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Posttraining infusion of cholinergic drugs into the ventral subiculum modulated memory in an inhibitory avoidance task: Interaction with the bed nucleus of the stria terminalis

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ABSTRACT

The ventral subiculum (vSUB), a hippocampal efferent target implicated in learning and stress coping, receives cholinergic input and sends glutamatergic output to the bed nucleus of the stria terminalis (BNST). This study examined the roles of vSUB muscarinic activation and its interaction with BNST *N*-methyl-D-aspartate and noradrenergic receptors in formation of aversive memory. Male Wistar rats with cannulae implanted into the vSUB or BNST were trained on a step-through inhibitory avoidance task. Shortly after training, they received cholinergic drugs infused into the vSUB and/or glutamatergic or noradrenergic drugs infused into the BNST. Results of the 1-day retention tests showed that intra-vSUB infusion of oxotremorine (0.01 μg) or scopolamine (0.3 or 3.0 μg) enhanced or impaired retention, respectively. Both effects were dose- and time-dependent, and 0.001 μg oxotremorine attenuated the amnesia induced by 3.0 μg scopolamine. The oxotremorine-induced memory enhancement was blocked by intra-BNST infusion of DL-2-amino-5-phosphonovaleric acid or propranolol at a dose not affecting retention; the amnesia induced by scopolamine was blunted by intra-BNST infusion of glutamate or norepinephrine at a dose with a negligible effect on retention. These data suggest that in an inhibitory avoidance task muscarinic activation of the vSUB modulated memory formation by interacting with the BNST glutamatergic and noradrenergic functions.

1. Introduction

The ventral subiculum (vSUB) as part of the hippocampal formation receives profuse input from the CA1 area (Amaral, Dolorfo, & Alvarez-Royo, 1991) and projects to various cortical and subcortical regions including the medial prefrontal cortex (Jay & Witter, 1991), nucleus accumbens (Groenewegen, Vermeulen-Van der Zee, te Kortschot, & Witter, 1987) and amygdala (Canteras & Swanson, 1992). In relaying information to and from structures implicated in learning and memory, the vSUB is expected to be involved in such a function. Indeed previous studies have shown that neurotoxic or electrolytic lesions of the vSUB or transient suppression of its function with anesthetics influenced learning and memory in various tasks (Floresco, Seamans, & Phillips, 1996, 1997; Govindaiah, Rao, Raju, & Meti, 1997; Laxmi, Bindu, Raju, & Meti, 1999; Maren, 1999; Sun & Rebec, 2003). However, the neurochemical mechanism underlying such a function remains to be elucidated.

The vSUB receives heavy cholinergic input arising from the medial septum and vertical limb of the diagonal band nucleus, which innervates the whole hippocampal formation throughout its rostrocaudal extent (Blaker, Armstrong, & Gage, 1988; Frotscher, Schlander, & Leranth, 1986; Mesulam, Mufson, Wainer, & Levey, 1983). Activation of cholinergic fibers in the hippocampal region was detected during acquisition and expression of the inhibitory avoidance task (Giovannini et al., 2005). Manipulating the hippocampal cholinergic activity was shown to affect retention of learned responses in various tasks (Izquierdo et al., 1992; Rogers & Kesner, 2004; Wallenstein & Vago, 2001). Thus, it would be interesting to know whether cholinergic activation of the vSUB also plays a role in learning and memory.

A previous study indicated that glutamate is a major vSUB efferent transmitter, and the bed nucleus of the stria terminalis (BNST) receives glutamatergic projection from the vSUB (Walaas & Fonnum, 1980). It has been shown that glutamate acting on *N*-methyl-D-aspartate (NMDA) receptors released norepinephrine (NE) in the BNST (Forray, Andres, Bustos, & Gysling, 1995; Forray, Gysling, Andres, Bustos, & Araneda, 2000). Recent studies implicated the BNST in processing affective memory (Chen, Chen, Chen, & Liang, 2004; Liang, Chen, & Chen, 2001; Schweimer, Fendt, & Schnitzler, 2005; Sullivan et al., 2004). Our laboratory has shown that in an inhibitory avoidance task intra-BNST infusion of NE enhanced memory (Liang et al., 2001), the effect was mimicked by infusion of glutamate into the BNST and memory enhancement induced by NE or glutamate was blocked by concurrent infusion of

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propranolol (Liu, Chen, & Liang, submitted for publication). The above evidence suggests a hypothesis that learning experience may activate cholinergic input to the vSUB and engage its glutamatergic output to the BNST, which in turn activates the BNST NE function to enhance memory. This hypothesis predicts that intra-vSUB infusion of cholinergic agonists or antagonists after training should correspondingly cause memory enhancement or impairment that should be attenuated, respectively, by blocking or activating the NE and glutamatergic systems in the BNST.

