

## Memory Effects of Benzodiazepines: Memory Stages and Types versus Binding-Site Subtypes

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### SUMMARY

**Benzodiazepines are well established as inhibitory modulators of memory processing. This effect is especially prominent when applied before the acquisition phase of a memory task. This minireview concentrates on the putative subtype selectivity of the acquisition-impairing action of benzodiazepines. Namely, recent genetic studies and standard behavioral tests employing subtype-selective ligands pointed to the predominant involvement of two subtypes of benzodiazepine binding sites in memory modulation. Explicit memory learning seems to be affected through the GABA<sub>A</sub> receptors containing the  $\alpha_1$  and  $\alpha_5$  subunits, whereas the effects on procedural memory can be mainly mediated by the  $\alpha_1$  subunit. The pervading involvement of the  $\alpha_1$  subunit in memory modulation is not at all unexpected because this subunit is the major subtype, present in 60% of all GABA<sub>A</sub> receptors. On the other hand, the role of  $\alpha_5$  subunits, mainly expressed in the hippocampus, in modulating distinct forms of memory gives promise of selective pharmacological coping with certain memory deficit states.**

### KEYWORDS

acquisition, explicit memory, procedural memory, GABA<sub>A</sub> receptor,  $\alpha_1$ -subunit,  $\alpha_5$ -subunit

### INTRODUCTION

A few amino acids exist in high concentrations in the central nervous system (CNS), playing a neurotransmitter role. Among them is  $\gamma$ -amino butyric acid (GABA), which acts through two types of receptors. GABA<sub>A</sub> receptors mediate the most of fast inhibitory neurotransmission in the mammalian brain and are involved in the regulation of vigilance, anxiety, muscle tension, epileptogenic activity, and memory functions (Korpi et al., 2002; Rudolph & Möhler, 2004). In addition to the site of action of GABA itself, there are several modulatory sites at GABA<sub>A</sub> receptors. These sites mediate the actions of many substances, notably benzodiazepine drugs (Chebib & Johnston, 2000; Korpi et al., 2002).

The characterization of the diverse pharmacological effects of the benzodiazepines (sedative, hypnotic, anxiolytic, muscle relaxant, anticonvulsive, and amnesic actions) can be considered a major success of behavioral pharmacology (Sanger et al., 2003). Since the introduction of chlordiazepoxide in 1960, benzodiazepines have been extensively prescribed to cope with anxiety, insomnia, muscle spasm, and epilepsy. These drugs

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are still thought of as a pharmacological gold standard for treating anxiety disorders (Sramek et al., 2002). Nevertheless, the unwanted effects of the benzodiazepines have become obvious over the years. Psychomotor and cognitive impairment is common, and such more serious neuropsychiatric reactions as amnesic and aggressive episodes, can occur (Lader, 1999). Drug-induced impairment of mnesic function could be desirable in certain situations (perioperative surgical periods, procedures like endoscopies) (Buffett-Jerrott & Stewart, 2002). On the other hand, most patients taking benzodiazepines do not complain of memory problems (Barbee, 1993). Nevertheless, the amnesic action, most commonly thought of as an unwanted effect, will be treated in such a way in this paper.

Three kinds of allosteric modulators act through the benzodiazepine binding site: positive (agonist), neutral (antagonist), and negative (inverse agonist) modulators (Chebib & Johnston, 2000). It is well established that agonists at the benzodiazepine site present anxiolytic and amnesic properties, whereas inverse agonists, such as  $\beta$ -carbolines, exert anxiogenic and learning-enhancing actions (Venault et al., 1986, 1987; Jensen et al., 1987; Krazem et al., 2001). The bidirectional influences of GABA<sub>A</sub> receptor modulation on memory processing have been thoroughly reviewed (Chapouthier & Venault, 2002). In the present minireview, we concentrate on the amnesic effects of the benzodiazepines and particularly on the results of contemporary investigations into the GABA<sub>A</sub> receptor subtypes that contribute to this action. These findings stem from both genetic studies and standard behavioral paradigms employing subtype-selective ligands.

