GABA and Muscimol as Reversible Inactivation Tools in Learning and Memory

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ABSTRACT

Reversible inactivation of brain areas is a useful method for inferring brain-behavior relationships. Infusion of GABA or of the GABA receptor agonist muscimol is considered one interesting reversible inactivation method because it may not affect fibers of passage and may therefore be compared to axon-sparing types of lesions. This article reviews the data obtained with this method in learning and memory experiments. A critical analysis of data, collected in collaboration with Simon Brailowsky, with chronic GABA infusion is presented, together with an illustration of data obtained with muscimol-induced inactivation.

KEYWORDS

amygdala, GABA, frontal cortex, learning, memory, muscimol, nucleus basalis magnocellularis

INTRODUCTION

Considerable insight into the molecular mechanisms that are involved in learning and memory has been gained in recent years (for example, Lynch, 1998). Nevertheless, as stated by Bures and Buresova (1990):

> *In spite of its importance, research specifying plastic phenomena at the microscale cannot lead to understanding of the mechanisms of learning and memory without a commensurate progress of system studies showing where and when the cellular changes take place.*

In this regard, neuropsychological analysis of brain-injured patients has profoundly influenced the present conception of memory systems (for example, Tulving, 1991). In animal studies, new paradigms have been introduced to explore the multiplicity of the processes underlying these memory systems, and new techniques (for example, expression of immediate early genes) have been adapted to identify the brain networks supporting these processes. Lesion techniques in animals have also improved in neuroanatomical selectivity, using excitotoxic compounds (for example, ibotenate, AMPA [α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid], quisqualate) that destroy cell bodies without affecting the fibers of passage. For instance, in the ongoing debate on the role of the hippocampus in learning and memory, it has been found that part of the deficits (in particular, some nonspatial learning deficits), induced by mechanical or electrolytic lesions, may to be due to damage to neighboring structures rather than to the hippocampus itself (for example, Jarrard, 1993). Despite this progress, the various shortcomings of lesions studies for inferring brain-behavior relationships must be recognized. One drawback is that inference about a relation between brain damage and a behavioral deficit implicitly supposes that the undamaged components of the system continue to function normally (see Jaffard & Meunier, 1993; Farah, 1994), which is unlikely

to be the case. Somewhat related to the preceding, lesion effects are usually tested after a necessary recovery period from surgery; during that time, various restorative and/or adaptive processes occur that may obscure the primary effect of the lesion. For example, several studies have reported partial or complete recovery of cholinergic markers within the cortex after unilateral excitotoxic lesions of the nucleus basalis magno-cellularis (NBM), provided that a sufficient recovery period (3 mo) was respected (for example, Wenk & Olton, 1984; Gardiner et al., 1987; Casamenti et al., 1988). Returning to Bures and Buresova's statement, brain lesions certainly contribute to our knowledge of where in the brain plastic changes may occur during learning. Because they are irreversible, however, brain lesions rarely indicate when plastic changes occur. In this regard, reversible inactivation of brain areas has proved to be an efficient tool to complement lesion studies in various fields of research, including the study of learning and memory. This article aims to briefly present data obtained with GABA or GABA agonists as reversible inactivation tools, with a special emphasis on data obtained in collaboration with Simon Brailowsky.

GABA AND REVERSIBLE INACTIVATION

GABA-induced inactivation has a rapid onset and a short duration; its principal use has been in anesthetized animals. For example, acute injection of GABA into the anterodorsal tegmentum of anesthetized rats (0.25 to 1.0 mg/μL saline, injection volume of 0.1 or 0.2 μL) was found to block the locomotion that is elicited by hypo-thalamic stimulation within 5 min of the injection, with recovery occurring within 10 to 20 min (Sinnamon & Benaur, 1997). A similar onset and recovery time of the reaction time to a stimulus-triggered movement was recently reported by Martin and Ghez (1999) after GABA injection into the magnocellular red nucleus of cats. Spatial and temporal characteristics of the inactivation induced by GABA, administered into cortical sites, has been recently reviewed by Hupé et al. (1999). Repeated injections of small doses of GABA have been reported (a) to induce a more homogeneous inactivation than a single injection of larger amounts does, and (b) to increase the duration of inactivation (Hupé et al., 1999).

