, there is the possibility of "naturally occurring" interactions between memory and anxiety through the regulation or modulation of those transmitters. For example, in early studies of BDZ, Thiebot (1985) pointed to the interference of putative amnestic-like effects of BDZ and their anxiolytic properties. It is therefore of interest to compare the simultaneous drug effects on anxiety and memory. For this, Graeff et al. (1993) designed a new experimental model, the elevated T-maze claimed to be useful for simultaneous measurement of anxiety and memory. In this model, in line with previous results, diazepam demonstrated both anxiolytic and amnestic effects on inhibitory avoidance (Graeff et al., 1993). Moreover, the fact that endogenous substances released during anxiety or stress (i.e., some BDZ and steroids) are reported to activate memory allowed Izquierdo and Medina (1991) to speculate whether BDZ released during anxiety induced by training could provide a feedback for cognition regulation. This raises a general question about the biological rationale of such overlapping: is memory consolidation a protective factor in anxiety? In other words, is anxiety in some situations (both in animals and humans) required for a better memory to reduce the negative effects of the reexposure to threatening conditions?

In general, if the prior exposure to anxiety influences performance, this may be taken as evidence for the possible memory-anxiety interaction. If so, it seems that the state of anxiety may interfere with, or regulate, memory perception or consolidation. In that case, however, we have to expect that pharmacological effects on memory produced by drugs should be different in subjects with high and low states of anxiety.

EFFECTS OF DIFFERENT LEVELS OF ANXIETY ON MEMORY

Numerous experiments have been performed in order to assess the effects of anxiety or stressful stimuli on memory and learning. Those experiments included both various animal tasks and sophisticated psychological tests in humans (Table 3, see also Adamec, 1991; Mathews et al., 1995; Bradley et al., 1994). However, the available literature on differential effects on memory produced in subjects with high and low levels of anxiety is very inconsistent. In general, it demonstrates mostly a slight or no difference between subjects from both anxiety groups (Table 3).

Although such inconsistencies may have the same principal reasons as those on animal behavioural pharmacology of memory discussed earlier, however, some additional aspects have to be considered.

Firstly, there is a possibility of complex psychopharmacological profiles of the drugs which produce alterations of anxiety and memory (Venault et al., 1986; Potier et al., 1988). Briefly, it has been suggested that some GABAergic substances (including possible endogenous regulators usually released in stress or anxi-

ety) produce complex polyphasic dose-dependent actions on the GABAergic receptors. This explains why these drugs may have different effects on memory depending on the intensity of anxiety (Venault et al., 1992). Thus, slight inhibition of GABA may increase memory, whereas medium inhibition induces anxiogenic-like effects (Venault et al., 1992) which are likely to hinder learning. In line with this hypothesis, interesting results were obtained by File and Pellow (1988) and Potier et al. (1988). File and Pellow demonstrated differential dose-dependent effects of BDZ inverse agonists on memory. Potier et al. (1988) also revealed that different BDZ receptor occupancy by an inverse agonist could produce different behavioural effects; for example, 5% occupancy results in memory facilitation, whereas 30% produce proconflict and 40% convulsant effects.

Secondly, in respect to the question of differential effects on memory, produced by low- and high-level anxiety, it seems that the problem may be partially resolved by conducting further behavioural experiments in animals to study whether the pretraining exposure to moderate anxiety could alter memory in any of simple memory tests. For example, some interesting results were obtained by when retesting animals in the elevated plus-maze (File, 1995). Although not discussed in terms of "anxiety-memory" interrelations, the results indicate that the previous maze experience modified the behavioural responses in animals produced by different drugs. One explanation may be that the decrease of exploratory behaviour in the retest may be associated with habituation to the maze, thus resulting in alteration of behavioural patterns. Moreover, it would appear that the nature of the anxiety provoked by maze retest is different from that provoked by initial exposure (see review in Rodgers and Cole, 1994). In recent "drug-free" studies, Shilliam and Marsden (1995) investigated behaviours of rats repeatedly exposed to the elevated plus-maze. They showed an increase in aversive behaviour on day 3 with almost reversed effects on day 5. Perhaps the anxiety produced by first exposure resulted in the increased "aversive" memory of threatening surrounding in the elevated plus maze (see also Dawson et al., 1994).