To test this conjecture, the present study examined the roles in memory formation of muscarinic activation in the vSUB and the interaction between such activation and glutamatergic or NE neurotransmission in the BNST. Rats with implanted cannulae in the target regions were trained on a step-through inhibitory avoidance task and received immediately after training infusion of muscarinic drugs into the vSUB with or without simultaneous infusion of glutamatergic or NE drugs into the BNST. It was expected that in a 1-day retention test posttraining intra-vSUB infusion of oxotremorine would improve memory and this effect should be attenuated by intra-BNST infusion of DL-2-amino-5-phosphonovaleric acid or propranolol. Conversely, posttraining intra-vSUB infusion of scopolamine would impair memory and that should be restored by intra-BNST infusion of glutamate or NE.

2. Materials and methods

2.1. Subjects

Male Wistar rats weighing 300–350 g obtained from Animal Center of National Taiwan University were used in this study. Upon arrival, they were individually housed in our animal facility under a 12:12 h light:dark cycle with food and water continuously supplied. The room was maintained at 22 ± 2 °C temperature and 60–70% humidity. Animal care and experimental procedures followed Guidelines for Animal Research by Agriculture Council of ROC and Ethical Codes of Taiwanese Psychological Association and were approved by Institutional Animal Care and Use Committee at National Taiwan University.

2.2. Brain surgery

Rats received brain surgery to implant guide cannulae bilaterally into the vSUB and/or BNST after being acclimated to the housing facility. They were anesthetized with sodium pentobarbital (50 mg/kg, ip) after an atropine (0.5 mg/kg, ip) injection to prevent respiratory congestion. Both drugs were obtained from Sigma (St. Louis, Mo. USA) and dissolved in 0.9% saline. The anesthetized rat was mounted on a stereotaxic instrument (David Kopf Instruments, DKI-900, Tujunga, CA, USA). The skull was exposed and burr holes were drilled over the vSUB or BNST target. The guide cannula was made of 23-Gauge stainless steel tube at the length of 15 mm with 0.63 mm outer diameter and 0.33 mm inner diameter. They were bilaterally implanted into the vSUB or BNST. Coordinates for the vSUB were AP. −6.0 mm, ML. ±5.0 mm, and DV. −6.7 mm with the incisor bar at a −3.3 mm position (Paxinos & Watson, 2005); and those for the BNST were AP. +1.4 mm, ML. ±1.3 mm, and DV. −5.5 mm with the incisor bar at a +5.0 mm position (Pellegrino, Pellegrino, & Cushman, 1979). Three jewelry screws were implanted over the skull at triangular positions as anchors. The whole complex was affixed on the skull with dental cement. A stylet at a length of 16 mm was inserted into the cannula to maintain patency. Rats were allowed to recuperate from the surgery for at least 10 days and received daily checking and handling 5 to 7 days before a behavioral test.

2.3. Drug and brain infusion

Scopolamine hydrobromide and oxotremorine sesquifumarate were obtained from Tocris Cookson Ltd. (Bristol, UK). DL-2-amino-5-phosphonovaleric acid (APV), (−)-norepinephrine hydrochloride and DL-propranolol were obtained from Sigma (St. Louis, MO, USA). L-Glutamate was obtained from RBI (Natick, MA, USA). All drugs were measured as the salt weight and dissolved into a specific brain buffer which in 100 ml contained 0.9 g of NaCl, 0.115 g of Na_2HPO_4 and 0.0228 g of NaH_2PO_4. The solvent served as the vehicle for control infusion.

Drug or vehicle solution was infused into the vSUB and/or BNST as follows: Briefly, a piece of PE-20 polyethylene tubing was connected to a 10 μl Hamilton syringe on one end and cemented to a 30-Gauge dental needle bent at a length of 16 mm on the other end. The tubing was first filled with distilled water and then the drug solution with a small air bubble in-between to avoid mixture. Bilateral infusion was administered simultaneously into the vSUB and BNST of a conscious rat after training in a way to minimize stress to the rat. When two drugs were given to one target, they were prepared in a soup and co-infused. Immediately after a training trial, the rat was gently held and the infusion needles were inserted into the cannula after removing the stylet. Drug solution was dispensed at a rate of 0.5 μl per min by a syringe pump (CMA/100, Carnegie Medicine, Stockholm, Sweden); the total volume of infusion was 0.5 μl for each side. At the completion of infusion the needle was left in the cannula for an additional minute to allow drug diffusion. The stylet was replaced to prevent back flow immediately after withdrawal of the needle. The average time completing drug infusion was about 3.5 min after administration of the shock. Drug diffusion area was estimated in a few animals either by eye inspection on dye diffusion after infusion of 0.5 μl Evans blue (0.25%) or by magnetic resonance imaging of diffused liquid in the brain 30 min after infusion of 0.5 μl scopolamine.