#### MEMORY STAGES AND BENZODIAZEPINES

Memory is composed of three stages: acquisition, consolidation, and retrieval (Abel & Lattal, 2001). Yet, no one has ever *measured* learning or memory: these processes can be inferred only from

behavior (Cahill et al., 2001). A memory task represents a behavioral procedure to which an animal is repeatedly (usually twice) exposed. The first exposure is the learning or acquisition session, whereas the effects of training are assessed, after an appropriate delay, in retention session(s). Experimental treatments can be applied (a) shortly before the learning session, (b) just after the learning session, or (c) before the retention session. Such interventions are intended to affect the acquisition, consolidation, and retrieval stages of memory, respectively. Experimentally isolating the different stages of memory can be quite difficult, however, because experimental techniques can affect two or more stages, depending on the time course of the manipulations (Abel & Lattal, 2001). Additionally, behavior is affected by processes other than learning and memory. Notably, pre-session treatment can indirectly affect acquisition or retention performance through influences on such factors as motor function, attention, sensory receptor sensitivity, motivation, and general arousal level (Cahill & McGaugh 1998; McGaugh & Izquierdo, 2000).

Benzodiazepines have been repeatedly found to impair memory acquisition (in clinical terminology, they cause anterograde amnesia). In other words, the compounds affect the type of learning that depends on building novel associations in memory; this effect will be discussed later. Exceptionally rarely, benzodiazepines administered just after the acquisition session can impair retention performance in a memory task like passive avoidance (Jensen et al., 1979). With regard to the retrograde memory effects, despite the reservations of one author (Cole, 1986), the results of most animal studies rule out an action of benzodiazepines on retrieval in different memory tasks (Venault et al., 1986; McNamara & Skelton, 1991). In tests that included a significant emotional component, however, several results pointed to the inhibitory (Cole and Michaleski, 1984; Cole, 1986) as well as the facilitative (Savic et al., 2003;

Obradovic et al., 2004) influences of the benzodiazepines on memory retrieval. In fact, as suggested by the Yerkes-Dodson hypothesis (1908), one can expect a curvilinear relation between arousal and/or anxiety and performance, such that a moderate level of anxiety can benefit cognitive performance, depending on task difficulty (Eysenck, 1985).

Similar to reports of animal studies, the frequent conclusion from human studies is that benzodiazepines do not significantly influence memory retrieval (Ghoneim & Mewaldt, 1975; Lister, 1985). Nevertheless, retrieval impairment in young adult males has been reported (Block & Berchou, 1984), and memory facilitation in humans is sometimes seen as well (Hinrichs et al., 1984; File et al., 1999; Fillmore et al., 2001). Hinrichs & coworkers hypothesized that this phenomenon is not a true facilitation of retrieval processes but rather could be the result of reduced interference from items presented after drug administration as a paradoxical consequence of drug-induced anterograde amnesia. Nevertheless, facilitating effects on retrieval processes that are more specific have also been proposed (File et al., 1999).

#### **AMNESIA INDUCED BY BENZODIAZEPINES: FINDINGS OF STUDIES ON HUMANS**

Amnesic effects in humans were first recognized by anesthesiologists using benzodiazepines as pre-medication (Brandt & Oakes, 1965; Haslett & Dundee, 1968). Such effects have been repeatedly confirmed (for example Rodrigo & Lusiardo, 1988; Kain et al., 2000), and thoroughly reviewed (Lister, 1985; Curran, 1991; Buffett-Jerrott & Stewart, 2002). We should note that most of these studies investigated the effects of acute doses of benzodiazepines in healthy volunteers having no history of benzodiazepine or other psychotropic medication use. Unfortunately, the

amnesic effects of benzodiazepine-like drugs have been increasingly misused to facilitate crimes like sexual assault and robbery (Gouille & Anger, 2004).