The last aspect to be considered relates to the problem of the effects on memory produced by high level of anxiety. Although moderate anxiety seems to stimulate cognition, it is a well-established fact that exposure to severe stress may result in amnesia both in animals and humans. Acute administration of anxiogenics like pentylenetetrazole has a similar impact (Rodin, 1958). Although the mechanisms of such reactions are unclear, it seems that the reported release of some endogenous ("proamnestic") substances such as BDZ may provide the mechanism for such "adaptive" inhibition (Izquierdo and Medina, 1991). Although there is a great deal of biological rationale in such "adaptive" memory inhibition, however, there is very little information on this issue. Likewise, the important question as to whether memory in this case is just suppressed or eliminated remains unclear.

CONCLUSION

The present discussion about the behavioural effects of GABAergic drugs and possible changes in cognitive processes underlying these effects remains somewhat open (see criticism in Sarter et al., 1995). Apart from speculations on biological rationale of a degree of "anxiety or stress may be necessary for learning" (Izquierdo and Medina, 1991), there is a neurobiological rationale for linking memory and anxiety. Thus, according to these authors, memories, being labile immediately after acquisition, are susceptible to both deleterious and facilitatory influences. This will finally determine which memory is eventually stored, and therefore memory consolidation is likely to be a mechanism of brain integration between memory and anxiety. As stressed earlier, inhibition of GABAergic system may result in significant increase of anxiety both in humans and animals (Sieghart, 1992). This generally accepted concept of anxiety explains why most of GABAergic drugs (see Table 1), exert anxiolytic or anxiogenic activity depending on the mode of the action on this central GABAergic inhibitory system (Table 2). Moreover, it is a well-established fact that most of the proconsolidation mechanisms are facilitatory (McGaugh, 1988), and therefore are somewhat opposite to the inhibitory processes initiated and controlled by the GABAergic system. Furthermore, in light of that concept, the state of anxiety may be considered as a naturally occurring inhibition of GABAergic systems (Haefely, 1992; Sieghart, 1992). Like the action of exogenous GABA-inhibiting drugs, this endogenous process has similar impact on balance between central inhibitory and facilitatory systems, and therefore may serve as a principal mechanism of memory activation and regulation.

Interestingly, whilst producing speculations on the general positive "biological" role of low-level anxiety or stress, the latter idea has some support from several different groups of studies. Firstly, it is the comparative analysis of behavioural pharmacology of memory and anxiety (Table 2) including long-lasting effects of drugs on anxiety. Second, evidence includes "drug-free" behavioural studies such as the original behavioural experiments of Adamec and Shallow (1993; see also review in File, 1995). For example, studying anxiety produced in rats by a single exposure to a cat, Adamec found that anxiety (measured in the elevated plus-maze) was increased over controls from 1 to 21 days after exposure to a cat. Such long-lasting effects on animal behaviour demonstrate clearly the involvement of memory mechanisms stimulated by exposure to stressful stimuli. Despite the fact that the organism may benefit from facilitation of memory produced by

slight previous anxiety, or memory blockage after severe stress, the relationships between the "biology" and "psychology" of anxiety are rather complex. For example, high anxiety state is often accompanied by anxious cognitions. The latter may hinder positive impact of anxiety-memory interactions, finally resulting in increase of anxiety through "accumulation" of negative memories. This may be well illustrated by the observation that depressed or anxious patients are more likely to recall past failures than successes. In that case, however, the balance between positive and negative memories may have a major impact on emotional state of a subject. Perhaps pharmacological correction of the memories by GABAergic drugs (applied, for instance, in patients during remissions of depression, anxiety or phobias) might be of additional help in therapy.

Finally, accompanied by intensive studies in the field of pharmacological regulation of anxiety, the "memory-anxiety" GABAergic concept may point to the new directions for a rational search for new classes of memory-activating drugs.

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