2.4. Inhibitory avoidance task

The inhibitory avoidance apparatus was a trough-shape alley (top: 95 cm × 20 cm × 17 cm; bottom: 95 cm × 6 cm × 17 cm) divided by a sliding door into two sides, one (40 cm in length) was lit by a 20-W light bulb and the other was dark. All rats were subjected to a pretraining procedure. It was handled by the experimenter and placed into the lit side of the training apparatus facing away from the sliding door. When the rat turned around, the door was opened to allow free exploration into the dark side for 20 s before being retrieved. This was repeated for two more times before the rat returning to its home cage. The infusion procedure was also simulated by withdrawing the stylet, checking patency and replacing the stylet back into the cannula. This pretraining procedure was adopted for two reasons: First, it adapted rats to the task or manipulation, and reduced spurious behavior that might otherwise occur in the BNST-implanted rats from time to time to disrupt training or testing. Second, because electrophysiological recording in the vSUB or BNST was planned in the next phase, to render the results from various studies in this series comparable the present procedure should be made compatible to that in a recording study; in the latter case a pretraining session was mandatory for collecting the baseline neuronal activity before learning (Chang, Liang, & Yen, 2005). In the training session on the next day, the rat was placed into the lit side. As it stepped into the dark side, it received an inescapable shock given through a constant current shocker controlled by a timer (Lafayette Instruments, Model 80240 and Model 58010, Indiana, USA). The shock intensity and duration were selected as optimal for demonstration of an enhancing or impairing effect and would be depicted in each individual experiment. Shortly after administration of the shock the rat was removed from

the alley to receive the infusion and then returned to its home cage. One day after the foot-shock training, retention was tested. The rat was again placed into the lit side and the latency of stepping into the dark side was recorded as the retention score (in seconds). If a rat did not step through in 600 s, the test trial was terminated and a ceiling score of 600 was assigned.

2.5. Histology

After completion of all studies, rats were sacrificed with an overdose of sodium pentobarbital and perfused through the heart with physiological saline followed by 10% formalin at the end of all experiments. The brain was removed and stored in 10% formalin with 25% sucrose for at least 48 h. The brain was sectioned (60 μm) and stained with cresyl violet. The rats were included in data analysis if cannulae placements were bilaterally located within the target areas. A total of 14 rats were excluded for misplacement, four of them missed the BNST, and ten missed the vSUB.

2.6. Data analysis

Because the distribution of retention scores in an inhibitory avoidance task was truncated at 600 s, therefore medians and interquartile ranges were used to represent the central and dispersion tendencies, respectively. The data were analyzed with nonparametric statistics: A Kruskal–Wallis one-way analysis of variance was used to detect overall differences among groups followed by two-tailed Mann–Whitney *U*-tests to compare the difference between pairs of groups.

In each experiment, some rats bearing cannulae in the vSUB and receiving drug or vehicle infusion developed behavioral seizure. Because seizure activity was reported to exert general influences on brain functions and have deleterious effects on memory formation (Becker, Letzel, Letzel, & Grecksch, 1997; McGaugh & Gold, 1976), it might thus complicate the result interpretation; these animals were excluded from the data analyses. A total of 62 rats were excluded (15 in the vehicle group, 47 in different drug groups) and they were distributed across different experiments.

3. Results

3.1. Experiment 1: Posttraining intra-vSUB infusion of oxotremorine enhanced retention

The first experiment examined the effect of infusing a muscarinic receptor agonist, oxotremorine, into the vSUB on retention. Five groups of rats with cannulae bilaterally implanted into the vSUB were trained on the task with a 0.6 mA/0.6 s foot shock. Immediately after training, four groups received intra-vSUB infusion of vehicle or oxotremorine at the dose of 0.001, 0.01 or 0.1 μg. The fifth group received intra-vSUB infusion of 0.01 μg oxotremorine 6 h after training.

The results are shown in Fig. 1. Posttraining intra-vSUB infusion of oxotremorine caused dose- and time-dependent enhancement of memory. A Kruskal–Wallis one-way ANOVA revealed a significant difference among the five groups ($H(4) = 20.05$, $p < .001$). Paired comparisons revealed that rats receiving 0.01 μg oxotremorine had significantly better retention scores than the vehicle controls ($U = 3$, $p < .001$), while rats receiving 0.001 μg oxotremorine did not ($U = 38$, $p > .1$). The difference in retention scores between rats given 0.1 μg oxotremorine and the vehicle controls approached statistical significance ($U = 17$, $p = .08$). Moreover, rats receiving the infusion of 0.01 μg oxotremorine 6 h after training did not differ from the vehicle controls in retention ($U = 54$, $p > .10$) and had poorer retention scores than those receiving 0.01 μg oxotremorine immediately after training ($U = 14.5$, $p < .01$).

