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Modulation of Spatial Alternation and Anxiety by Septal Scopolamine Systemic Diazepam in Mice

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BELOTTI, M., B. CAGNIARD, M.-P. MANO AND D. GALEY. *Modulation of spatial alternation and anxiety by septal scopolamine systemic diazepam in mice.* PHARMACOL BIOCHEM BEHAV **60**(3) 733–738, 1998.—To investigate the behavioral consequences of benzodiazepines in subjects whose septo-hippocampal cholinergic (ACh) activity was impaired, C57BL/6 mice received an injection of 2.5 μg/0.2 μl of scopolamine into the medial septal area with an IP injection of 0.5 mg/kg of diazepam. The consequences of these treatments administered in combination or alone were evaluated on anxiety measured in an elevated plus-maze and on spontaneous alternation carried out in a T-maze, using two different intertrial intervals (ITI: 5s or 30s). In these conditions, only the combined treatment provoked a decrease of the anxiety level, which was associated with an impairment of spontaneous alternation restricted to the 5s ITI. Because mice were not impaired during the sequential 30s ITI, this seems to rule out the possibility that this alternation deficit resulted from a working memory loss. These results suggest an involvement of a septal ACh–GABA-A/BDZ interaction in the exaggeration of cognitive deficits produced by benzodiazepines in patients characterized by a cholinergic hypofunction. © 1998 Elsevier Science Inc.

Septum Septo-hippocampal cholinergic pathway Scopolamine Diazepam Anxiety Spatial working memory

DESPITE a considerable amount of existing data, the exact roles played by the hippocampus and the septo-hippocampal cholinergic (ACh) system in normal and pathologic aspects of learning and memory are still a matter of debate. According to certain theories, these structures are involved in the encoding and use of spatial information (34,41,42,49), working (7,18,29,35,48) and/or spatial working memory (17,23,24), and the production of internal inhibition (9,13,14).

On the other hand, it has been postulated that activation of the septo-hippocampal ACh system and closely related structures (the behavioral inhibition system) underlies anxiety (21,22). This hypothesis is supported by recent data showing that the septal region, which contains a high density of GABA-A/benzodiazepine (BDZ) receptors complex (31), possesses the highest concentration of endogenous benzodiazepine-like compounds (i.e., endozepines) in the brain (51). Thus, it can be considered that the septal region constitutes a major interface between emotional and cognitive processes (22). In line with such studies, septo-hippocampal ACh hypofunction has been linked to intellectual decline observed in geriatric populations diagnosed with Alzheimer's and related diseases (1,5,10). Furthermore, these patients and normal aged persons who are commonly prescribed BDZs might be particularly sensitive to the debilitating effects of these compounds (2). The perturbation of central ACh activity associated with these disorders will be a critical factor for this susceptibility (45).

The activity of septal ACh neurons is trans-synaptically modulated directly or indirectly by numerous neurotransmitter systems (8,11,50). For example, GABAergic neurons in the lateral septum exert a powerful inhibitory influence on ACh cells in the medial septal complex (MS) (6,28). Because the MS contains a high density of endozepines and GABA-A/BDZ receptor complex, it is likely that BDZ participates in the intraseptal modulation of the septo-hippocampal ACh pathway by GABA afferents. Indeed, intraseptal injection of BDZ compounds decreased hippocampal ACh activity in a dose-dependent manner (46). This effect occurs probably by

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increasing the affinity of GABA for GABA-A receptor complex that induces the decrease of postsynaptic ACh neuronal activity (30,40). Thus, it seems reasonable to postulate that in patients suffering from cholinergic hypofunction, the exaggeration of cognitive deficits induced by BDZ is partly related to the ability of these compounds to inhibit the residual level of activity of ACh neurons in the MS. Consequently, the direct modulation of septo-hippocampal ACh neurons activity associated with an IP application of BDZ in animals constitutes a valuable tool for studying the involvement of the septo-hippocampal system in these emotional/cognitive disorders.