Although the short duration of GABA-induced inactivation is not compatible with learning and memory tests, this inconsistency can be compensated for by infusing the GABA constantly over a period of time, using sub-cutaneous osmotic minipumps (Alzet®). Through the appropriate choice of the minipump model, duration and rate of infusion (for example, 1 μL/h for 7 d using the 2001 model) can be chosen to fit the experimental design. In a series of studies, Brailowsky and collaborators (1989) showed that chronic GABA infusion is an efficient method to inactivate brain regions involved in memory processes. Delayed responses depend on the prefrontal cortex (for example, Kolb, 1984). Infusion of GABA (50 μg/μl) over 7 days after acquisition of the task was found to impair the delayed response in monkeys (Brailowsky et al., 1989) and rats (Di Scala et al., 1990; Meneses et al., 1993). This deficit was found to be relatively stable over the treatment period (for example, Meneses et al., 1993), and rapid recovery of performance occurred upon cessation of the treatment. In this cortical area, histological examination of the sites of infusion did not reveal clear signs of lesions (at least, not larger than those after vehicle infusion, Di Scala et al., 1990; Meneses et al., 1993).

The NBM, the main source of cortical acetylcholine afferents, has been implicated in attentional and working memory processes (Dunnett et al., 1991; Muir et al., 1993; McDonald & Overmier, 1998). As cholinergic NBM neurons receive a massive GABAergic innervation (for example, Wood & Richard, 1982; Zaborsky et al., 1986; Ingham et al., 1988),

acting on NBM GABA receptors constitutes a means to modify the activity of these neurons. Infusion of small doses of GABA (10 μg/μL/h) induces a delay-dependent deficit in a previously learned win-shift task in a radial maze (Majchrzak et al., 1990). This effect is consistent with the reported deficit after excitotoxic (ibotenate) lesion of the NBM (for example, Bartus et al., 1985). Infusions of higher doses (50 or 100 μg/μL/h) of GABA induces a delay-independent deficit in the win-shift task (Majchrzak et al., 1990), together with profound sensorimotor impairments (Will et al., 1988; Majchrzak et al., 1990; 1992a). With both doses, the deficits appeared to be reversible because performance recovered shortly after interruption of the infusion.

In a series of experiments, possible long-lasting (or irreversible) effects of GABA infusion into the NBM were evaluated. To characterize the spatial extent of the inactivation induced by GABA infusion, Majchrzak et al., (1992b) measured local cerebral metabolic rates for glucose (CMRglc) after 24-h infusions of GABA. The results showed that despite its efficacy on the memory task, infusion of a small dose (10 μg/μL/h) did not modify (in comparison with saline-treated animals) CMRglc within the NBM, in neighboring structures, or in NBM cortical projection areas (frontal and parietal cortex). In contrast, infusion of high doses of GABA (100 μg/μL/h) induced a strong reduction of CMRglc within the NBM, as well as in neighboring structures (for example, globus pallidus) and NBM projection areas (frontal and parietal cortex, amygdala, reticular thalamic nucleus). Such distant hypometabolic effects of GABA infusion may reflect an NBM reduction of synaptic activity, but also may be due to degenerative processes. Indeed, Browne et al. (1998) have shown that intra-NBM injections of excitotoxic compounds (NMDA and AMPA) rapidly induce a reduction of glucose utilization in interconnected cortical areas.

Further evidence of irreversible lesion with a high dose (50 or 100 μg/μL/h) of GABA, but not with a smaller dose (10 μg/μL/h), was obtained using a variety of techniques. Infusion of a high dose of GABA (100 μg/μL/h) into the NBM induced neuronal damage within this nucleus, which could be observed on Cresyl violet-stained sections (see Fig. 1).

The loss of magnocellular cholinergic neurons was confirmed by reduced acetylcholinesterase (AChE) and choline acetyltransferase (ChAT) activities in the frontal and parietal cortices (see Fig. 2; Will et al., 1988; Majchrzak et al., 1990; 1992; Majchrzak, 1992). In another study (Ballough et al., 1992), two well-established bioindicators of neurotoxicity, azure B-RNA and Feulgen-DNA expression, were used to examine the putative cytopathic effects of GABA infusion into the basal forebrain. This method revealed a reduced neuronal RNA metabolism shortly (24 h) after infusion, even when using the small dose. In the latter case, however, this effect disappeared within an 8-d postinfusion delay.