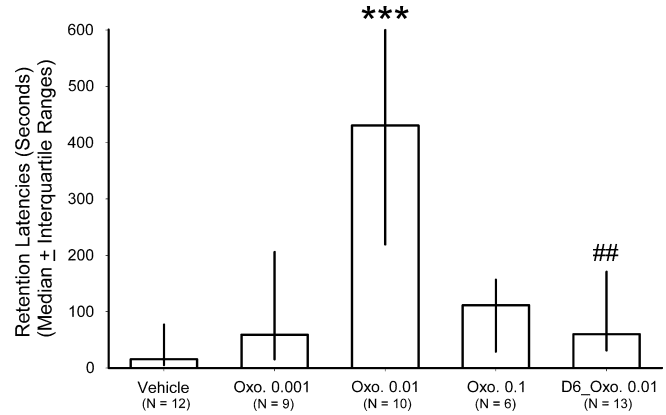

Fig. 1. The enhancing effect of posttraining intra-vSUB infusion of oxotremorine (Oxo.) at the dose of 0.001, 0.01, or 0.1 μg on retention of an inhibitory avoidance response. D6 denotes 6 h-delay infusion. *N* denotes the number of subjects in each group. $^{***}p < .001$ compared with the vehicle group; $^{\#\#}p < .01$ compared with the Oxo. 0.01 μg group.

3.2. Experiment 2: Posttraining intra-vSUB infusion of scopolamine impaired retention

The second experiment pursued whether the muscarinic antagonist scopolamine would have an impairing effect. Six groups of rats with implanted vSUB cannulae were trained on the task with a 1.0 mA/1.0 s foot shock and had intra-vSUB infusion of the following drug solutions immediate after training: vehicle, scopolamine at a dose of 0.03, 0.3 or 3.0 μg, or 3.0 μg scopolamine plus 0.001 μg oxotremorine mixed in a soup. A final group received intra-vSUB infusion of 3.0 μg scopolamine 6 hrs after training.

Fig. 2 shows the effect of posttraining intra-vSUB infusion of scopolamine on retention: Posttraining intra-vSUB infusion of scopolamine produced a pronounced dose- and time-dependent memory deficit, which could be attenuated by oxotremorine given concurrently. A Kruskal–Wallis one-way ANOVA revealed a significant difference among the groups ($H(5) = 17.63$, $p < .01$). Paired comparisons revealed that rats receiving 0.3 or 3.0 μg scopolamine shortly after training had significantly poorer retention scores than those receiving vehicle ($U = 24$ and 34 for the 0.3 μg and 3.0 μg

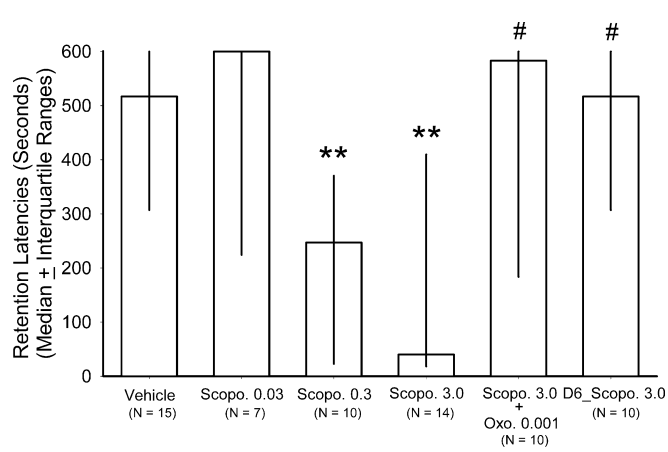

Fig. 2. The impairing effect of posttraining intra-vSUB infusion of scopolamine (Scopo.) at the dose of 0.03, 0.3, or 3.0 μg on retention of an inhibitory avoidance response and attenuation of the amnesic effect by 0.001 μg oxotremorine (Oxo.). D6 denotes 6 h-delay infusion. *N* denotes the number of subjects in each group. $^{**}p < .01$ compared with the vehicle group; $^{\#}p < .05$ compared with the Scopo. 3.0 μg group.

groups, respectively; $p < .01$), but rats receiving 0.03 μg scopolamine had retention scores not statistically different from those of the vehicle controls ($U = 46$, $p > .10$). Moreover, the difference in retention scores between the group receiving 3.0 μg scopolamine immediately after training and the group receiving the same drug 6 h after training was statistically significant ($U = 28$, $p < .05$), but that between the vehicle and delayed drug infusion groups was not ($U = 65$, $p > .10$). Rats receiving 3.0 μg scopolamine plus 0.001 μg oxotremorine had retention scores not different from the vehicle controls ($U = 68$, $p > .10$), but significantly better than rats receiving 3.0 μg scopolamine ($U = 31$, $p < .05$).

3.3. Experiment 3: Intra-BNST infusion of APV or propranolol attenuated the memory enhancing effect of intra-vSUB infusion of oxotremorine

This experiment assessed possible interaction between the vSUB and BNST by examining if the memory enhancing effect of oxotremorine in the vSUB could be attenuated by a non-impairing dose of APV or propranolol simultaneously given into the BNST. Rats bearing cannulae implanted into the vSUB and BNST were trained on the task with a 0.6 mA/0.6 s foot shock. Immediately after training, six groups received one of the following drug treatments infused into the vSUB/BNST targets: vehicle/vehicle, vehicle/APV, vehicle/propranolol, oxotremorine/vehicle, oxotremorine/APV, or oxotremorine/propranolol. The dose of oxotremorine was 0.01 μg, which caused robust memory enhancement based on results of the first experiment; while the doses of APV and propranolol were 1.0 μg and 5.0 μg, respectively, which did not affect memory if infused alone based on our past findings (Liang et al., 2001; Liu et al., submitted for publication).