For this purpose, we injected 2.5 μg/0.2 μl of scopolamine into the MS of C57Bl/6 mice. This treatment was also administered in combination with an IP injection of diazepam (0.5 mg/kg). The consequences of these reversible pharmacological treatments were evaluated on the anxiety level measured in an elevated plus-maze and on spatial working memory performance. The spatial working memory was analyzed under two different conditions of delay through a spontaneous alternation procedure carried out in a T-maze.

METHOD

Animals

Forty-nine male mice of the inbred strain C57BL/6 Jico obtained from IFFA-Credo, Lyon, France, were used. Upon arrival in the laboratory, at the age of 8 weeks, they were housed collectively with ad lib food and water access, in a constant-temperature room (22°C), maintained on a 12 L:12 D cycle. All experiments were carried out during the light period (0800–2000 h). Mice were aged 14–18 weeks and weighed about 28–30 g at the beginning of the experiments.

Drugs

Diazepam solution (Valium, Roche, France) was diluted with 0.9% physiological saline solution and administered IP at the dose of 0.5 mg/kg. Scopolamine–HCl (SIGMA, France) was dissolved in 0.9% physiological saline solution and injected intraseptally (IS) at the dose of 2.5 μg/0.2 μl.

Surgery

Thirty-nine animals received, under anesthesia (sodium thiopental 70 mg/kg IP), the implantation of a guide cannula (8 mm long, o.d. 0.46 mm, i.d. 0.255 mm). The tip of the guide cannula was positioned 1.30 mm vertically from the medial septal nucleus to minimize damage to this area. The stereotaxic coordinates used were the following: 1 mm anterior to the bregma, 0 mm refering to sagittal line, and 2.3 mm ventral from the skull surface. The guide was fixed to the skull bone by three screws covered with dental cement. Following operation, the animals were replaced in the animal room for a recovery period of 10 days before the experiments began.

Ethical Statement

All surgical and experimental procedures were in accordance with official French regulations for the care and use of laboratory animals.

Intraseptal Injection Procedure

Intraseptal injection was carried out in freely moving mice through an injection needle (9.3 mm long, o.d. 0.23 mm) that was inserted into the guide cannula and that protruded 1.30 mm beyond the tip of the guide. The injected volume (0.2 μl) was delivered over a 3-min period, via a 2 μl. Hamilton syringe connected by polyethylene tubing. The needle was retained in the guide for an additional 3-min period before removal, to ensure diffusion. The drug vehicle was injected under identical conditions. As soon as the intraseptal injection was ended, diazepam was administered so that all treatments were completed 20 min before each testing situation.

Groups

Ten mice were allocated to the intact control condition (control group). To evaluate the effects of each treatment on behavior, nine mice received scopolamine injection into the MS area together with an IP injection of the physiological saline solution (IS scopolamine group). Ten mice were treated with an IP injection of diazepam together with an intraseptal injection of saline solution (IP diazepam group). Ten mice were given the physiological saline solution together IP and IS to evaluate the consequences of the double injection procedure itself (saline group). Finally, 10 mice received diazepam IP + scopolamine IS in combination (scopolamine-diazepam group).

Behavioral Studies

Anxiety. The protocol used was the same as that previously described (3). Anxiety level was evaluated by the comparison of exploratory activities measured in two tasks with different anxiogenic potentials: (a) the elevated plus-maze constitutes a strong anxiogenic environment. This test of anxiety is based on the strength of the antagonism between the natural exploratory tendencies towards novelty and the avoidance of open spaces by animals.

The maze, situated in a quiet room, is a gray plus-shaped Plexiglas maze. This apparatus is elevated to a height of 55 cm and consists of two open arms (30 × 7 cm) and two enclosed arms (30 × 7 × l7 cm). Each arm extends from a central platform (7 × 7 cm) that is illuminated by a light bulb providing a 100 lx intensity. Behavioral data were collected by an observer who sat quietly behind a screen.