Benzodiazepine-induced amnesia resembles certain forms of organic amnesia, and many efforts to model organic amnesia pharmacologically have been employed (Brown et al., 1982; Weingartner, 1985). Hence, such drugs can be useful tools for studying normal and abnormal memory mechanisms (Duka et al., 1996). Moreover, Danek et al. (2002) related the transient global amnesia in a previously healthy woman to the putative endogenous benzodiazepines. Namely, the resolution of an unexplained amnesic episode coincided with the test administration of 0.5 mg flumazenil: the patient's first memories corresponded to the short period after the injection of benzodiazepine antagonist.

#### **AMNESIA INDUCED BY BENZODIAZEPINES: FINDINGS OF STUDIES ON ANIMALS**

The number of experiments involving the testing of cognitive functions has increased remarkably (Sarter, 2004). However, in addition to limitations regarding differentiation of memory stages/distinct actions of treatment (given above), we should mention that to distinguish between the changes in behavior that occur because an animal remembers prior events and changes in behavior that occur merely because these prior events have happened is difficult (Morris, 2001). Hence, the results obtained in animal studies of memory should be interpreted cautiously.

According to a recent survey (Myhrer, 2003), the tests most widely used to assess learning and memory in laboratory rodents encompass the Morris water maze, the radial maze, passive avoidance, and spontaneous alternation. In these paradigms, benzodiazepines were repeatedly shown as acquisition-impairing agents; a review of findings was given in Myhrer (2003).

TABLE 1

GABA<sub>A</sub> receptor benzodiazepine binding site subtypes mediating distinct pharmacological effects of diazepam in knock-in mice.

Effect	Receptor subtype			
	$\alpha_1$	$\alpha_2$	$\alpha_3$	$\alpha_5$
Sedation	+(1)	-(2)	-(2)	-(3)
Anxiolysis	-(1)	+(2)	-(2)	-(3)
Anterograde amnesia	+(1)	n.d.	n.d.	n.d. <sup>#</sup>
Miorelaxation	-(1)	+(4)	±(4)	+(3)
Anticonvulsant activity	+(1)	-(2)	-(2)	-(3)
Hypnosis (EEG changes)	-(5)	+(6)	-(7)	n.d.
Tolerance (to sedation)	-(8)	-(8)	-(8)	+(8)

+, behavioral effect of diazepam was absent in mice with point mutation in the designated subunit.

±, behavioral effect of diazepam was diminished in mice with point mutation in the designated subunit, when drug was administered at very high dose (30 mg/kg).

-, point mutation did not change the effect of diazepam, in comparison with wild-type mice.

n.d. not determined.

<sup>#</sup> Studies with pharmacologically untreated  $\alpha_5$ -knock-in (Crestani et al., 2002) and  $\alpha_5$ -knock-out (Collinson et al., 2002) mice pointed to the role of the  $\alpha_5$ -subunit in modulation of cognitive processes.

Cited from: (1) Rudolph et al. (1999); (2) Löw et al. (2000); (3) Crestani et al. (2002); (4) Crestani et al. (2001); (5) Tobler et al. (2001); (6) Kopp et al. (2004); (7) Kopp et al. (2003); (8) van Rijnsoever et al. (2004)

#### BENZODIAZEPINE SITE(S) OF ACTION AND GABA<sub>A</sub> SUBTYPES INVOLVED IN LEARNING AND MEMORY PROCESSING

The huge diversity of GABA<sub>A</sub> receptor subtypes has become clear in recent years (Barnard et al., 1998). GABA<sub>A</sub> receptors are pentameric membrane proteins that operate as GABA-gated chloride<sup>-</sup> channels. The receptors are assembled from several families of subunits, of which at least 19 subunits occur in the CNS. Nevertheless, the vast majority of

receptors appear to be an association of two  $\alpha$ -subunits, two  $\beta$ -subunits, and a single  $\gamma$ -subunit, which make up a central ion channel. The majority contain a benzodiazepine binding site located at the interface of the  $\gamma_2$ -subunit and the respective  $\alpha$ -subunit ( $\alpha_1$ ,  $\alpha_2$ ,  $\alpha_3$  or  $\alpha_5$ ) (Korpi et al., 2002).