The results are shown in Fig. 3. In replicating the findings of Experiment 1, intra-vSUB infusion of 0.01 μg oxotremorine enhanced memory, but this enhancing effect was attenuated by simultaneous intra-BNST infusion of 1.0 μg APV or 5.0 μg propranolol that did not impair retention by itself. A Kruskal–Wallis one-way ANOVA revealed a significant difference among the groups ($H(5) = 17.91$, $p < .001$). Paired comparisons revealed that the oxotremorine/vehicle group had significantly better retention scores than the vehicle/vehicle group ($U = 17$, $p < .01$), yet the group receiving the vehicle/APV or vehicle/propranolol treatment did not differ from the vehicle/vehicle group ($U = 31$ and 47 for the respective comparisons, $p > .10$). The oxotremorine/APV and oxotremorine/propranolol groups had poorer retention than the oxotremorine/vehicle group ($U = 23$ and 9 for the respective comparisons, $p < .01$), but they did not differ from the vehicle/vehicle group ($U = 83$ and 51 for the respective comparisons, $p > .10$) or the group receiving only the attenuating agent ($U = 26$ and 42 for the respective comparisons; $p > .10$).

3.4. Experiment 4: Intra-BNST infusion of glutamate or NE attenuated the amnesic effect of intra-vSUB infusion of scopolamine

This experiment tested if the amnesic effect of scopolamine given to the vSUB could be ameliorated by glutamate or NE at a non-enhancing dose infused into the BNST. Rats with cannulae implanted into the vSUB and BNST were trained on the task with a 1.0 mA/1.0 s foot shock. Immediately after training, six groups received one of the following drug treatments infused into the vSUB/BNST targets: vehicle/vehicle, vehicle/glutamate, vehicle/NE, scopolamine/vehicle, scopolamine/glutamate, or scopolamine/NE. The dose of scopolamine was 3.0 μg, which caused a robust memory impairing effect based on the results of Experiment 2. The doses of glutamate and NE were 0.2 μg and 0.02 μg, respectively, that based on our past findings did not cause any apparent facilitating effect on memory (Liang et al., 2001; Liu et al., submitted for publication).

The results are shown in Fig. 4. In replicating the findings of Experiment 2, 3.0 μg scopolamine given into the vSUB induced robust amnesia, but this effect was ameliorated by concurrent intra-BNST infusion of 0.2 μg glutamate or 0.02 μg NE that caused no apparent enhancing effect. A Kruskal–Wallis one-way ANOVA revealed a significant difference among the groups ($H(5) = 16.93$, $p < .01$). Paired comparisons revealed that the scopolamine/vehicle group had significantly poorer retention scores than the vehicle/vehicle group ($U = 17.5$, $p < .01$), but the vehicle/glutamate or vehicle/NE group did not differ from the vehicle/vehicle group ($U = 31$ and 30.5 for the respective comparisons, $p > .10$). The group receiving the scopolamine/glutamate or scopolamine/NE treatment had better retention than the scopolamine/vehicle group ($U = 10$, $p < .01$ for the attenuation effect of glutamate; $U = 22$, $p < .05$ for that of NE), but they did not differ from the vehicle/vehicle group ($U = 30$ and 42 for respective comparisons, $p > .10$) or the group receiving only the attenuating agent ($U = 14$ and 23 for the respective comparisons, $p > .10$).

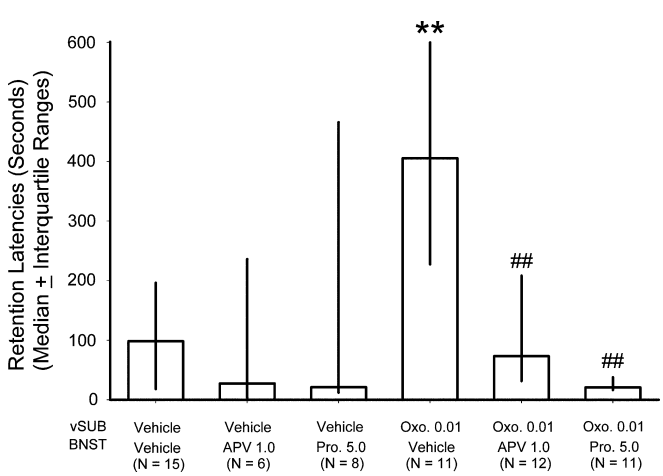

Fig. 3. Attenuation of the memory enhancing effect of 0.01 μg oxotremorine (Oxo.) infused into the vSUB by concurrent intra-BNST infusion o f 1.0 μg DL-2-amino-5-phosphonovaleric acid (APV) or 5.0 μg propranolol (Pro.) that caused no apparent amnesic effect. *N* denotes the number of subjects in each group. $^{**}p < .01$ compare with the Vehicle/Vehicle group; $^{\#\#}p < .01$ compared with the Oxo./Vehicle group.