Taken together, the data indicate that GABA injection is an efficient method to inactivate a brain area; the data also indicate that the effects of chronic GABA infusion may not be reversible, mainly when high doses are used. A series of biological parameters (see above), as well as the mere existence of the GABA-withdrawal syndrome (see Brailowsky et al., 1987; Fukuda et al., 1987; Brailowsky et al., 1988; 1989) are indicative of plastic and/or degenerative effects.

MUSCIMOL-INDUCED REVERSIBLE INACTIVATION

Muscimol rapidly induces a hyperpolarization lasting several hours, with the overall duration depending on the dose (see Martin & Ghez, 1993; 1999). In a series of articles, Martin and colleagues (for example, Martin, 1991; Martin & Ghez, 1999) provided a thorough analysis of muscimol-induced inactivation, together with

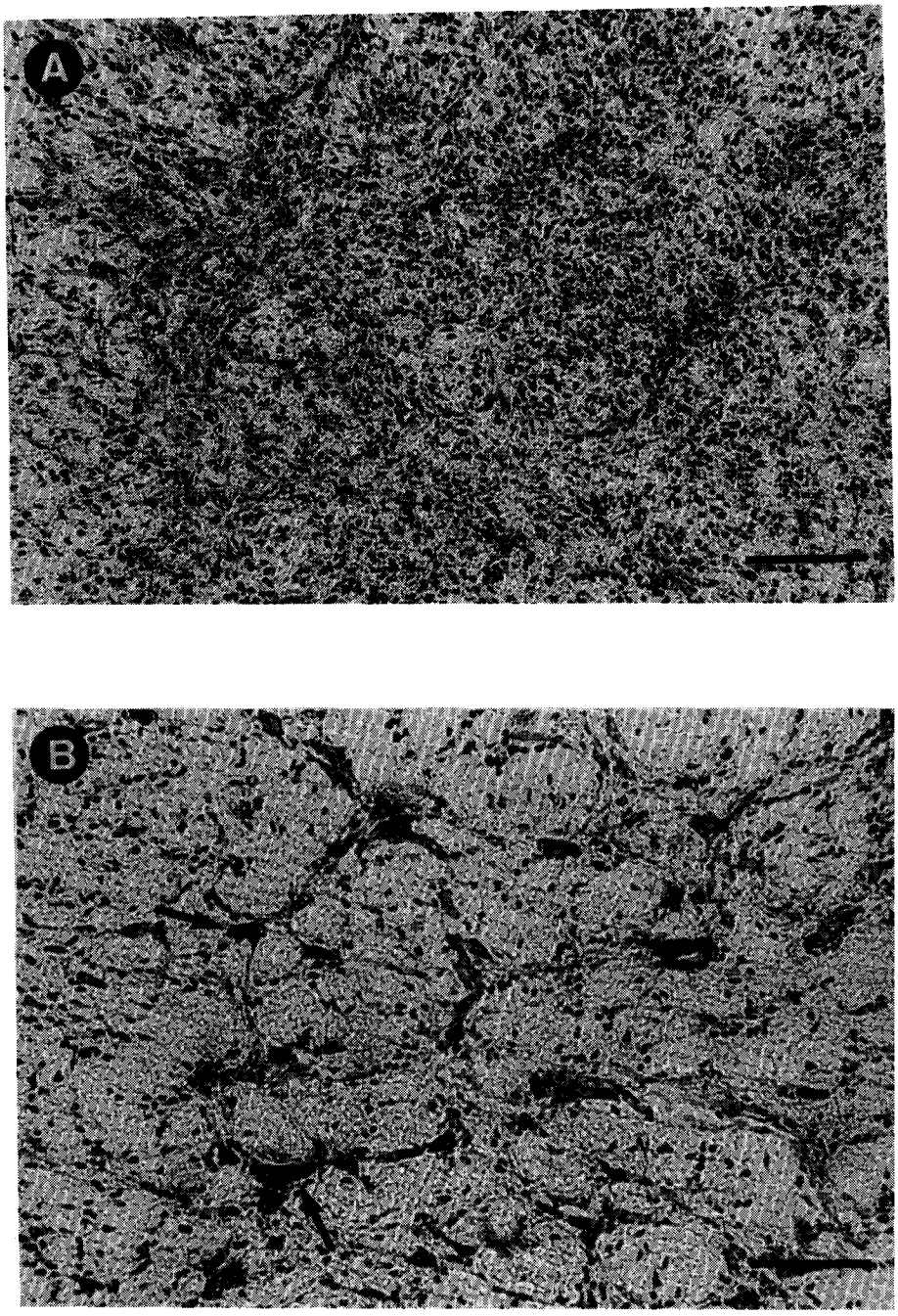

Fig. 1: Photomicrographs of coronal sections of (A) the NBM of a rat after 24-h GABA (100 μg/μL/h) infusion, and (B) the contralateral noninfused NBM. The brain was processed for Cresyl violet staining 8 days after the infusion. The arrows in B indicate the magnocellular neurons that are lacking in A; note the strong gliotic reaction in A. Scale bars: 100 μm.

comparisons with other reversible inactivating agents (GABA, lidocaine). These experiments showed that autoradiographic measurement of [^{14}C] glucose uptake, following injection of muscimol (1μg/μL) into the cerebral cortex of rats, revealed a small area (1 mm) of strong hypometabolism, surrounded by an area of milder hypometabolism. This hypometabolic area exceeded the spread of the drug that was evaluated with [^{3}H] muscimol injection, indicating that the area of hypometabolism may be due to reduced synaptic activity in interconnected neurons. In this regard, muscimol and lidocaine induced the same type of inactivation.

Muscimol-induced inactivation has been used in diverse species in a variety of behavioral experiments (for example, Di Scala et al., 1983; Martin & Ghez, 1993; Gallese et al., 1994; Mason et al., 1998), including learning and memory experiments (for example, Matsumara et al., 1991; Hardiman et al., 1996; Krupa et al., 1996; Ramnani & Yeo, 1996; Milak et al., 1997; Baunez & Robbins, 1999). The following section does not attempt to provide an exhaustive review of these experiments, but rather illustrates some questions that can be addressed with this type of