Recent research using genetically modified mice has pointed to the specific contribution of individual receptor subtypes to the pharmacologic spectrum of benzodiazepines (Table 1). Specifically, the sedative and anterograde amnesic effects of

TABLE 2

Involvement of different GABA<sub>A</sub> subunits in memory effects of benzodiazepines: findings from studies with subtype selective ligands vs. knock-in mice vs. knock-out mice. Only behavioral tests used in at least two types of studies are included.

Type of study	Receptor subtype	Type of memory/test		
		Explicit/ passive avoidance	Procedural/active avoidance	Working/delayed matching to place version of the Morris water maze test
studies with subtype selective ligands	$\alpha_1$	-(1: Ant), +(2: A, Ant)	+(3: A, Ant)	n.d.
	$\alpha_5$	n.d.	n.d.	+(4, IA)
studies with knock-in mice	$\alpha_1$	+(5)	n.d.	n.d.
	$\alpha_5$	n.d.	n.d.	n.d.
studies with knock-out mice	$\alpha_1$	n.d.	n.d.	n.d.
	$\alpha_5$	n.d.	-(6)	+(6)

+, the given subunit involved in modulation of memory type tested

-, the given subunit not involved in modulation of memory type tested

A: subtype selective agonist; Ant: subtype selective antagonist; IA: subtype selective inverse agonist

n.d. not determined.

Results from: (1) Belzung et al. (2000); (2) Savic et al. (2005a); (3) Savic et al. (2005b); (4) Street et al. (2004); (5) Rudolph et al. (1999); (6) Collinson et al. (2002)

benzodiazepines were mainly attributed to  $\alpha_1$ -containing GABA<sub>A</sub> receptor subtypes, anxiolytic action to the  $\alpha_2$ -containing receptors, anti-convulsant activity (partially but not fully) to the  $\alpha_1$ -containing receptors, and muscle-relaxant effect largely to the  $\alpha_2$ -containing receptors (Rudolph et al., 1999; McKernan et al., 2000; Low et al., 2000). However, in attempts at elucidating the functional relevance of structurally diverse GABA<sub>A</sub> receptor subtypes, the pharmacologic approach, using subtype selective ligands, complements the genetic studies and is necessary to corroborate and amplify insights provided by genetic studies (Millan, 2003).

#### TYPES OF MEMORY AND EFFECTS OF BENZODIAZEPINES: SUBTYPE SPECIFICITY?

Memory can be classified according to its duration (short-term and long-term memory) and according to content (explicit and implicit ones). The distinction between explicit (declarative) memory and implicit (non-declarative) memory depends on whether a memory is accompanied by conscious recollection. Whether any non-human species displays explicit memory, defined as an ability to report the memory, is highly disputable (Izquierdo et al., 1999; Morris, 2001; Squire, 2004). Nevertheless, animals can recall the 'what,

where and when' of discrete events and display this in an overt behavior (Clayton et al., 2001).

Explicit memory is often assumed to be the only aspect of memory that is vulnerable to amnesia. Studies of neuropsychological patients have shown that individuals who suffer from amnesia have impairment on explicit memory tasks but no performance deficit on measures of implicit memory (Warrington & Weiskrantz, 1974) because many implicit memory tasks do not require associative processing. Nevertheless, whenever a task requires the associative processing of information, regardless of whether that information is explicit or implicit in nature, memory could be impaired (Park et al., 2004). Accordingly, we will concentrate on the published experiments that have aimed to discern subtype specificity of amnesic effects of benzodiazepines (Table 2), especially in the context of a distinction between the explicit and implicit—mainly procedural—memories. Such distinctions could be exemplified through two types of avoidance conditioning—the active and the passive.