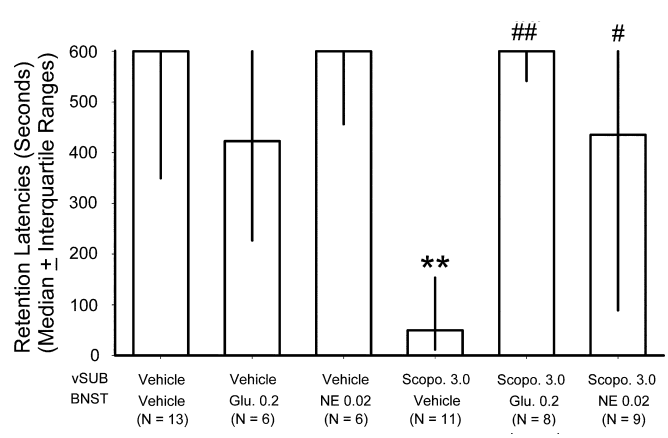

Fig. 4. Amelioration of the amnestic effect of 3.0 μg scopolamine (Scopo.) infused into the vSUB by concurrent intra-BNST infusion of 0.2 μg glutamate (Glu.) or 0.02 μg norepinephrine (NE) that cause no apparent memory enhancing effect. *N* denotes the number of subjects in each group. $^{**}p < .01$ compare with the Vehicle/Vehicle group; $^{\#\#}p < .01$ and $^{\#}p < .05$ compared with the Scopo./Vehicle group.

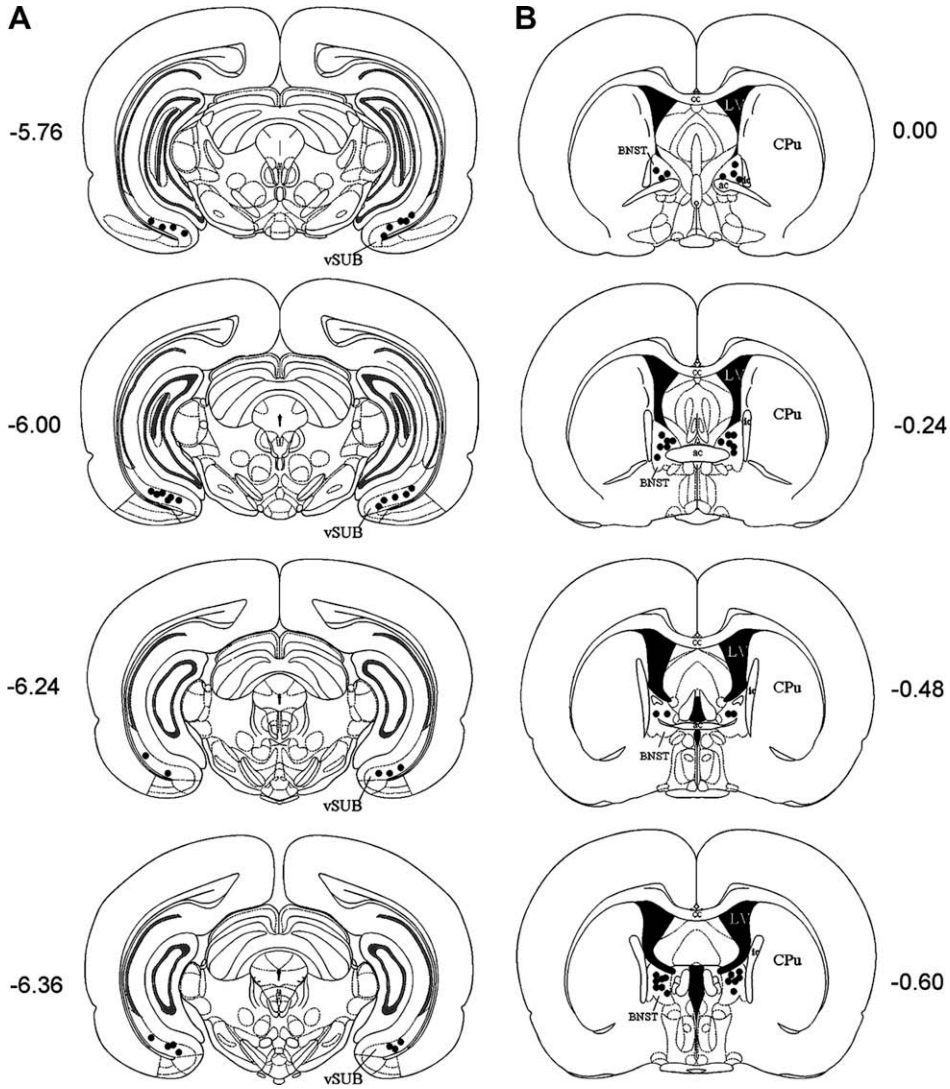

Fig. 5. Distribution of cannula placement sites in the vSUB (A) and BNST (B) for a sample of representative animals in the various experiments. Cannula tips are indicated by filled circles on plates adapted with permission from the Paxinos and Watson (2005)atlas. (ac, anterior commissure; BNST, bed nucleus of the stria terminalis; cc, corpus callosum; CPu, caudate putamen; LV, lateral ventricle; ic, internal capsule; vSUB, ventral subiculum.)