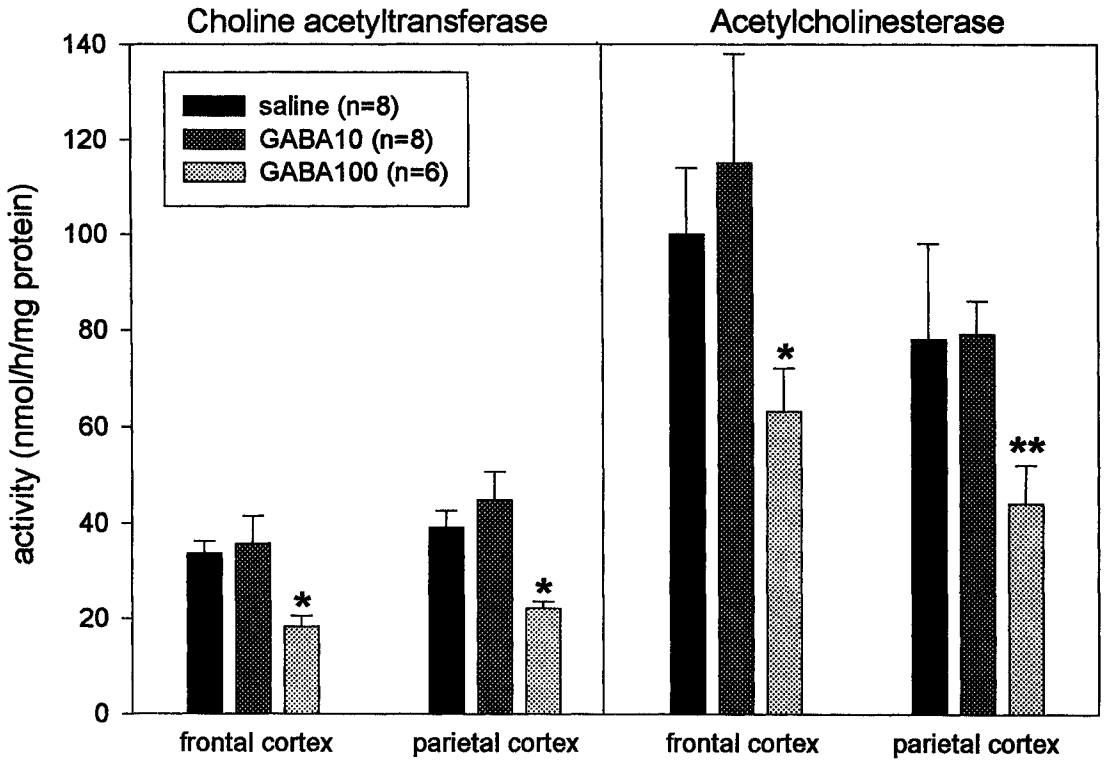

Fig. 2: The effect of GABA infusion into the NBM on cholinergic markers in frontal and parietal cortices. Saline or GABA (10 or 100 μg/μL/h) were infused over 24 h. Fourteen days later, the rats were sacrificed, and the frontal and parietal cortices were rapidly dissected. Choline acetyltransferase and acetylcholinesterase activities were assayed using enzymatic methods (Fonnum, 1975; Ellman et al., 1961). The highest concentration of GABA induced a significant reduction of both cholinergic markers as compared with saline (* $p<0.05$; ** $p<0.01$; Newman-Keuls post-hoc comparisons).

reversible inactivation.

As mentioned earlier, GABA receptors, located on NBM cholinergic neurons, may constitute a target to modify the activity of these neurons. Muscimol injection into the NBM was found to impair the performance of rats in attentional tasks, such as two- and five-choice reaction time (Muir et al., 1992; Pang et al., 1993) or conditioned discrimination (Dudchenko & Sarter, 1991). The effects were similar to those obtained with excitotoxic lesions of the NBM, including AMPA lesion, which is thought to have a preferential effect on cholinergic neurons (Muir et al., 1995; Everitt et al., 1987; Robbins et al., 1989). Working memory deficits in a double Y-maze were reported after intra-NBM injections of small doses of muscimol (0.1 μg; Beninger et al., 1992; DeSousa et al., 1994), whereas both working and reference memory deficits were obtained after injecting higher doses (1 μg Beninger et al., 1992).

Similar effects, confined to working memory, were obtained after quisqualate lesion (Biggan et al., 1991; Beninger et al., 1994), which induces restricted NBM lesions (Dunnett et al., 1987) when compared with the working and reference memory deficits that are obtained after ibotenate lesions (see Dunnett et al., 1991). The data support the idea that muscimol injection induces a reversible inactivation, the effects of which are similar to those of excitotoxic lesions. Moreover, in the NBM, such effects may be related to an action on cholinergic neurons, as excitotoxic compounds having some selectivity for these neurons have similar effects. Nonetheless, the deficits induced by intra-NBM injection of the selective cholinergic neurons toxin, ^{192}IgG-saporin, are smaller than those induced by muscimol in a variety of tests (Torres et al., 1994; Wenk et al., 1994; Baxter et al., 1995), suggesting that the behavioral deficits induced by muscimol may depend also on its effects on noncholinergic NBM neurons.