The test involved placing each mouse into a mobile cylinder located on the central platform of the maze for 10 s, and then, following withdrawal of the cylinder, allowing it to freely explore the apparatus for a period of 10 min. The following parameters were considered as constituting the anxiety index: 1) the number of entries into the open arms divided by the total number of arm entries (activity ratio), and 2) the time spent on the open arms divided by the time spent on both the open and closed arms (time ratio). A mouse was considered to have entered an arm when all four paws had crossed into the arm. The maze was cleaned after each mouse was tested. (b) Immediately after the plus-maze test, each mouse was placed onto the four-hole board. This partially enclosed and weakly illuminated (15 lx) apparatus, located in a separate quiet room, constitutes a less anxiogenic condition. This test enabled verification that the drug did not alter the normal exploratory abilities of animals. The floor of this black Plexiglas box (40 × 40 × 30 cm) has four holes, 3 cm in diameter, and equally spaced in the center of each quadrant. lnfrared photocells, directly beneath each hole, provide automatic measures of the number of head dips and time spent head dipping. In addition, four pairs of photocells mounted in the walls of the box provide automated measures of level of locomotor activity.

Animals were allowed to freely explore the four-hole board during a 6-min period. Three parameters were re-

corded: 1) the number of head dips through the holes, 2) the total time of head dipping, and 3) the number of visits to each of the four holes.

Spatial working memory. Spatial working memory performance was measured in a T-maze in two different delay conditions using measures of the spontaneous alternation behavior. This behavior is based upon the innate tendency of rodents to alternate the choice of the visited goal arm on each trial over a series of successive runs in a T-maze.

The T-maze, constructed of grey Plexiglas, consists of a start box (15 × 10 cm) extended by a straight alley, without walls, 35 cm in length and terminating at right angles by two symmetrical side arms (30 × 10 cm) that were also open. The start box and side arms could be individually closed by sliding doors. The maze is located in a room decorated with various pictures and objects to facilitate spatial orientation.

One week after the anxiety measure all subjects were submitted to daily session of six successive trials. For each trial, subjects were closed in the start box for 5 s. The door into the straight alley was then opened and the mouse was able to freely choose the right or left arm of the T-maze where it was then enclosed for 15 s. At the end of this time the mouse was replaced into the start box. These preliminary training sessions were then repeated during a minimum of 4 consecutive days until the spontaneous alternation rate was stabilized above 70% correct. The next day the pharmacological treatments were applied according to the procedure described above. Then, all subjects were submitted to a testing session of nine successive trials separated either by a 5-s intertrial interval (three first trials where mice stay 5 s in the start box) or by a 30-s interval (six next trials where mice stay 30 s in the start box).

Alternation behavior has been widely used as a behavioral tool to study either the sensitivity to proactive interference between information using a sequential alternation procedure or the rate of forgetting as the intertrial delays increased (4,12,43). Both of these procedures that are included in our protocol involve a "working-episodic" memory component (33,43).

Histology

Upon the completion of the behavioral testing, animals were sacrificed, the brains removed, placed in a formaldehyde solution (10%) for 1 week, and then soaked in a 30% sucrose–formalin solution for 24 h. Subsequent histological analysis was performed on 80-μm frozen sections stained with thionin to evaluate, under a light microscope, the correct placement of the cannula.

Statistical Analysis

Because percent correct choices in alternation do not follow a normal distribution, they were submitted to arcsin transformation to conduct standard statistical analysis (ANOVA followed by Newman–Keuls post hoc comparisons when appropriate to identify significant differences).

RESULTS

Anxiety Measure

Elevated plus-maze. In this task, lower activity and time ratios indicate a greater level of anxiety. The mean activity and time ratios for mice of the different groups are shown in Fig. 1. A one-way analysis of variance showed a significant effect of treatments on both activity, $F(4, 44) = 5.82$, $p < 0.001$, and time, $F(4, 44) = 15.04$, $p < 0.0001$, ratios. More precisely, animals of the scopolamine–diazepam group displayed a significant increase of these measures ($p < 0.01$ in comparison with each of the other groups). In contrast there was no significant difference of measures between mice of IS scopolamine and saline groups and between IP diazepam and saline groups for both ratios.