3.5. Histology

With a total of 308 rats used in this study, the final behavioral and histological analyses included 116 vSUB implanted animals and 116 vSUB/BNST-implanted animals. Distribution of cannula tips for a sample of representative animals within the target areas is shown in Fig. 5. The needle tips were distributed throughout the target regions of those accepted subjects but no apparent correlation between retention scores and locations of needle tips was noticed.

4. Discussion

Major findings of the present study can be recapitulated as follows: Immediately after training on a step-through inhibitory avoidance task, intra-vSUB infusion of oxotremorine improved retention and intra-vSUB infusion of scopolamine impaired it. Further, the memory enhancing effect of oxotremorine was attenuated by APV or propranolol concurrently infused into the BNST, and the memory impairing effect of scopolamine was ameliorated by NE or glutamate simultaneously infused into the BNST. These results suggest that the vSUB cholinergic activity influenced memory by interacting with the glutamatergic and noradrenergic systems in the BNST.

In the present study, drugs were given after a training trial, thus they could not affect emotion or motivation states and sensory-motor processes during acquisition. The time-dependent effect of the posttraining drug infusion renders an interpretation of drug influences on the test performance implausible. The dose-dependency of the drug-induced memory effects and the attenuation of scopolamine-induced amnesia by oxotremorine suggest that the observed effect was due to specific pharmacological action on muscarinic receptors. The attenuation effects observed in experiments 2, 3 and 4 could not be due to a pure addition of memory enhancing and impairing effects that bear no relevance on mechanism, since the attenuation agents used in these experiments were applied at a dose not having any effect of their own according to the present or existing results of this laboratory (Liang et al., 2001; Liu et al., submitted for publication).

Drugs in the BNST or vSUB may leak into the ventricle for location proximity and affect other brain regions. Yet in four rats with their BNST cannulae misplaced into the ventricle no attenuation effect was noticed. Further, for the drugs used in this study to be

effective by intra-ventricular infusion, doses higher than the present ones were needed (Paoli, Spignoli, & Pepeu, 1990), as our amnesic dose of scopolamine (0.3 and 3.0 μg) caused no effect by giving into the ventricle (Eidi, Zarrindast, Eidi, Oryan, & Parivar, 2003). Diffusion of 1 μl volume encroached into an area of 1.5–2.0 mm in diameter (Martin, 1991; Meyers, 1966). Our evaluation showed that infusion of 0.5 μl would diffuse within 1.0 mm in diameter. Among the adjacent areas implicated in memory (Ambrogi Lorenzini, Baldi, Bucherelli, Sacchetti, & Tassoni, 1997; LeDoux, 2007; McGaugh, 2004), drugs in the vSUB can hardly reach the basolateral amygdala nuclei at an effective concentration, but may act on the ventral hippocampus. A former study has shown that memory enhancement caused by intra-BNST infusion of 1 μl naloxone was not due to its diffusion into the striatum (Liang, Messing, & McGaugh, 1983). Interpreting drug effects by actions on the infusion targets in this study is not discrepant with the claim in other studies infusing the same volume of drug into the BNST or vSUB (Andrzejewski, Spencer, & Kelley, 2006; Onaka & Yagi, 1998; Schweimer et al., 2005; Sun & Rebec, 2003), although potential contribution of regions adjacent to the infusion target, especially the ventral hippocampus or striatum, to the observed effects should be clarified in the future.

The present study assessed affective memory in an inhibitory avoidance task that has been regarded as a form of classical fear conditioning in which rats learn to freeze (Cammarota, Bevilaqua, Kerr, Medina, & Izquierdo, 2003). Our findings may be due to altered freezing behavior as oxotremorine and scopolamine could, respectively, enhance and impair contextual fear conditioning (Cangioli et al., 2002; Gale, Anagnostaras, & Fanselow, 2001; Wallenstein & Vago, 2001). Because freezing was not simultaneously recorded in the test, our data cannot resolve this issue. However, shocking rats directly in the dark alley to mimic contextual fear conditioning yielded avoidance performance much poorer than what regular inhibitory avoidance training would yield (Liang, 2006). Thus, conditioned freezing cannot fully account for the avoidance behavior; actually, experimental dissociation of the two has been reported (Vazdarjanova & McGaugh, 1998). Further, oxotremorine and scopolamine administered peripherally or centrally caused effects on active avoidance memory similar to those in this study (Flood, Smith, & Cherkin, 1985; Yu et al., 2006). As argued by a previous study (Chien et al., 2005), the freezing account was implausible when identical effects of a treatment were observed on two tasks requiring just opposite modes of avoidance behavior.