The passive avoidance paradigm might be viewed as measuring explicit memory, to the point that terms such as 'declarative' or 'explicit' can be applied to experiments using rodents (Izquierdo et al., 1999). The task is learned very rapidly, and memory can be easily and reliably assessed (McGaugh & Izquierdo, 2000). The anterograde amnesic effects of agonists at the benzodiazepine site in this paradigm are well established (Izquierdo et al., 1990; Salgueiro et al., 1997; Anglade et al., 1999). For the retention of this task, the preserved biochemical events in the hippocampus, one of the key brain areas involved in learning and memory, are necessary (Izquierdo & Medina, 1997). The possibility has been suggested that because of their low binding affinity for  $\alpha_5$ -containing receptors in the hippocampus,  $\alpha_1$ -selective agonists may produce less memory impairment than do non-selective agonists (Morselli, 1990). Studies with pharmacologically

untreated  $\alpha_5$ -knock-in (Crestani et al., 2002) and  $\alpha_5$ -knock-out (Collinson et al., 2002) mice pointed to the importance of the  $\alpha_5$ -subunit for performing certain memory tasks (trace fear conditioning and Morris water maze, respectively). In a recent passive avoidance study, we found that both, the non-selective agonist midazolam and the preferential  $\alpha_1$ -subunit selective agonist zolpidem induce amnesia in rats in a dose-dependent manner (Savic et al., 2005a). Similarly, zolpidem disrupts the acquisition of conditioned fear (Sanger et al., 1986) and passive avoidance (Tang et al., 1995; Edgar et al., 1997) in mice. Moreover, the results of the passive avoidance test and the lick suppression paradigm in  $\alpha_1$ -knock-in mice demonstrated that the anterograde amnesic effect of benzodiazepines could be attributed to  $\alpha_1$ -containing GABA<sub>A</sub> receptor subtypes (Rudolph et al., 1999). The involvement of the  $\alpha_1$ -subunit in the amnesic effects of benzodiazepines in the passive avoidance paradigm could be, at least in part, related to the immunocytochemical findings: abundant staining in the rat hippocampus for the  $\alpha_1$ - and  $\alpha_2$ -, in addition to the  $\alpha_5$ -subunit (Pirker et al., 2000).

Belzung et al. (2000) found that  $\beta$ -CCt failed to antagonize the amnesic effects of chlordiazepoxide in the passive avoidance task and the radial arm maze in mice. The complete reversal of amnesia by the non-selective antagonist flumazenil, or by the preferential  $\alpha_1$ -subunit selective antagonist  $\beta$ -CCt, was unattainable in the passive avoidance study in rats as well. Yet, the effects of zolpidem were significantly attenuated by both antagonists, whereas only flumazenil was effective when combined with midazolam (Savic et al., 2005a). The results of these studies indicate that other  $\alpha$ -subunit(s), in addition to the  $\alpha_1$ -subunit, contribute to the amnesic actions of non-selective benzodiazepine site agonists in an explicit memory task. First in line is the  $\alpha_5$ -subunit, located in the hippocampus (Möhler et al., 2004).

Furthermore, it was of interest to test mnemonic effects of the  $\alpha_1$ -selective agonists in a task that is