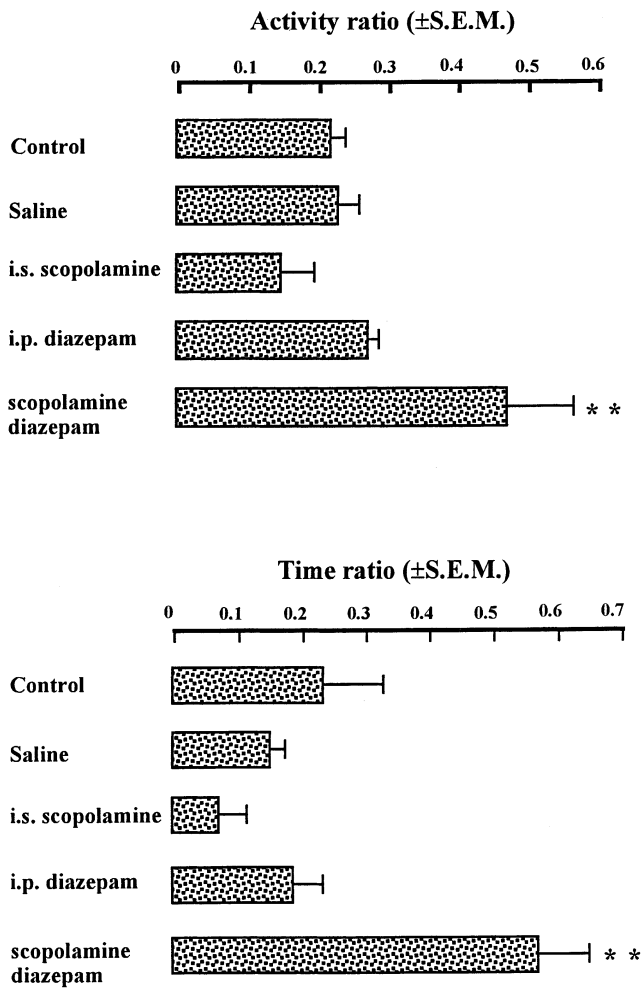

FIG. 1. Consequences of combined treatment (scopolamine intraseptally, 2.5 μg/0.2 μl and diazepam IP 0.5 mg/kg) on mean (±SEM) activity ratios (number of entries in open arms divided by the total number of arms entries) and time ratios (time spent in open arms divided by the time spent on open and closed arms). The more elevated are the ratios the less "anxious" are the subjects. $^{**}p < 0.01$ compared to the other groups.

Moreover, there were no significant differences between groups for the total number of arm entries as well as for the time spent on both the open and closed arms, $F(4, 44) = 2.16$, NS, and $F(4, 44) = 1.19$, NS, respectively.

Four-hole board. There were no significant differences between the five groups for the number of head dips, $F(4, 44) = 1.13$, NS, the time of head dipping, $F(4, 44) = 1.31$, NS, or the number of crossings, $F(4, 44) = 1.91$, NS.

Spatial Working Memory Investigation

The results obtained during preliminary training indicate that performance of all groups of mice were above 70% the

day before the evaluation of the treatments on spontaneous alternation (control group: 80 ± 4%; saline group: 88 ± 3%; IS scopolamine group: 82 ± 4%; IP diazepam group: 80 ± 3%; scopolamine–diazepam group: 86 ± 4%). As a result, no significant differences, $F(4, 44) = 0.93$, NS, were observed between groups before the testing session.

The effects of treatments on alternation scores are shown in Fig. 2. A significant treatments effect as a function of the intertrial intervals (ITI) appeared, $F(4, 93) = 5.01$, $p < 0.01$. Indeed, for the 30-s ITI, no difference in spontaneous alternation rate was observed, $F(4, 44) = 2.50$, NS, between the different groups that all alternated above chance level ($p < 0.01$). In contrast, for the 5-s ITI, treatments induced a significant group effect, $F(4, 44) = 3.76$, $p < 0.05$. Post hoc analysis revealed that in this condition, alternation rates of the scopolamine–diazepam group were much lower in comparison with those of the other groups ($p < 0.01$) and also in comparison with the performance of the same group for the 30-s ITI ($p < 0.01$).

Histological Data (Fig. 3)

This photomicrograph shows the placement of the cannula in the medial septal area. As can be seen, the cannula tip was positioned at the level of the medial septal nucleus.