The amygdala is involved at various stages of learning and memory, and reversible inactivation studies. Using tetrodotoxine (TTX), lidocaine (or novocaine), and muscimol have largely contributed to the identification of these processes (for example, Gallo et al., 1992; Willner et al., 1993; Jerusalinsky et al., 1994; Muller et al., 1997; Ambrogi-Lorenzini et al., 1999). In this regard, conditioned food-aversion procedures have been considered particularly appropriate to realize a "chronometric analysis" of the various processes that are involved in learning and memory, with the aid of reversible inactivation (see Bures, 1990; Bures & Buresova, 1990). In these procedures, intake of a food by the rat (a drinking solution, which may be identified by its taste or its odor) is followed by intoxication, induced by injection of lithium chloride, resulting in avoidance of the food upon subsequent encounter. Using TTX to inactivate a variety of brain structures at specific phases of a conditioned taste aversion, Bures and collaborators (Bures, 1990; Gallo et al., 1992) have exquisitely documented the involvement of the connections between the parabrachial nucleus, the amygdala, and the gustatory cortex in this learning. In a recent series of experiments, we used muscimol to study the neuroanatomical substrate that is involved in a particular instance of conditioned food aversion, which is conditioned odor aversion (COA). Conditioned odor aversion is the avoidance of a tasteless, odorized solution, the ingestion of which has preceded toxicosis; COA differs from the classic conditioned taste aversion (CTA) in that it does not tolerate long interstimulus intervals (ISI) between the solution intake and the induction of toxicosis (Hankins et al., 1973). Nonetheless, evidence exists of COA that is acquired despite long ISIs when the odor is presented together with a taste during acquisition; this procedure is called Taste-Potentiated Odor Aversion (TPOA). TPOA depends on the baso-lateral nucleus of the amygdala (BLA), as electrolytic or excitotoxic lesions of this nucleus were found to disrupt it (Bermudez-Rattoni et al, 1986; Hatfield et al., 1992; Ferry et al., 1995). Muscimol-induced inactivation of the BLA during the acquisition phase, but not

during the retrieval phase, of the procedure was found to be effective, suggesting that this nucleus is involved in the former process. Furthermore, to be effective, muscimol could be injected either before or after presentation of the odor-taste stimulus, suggesting that neuronal activity in the BLA is necessary after the sensory processing of the composite stimulus, that is for a memory process (Ferry et al., 1995). In this regard, muscimol injection differs from other reversible inactivation compounds in that injection of novocaine into the amygdala impairs TPOA if it is administered before, but not after, presentation of the odor-taste stimulus (Bermudez-Rattoni et al., 1983). Conversely, it is noticeable that whether injected before or after presentation of the odor-taste stimulus, muscimol selectively affects COA without affecting CTA (tested separately), which develop in parallel. This result is consistent with those of Gallo et al. (1992) showing that inactivating the amygdala by TTX before taste presentation does not impair CTA, whereas inactivating the amygdala after taste presentation only attenuates CTA. The data, if suggestive of subtle differences between different methods of reversible inactivation, do not support a clear-cut distinction between these methods.

DISCUSSION

The data briefly reviewed above clearly indicate that GABA or GABA-receptor agonists constitute valuable reversible inactivation tools for studying learning and memory. Our critical analysis of the data obtained with chronic infusions of GABA, one of Simon Brailowsky's favorite tools, suggests that depending on the dose used and the targeted area, some effects may not be reversible. To our knowledge, little attention has been given to possible long-lasting effects of other compounds that are used for reversible inactivation (see however, Hernandez & Schallert, 1990) and hence, comparison of the advantages and drawbacks of the various methods is not possible. The issue of reversibility is particularly important when animals are tested anew after the reversible inactivation, as it is then considered that the system is fully functional again. In this regard, little empirical evidence demonstrating complete reversibility of any pharmacological treatment is available.

Another concern with reversible inactivation in learning tasks is state-dependent retrieval (SDR). State-dependent retrieval means that information learned in a given state may not be (or may be poorly) retrieved when the subject is in a different state. Evidence for SDR has been obtained with systemic pharmacological treatments given at various stages (acquisition, extinction) of learning tasks (for example, Colpaert, 1990; Bouton et al., 1990; Oberling et al., 1996) and has been taken into account when discussing reversible inactivation data (for example, Muller et al., 1997). It is unknown to what extent drug injections into brain areas can produce SDR, and studies addressing this problem would certainly be welcome.

As a final comment, reversible inactivation techniques significantly contribute to the knowledge of "where and when" (Bures & Buresova, 1990) neuronal events for learning and memory take place in the brain. As first stated in this article, knowledge about the nature of such neuronal events has considerably progressed in recent years. Using research strategies similar to reversible inactivation, antisense oligonucleotide techniques offer the opportunity to interfere with neuronal events in precise locations in the brain and at chosen phases of a task (for example, Lamprecht et al., 1997; Guzowski & McGaugh, 1997; Ma et al., 1998). There is little doubt that such techniques will shortly complement the pharmacological analysis of brain systems of learning and memory.

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