not (predominantly) hippocampal-dependent. The improved performance of animals with hippocampal lesions in two-way active avoidance (Gray & McNaughton, 1983) suggested that this task should not be hippocampal-dependent. In accordance with such an interpretation, the  $\alpha_5$ -knock-out mice, compared with wild-type animals, performed significantly better in a water maze (hippocampal-dependent) model but not in an active avoidance test (Collinson et al., 2002). In a recent study, we found that both the non-selective agonist midazolam and the preferential  $\alpha_1$ -subunit selective agonist zolpidem induced amnesia in rats in a dose-dependent manner (Savic et al., 2005b). The results of those studies can be seen to demonstrate the amnesic activity of an  $\alpha_1$ -selective agonist in a procedural (Squire, 1992), hippocampal-independent (Gray & McNaughton, 1983; Collinson et al., 2002) memory task. As in the passive avoidance test, the amnesic effects were attenuated but not fully reversed by flumazenil and  $\beta$ -CCt (Savic et al., 2005b). Similarly, Celik et al. (1999) found that flumazenil (10 mg/kg) reverses the impairment of acquisition rate in the 5-day active avoidance paradigm only in rats injected daily with the lowest (0.5 mg/kg) but not with higher (1.0 mg/kg and 2.0 mg/kg) doses of diazepam (Celik et al., 1999). In our study, rats treated with the anxiolytic dose of midazolam (2.0 mg/kg) significantly deteriorated in retention performance relative to the first day session; the group co-injected with  $\beta$ -CCt, although still successful in the training session (an anti-anxiety activity), performed in the retention session on the control level, i.e. the amnesic effect was lacking (Savic et al., 2005b). The results suggest that the  $\alpha_1$ -subunit is substantially involved in procedural memory processing.

In conclusion, the results of experiments using the preferential  $\alpha_1$ -subunit selective antagonist  $\beta$ -CCt suggest that the inhibitory effects of benzodiazepine site agonists on the formation of explicit memory (passive avoidance test) involve other  $\alpha$ -subunits in addition to the  $\alpha_1$  subtype (Savic et al.,

2005a). Hippocampal GABA<sub>A</sub> circuits expressing the  $\alpha_5$ -subunit may be substantially involved in processing of this form of memory task (Möhler et al., 2004). On the other hand, these effects on the procedural memory may predominantly depend on the  $\alpha_1$ -containing GABA<sub>A</sub> receptors (Savic et al., 2005b). The pervading involvement of the  $\alpha_1$ -subunit in memory modulation is not unexpected because this subunit is the major subtype, present in 60% of all GABA<sub>A</sub> receptors (Möhler et al., 2002). On the other hand, the role of  $\alpha_5$ -subunits, mainly expressed in the hippocampus, in modulating distinct forms of memory, gives promise of coping with some memory deficit states through the selective inverse agonism in this receptor subpopulation (Street et al., 2004).

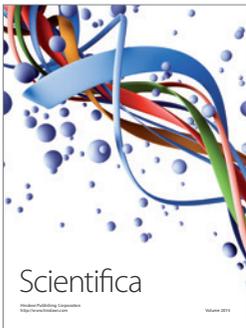
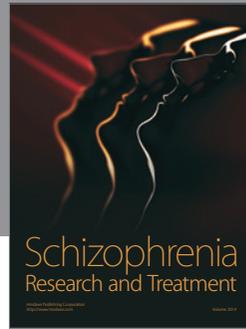
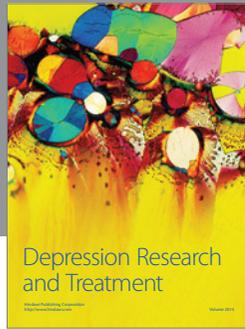
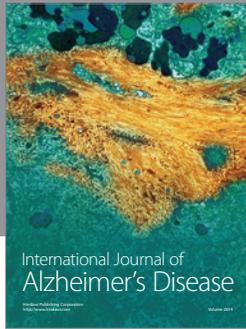
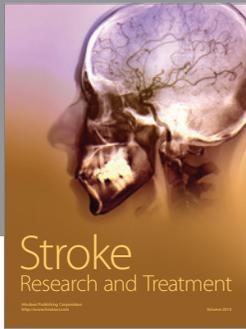
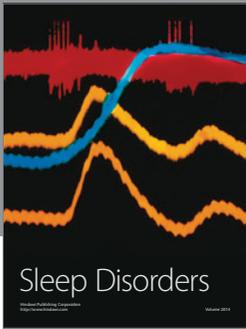
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