DISCUSSION

Our results suggest that in contrast with the consequences of either scopolamine or diazepam when injected singly, the two drugs applied in combination in the same animal induced a reduction of the anxiety level. This interpretation is strengthened by the results obtained from the four-hole board, which show that this effect does not result from a nonspecific increase in exploration abilities. In parallel, spontaneous alternation behavior was highly impaired, but only for the 5-s ITI, whereas for the 30-s ITI performance was unaffected. The decrease of anxiety level observed in these mice rules out the possibility that the spontaneous alternation deficit was produced by a stress effect of the combined treatment.

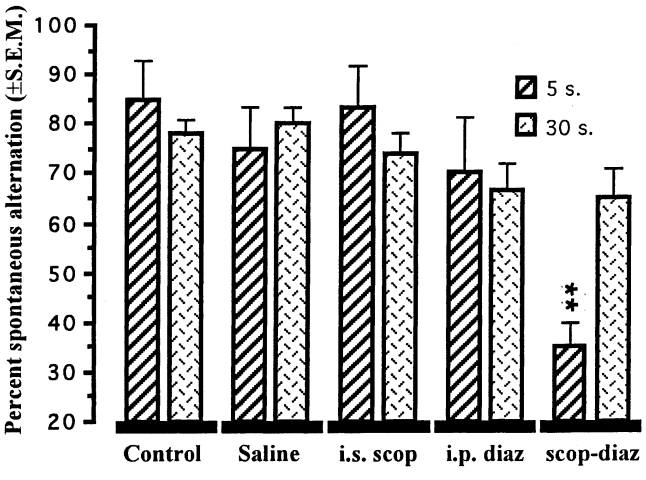

FIG. 2. Effects of combined treatment (scopolamine intraseptally, 2.5 μg/0.2 μl and diazepam IP 0.5 mg/kg) on mean percent alternation scores (±SEM) as a function of the delay interval (5 s or 30 s). $^{**}p < 0.01$ compared to the 30-s ITI.

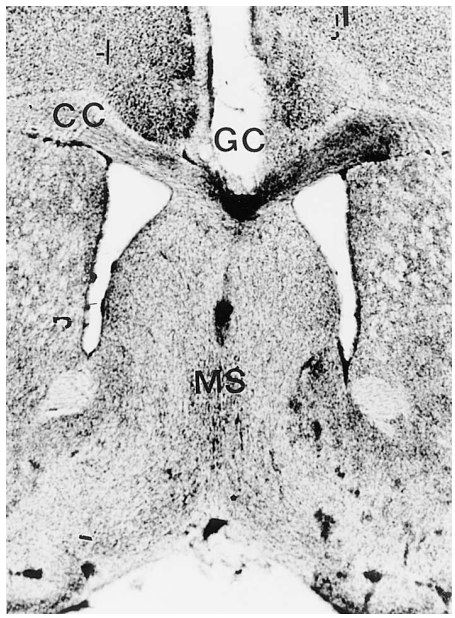

FIG. 3. Photomicrograph of a thionin-stained section of the brain showing a typical cannula placement in the medial septal complex. Abbreviations: CC, corpus callosum; GC, guide-cannula track; MS, medial septal area.

Spontaneous alternation behavior is known to be a reliable indicator of hippocampal function. For example, rats with neocortical, cingulate gyrus, or amygdala lesions alternate at normal levels (13). A recent study in the rat further (47) demonstrated that hippocampal but not amygdala lesions impaired choice accuracy in a spatial alternation procedure with a 5-s delay between trials. Spontaneous alternation behavior is very sensitive to manipulation of cholinergic receptors. Systemic IP injections of scopolamine in rats disrupt performance in this task (15,26). More relevant to our present data, intraseptal injections of muscimol or scopolamine, which both decrease the turnover rate of hippocampal ACh (20), induce an impairment of reinforced T-maze alternation (18). Consequently, our results suggest that the deficit we observe for the 5-s ITI was a consequence of an additive effect of both scopolamine and diazepam on septo-hippocampal ACh activity. This interpretation is supported by recent data demonstrating a high density of GABA-A receptors in the septal area (31) and by neurochemical studies showing a dose-dependent decrease of cholinergic activity in the hippocampus after intraseptal injection of scopolamine or BDZ and GABAergic agonists (16,18,20,46).

The anxiolytic effect of the combined treatment is more difficult to interpret. Indeed, because in our conditions the dose of diazepam used when injected alone is not effective in modulating the anxiety level, the possibility that a synergistic effect of scopolamine and diazepam occurs in the septal region might be suggested.

This interpretation posits that when a decrease of septo-hippocampal ACh activity is induced via the combined blockade of muscarinic receptors and the stimulation of septal GABA-A/BDZ mechanisms, there exists both a decrease of anxiety level and an impairment of spontaneous alternation performance. However, although an interaction with the septo-hippocampal ACh system is one explanation of the

data, other potential mechanisms could also account for this modulation of anxiety. For example, recent data (37) have reported that the BDZ agonist midazolam, applied in the lateral but not in medial septal nucleus, produced an anxiolytic-like effect in the elevated plus-maze. Moreover, the same authors (36) also report an anxiolytic effect after infusion of midazolam into the basolateral nucleus of the amygdala, which possesses connections with the lateral septum (27,32,38). These results suggest a role for the amygdalo-septal loop in the control of anxiety and the functional interaction of this circuit with the septo-hippocampal pathway will be important to establish.

The fact that, in our study, the spontaneous alternation rate was not affected during the six sequential trials with 30-s ITI would mean that the deficit at 5 s observed after the combined treatment only is neither a spatial working nor a memory deficit in the strict sense, that is an accelerated rate of forgetting or an increased susceptibility to proactive interference. This result also suggests that the impairment is not a nonspecific effect on the motivation to alternate. Although this deficit requires further characterization, it seems rather to reflect the indirect consequences of an inability to trigger some neurophysiological processes by an appropriate anxiety level.

One can consider the situation of alternation as an example of exploratory behavior in which the animal's choice is limited to two compartments (25). Thus, loss of alternation behavior in animals could indicate an impairment of exploratory functions. Glanzer's theory (19) suggests that the tendancy to alternate is related to stimulus satiation towards the most recently entered goal arm. A deficit of stimulus processing should, therefore, create a disturbance in alternation. In this sense, spontaneous alternation performance with short intertrial delays can be operationally considered as a reliable index of stimulus processing abilities.

In this context, lesions of the hippocampus and septum both induced attention deficits that were reproduced by blockade of cholinergic septo-hippocampal transmission [see (44) for review]. According to this author, the effects of the decrease of cholinergic septo-hippocampal activity on learning and memory processes seem to depend primarily upon the selective loss in processing of environmental stimuli and defective habituation to them.

It has been hypothetized (21,22) that the septo-hippocampal system (notably its ACh component), and related structures (mainly the Papez circuit, the prefrontal cortex, and some aminergic transmitter systems connected with these structures) belong to a behavioral inhibition system (B.I.S.). This system mediates both anxiety and increasing attention to the environment. Thus, the behavioral impairments we have observed fit well with a decrease of the activity of the B.I.S. through an ACh/GABA-A–BDZ interaction.

Types of learning, such as spontaneous alternation, which involve processing of variable and complex information, demand more stable continuous attention and are more vulnerable to ACh hypofunction (39). Consequently, a selective attention defect induced by the combined treatment might be responsible for the spontaneous alternation impairment for the 5-s ITI. In contrast for the longer ITI, mice might have a sufficient delay to achieve the stimulus processing they need to alternate.

Central ACh hypofunction has been linked to the intellectual decline observed in geriatric populations diagnosed with Alzheimer's disease (1,5,10). Consequently, BDZs might exaggerate the cognitive deficits observed in these patients or in normal aged patients (2). According to a previous hypotheses (45) our results also suggest that the perturbation of septo-hippocampal ACh activity associated with these disorders will be a critical factor for this susceptibility.

In conclusion, our data show that the combined treatment with intraseptal scopolamine and diazepam IP in animals appears to be an attractive model for studying the physiopathological basis of these disorders.

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