This study showed that posttraining intra-vSUB infusion of oxotremorine or scopolamine induced a time-dependent memory deficit or enhancement, respectively, thus the effects should be due to altering consolidation of memory (McGaugh, 2000). These findings extend the previous ones that chronic or transient damage to the vSUB impaired acquisition in various forms of tasks such as cue-induced reinstatement of cocaine seeking (Sun & Rebec, 2003), Morris water maze learning (Floresco et al., 1996), operant conditioning (Govindaiah et al., 1997), spatial discrimination (Laxmi et al., 1999) and classical fear conditioning (Maren, 1999). Our findings support a mnemonic role of the vSUB in addition to the various other functions ascribed to it (Cooper, Klipec, Fowler, & Ozkan, 2006; Herman & Mueller, 2006; O'Mara, 2005, 2006). These findings further show that in addition to a role of vSUB D_1 dopamine receptors in reward learning (Andrzejewski et al., 2006), vSUB muscarinic receptors are involved in formation of avoidance memory.

The finding that intra-vSUB infusion of a muscarinic antagonist impaired memory is coherent with a notion that under high footshock training, endogenous acetylcholine is normally released in the vSUB and critical for memory formation processing. Aversive learning indeed activated basal forebrain cholinergic neurons (Gold, 2003; Tinsley, Quinn, & Fanselow, 2004) and previous studies have shown that application of neurotoxin to these neurons induced deficits in an inhibitory avoidance task and classical fear conditioning to tone or context, which were attributed to reduced acetylcholine release in the hippocampus (Chang & Gold, 2004; Frick, Kim, & Baxter, 2004; Leanza, Nilsson, Wiley, & Bjorklund, 1995). As the vSUB also receives cholinergic input from these basal forebrain neurons (Mesulam et al., 1983), our findings suggest that deficiency in the vSUB cholinergic activity may contribute to the deficit observed in those previous studies as well.

The present study also found that manipulating NMDA or noradrenergic receptors in the BNST altered the effect of muscarinic agents infused into the vSUB, suggesting that the memory effect of perturbing vSUB muscarinic receptors depends upon the integrity of BNST glutamatergic and noradrenergic functions. These findings extend our previous data showing involvement of the BNST in memory formation in the inhibitory avoidance task (Liang et al., 2001) or Morris water maze (Chen et al., 2004). The vSUB and BNST may be two brain sites providing crucial inputs convergent on a target region enabling the formation of aversive memory. Alternatively, in view of glutamatergic fibers projecting from the vSUB to the BNST through the precommissural fornix (Walaas & Fonnum, 1980), the BNST could mediate memory modulatory influences conveyed by the vSUB output. This interpretation is consistent with, but not necessarily proved by, the previous findings that glutamate regulated endogenous norepinephrine release in the BNST through NMDA receptors located on the noradrenergic nerve terminals (Forray et al., 1995, 2000) and our data that posttraining intra-BNST infusion of glutamate enhanced retention in the inhibitory avoidance task and this effect could be blocked by APV or propranolol infused into the same region simultaneously (Liu et al., submitted for publication).

The exact information instigating the vSUB/BNST interaction in an inhibitory avoidance task is still an open question. Studies have shown that in this task the contextual/spatial and stress/shock components could be separately acquired (Liang, 1999) and distinct circuits were proposed to mediate or modulate processing of each component (Malin, Ibrahim, Tu, & McGaugh, 2007; Malin & McGaugh, 2006). Extensive evidence indicates that the vSUB plays a crucial role in integration of endocrinal and behavioral functions during stress (Herman & Mueller, 2006; O'Mara, 2005, 2006), such as regulating activity of the hypothalamic–pituitary–adrenal axis to cognitive stressors (Herman, Dolgas, & Carlson, 1998). The BNST through its projection to the hypothalamic and brainstem nuclei (Dong, Petrovich, & Swanson, 2000; Dong & Swanson, 2004, 2006a, 2006b; Moga, Saper, & Gray, 1989) is also implicated in regulating autonomic, endocrinal and behavioral responses to stress (Choi et al., 2007; Ciriello & Janssen, 1993; Davis, 1998; Dunn, 1987; Forray & Gysling, 2004; Gray et al., 1993). Thus these two areas may cooperate in processing shock information of the inhibitory avoidance task.

Alternatively, the vSUB is implicated in processing of spatial or contextual cue despite such a role is often attributed to its dorsal counterpart (O'Mara, 2005, 2006). Evidence has shown that pre- or posttraining lesions of the vSUB impaired contextual fear conditioning (Maren, 1999) and prevented context modulation of a conditioned response (Burhans & Gabriel, 2007). The vSUB was proposed to pass spatial or contextual information onto other brain regions for executing goal-directed behavior (Andrzejewski et al., 2006; Sun & Rebec, 2003), such as onto the medial prefrontal cortex for a win-shift response in a delayed spatial task and the nucleus accumbens for a random foraging response in a non-delayed spatial task (Floresco et al., 1997). Therefore, in an inhibitory avoidance task the BNST may receive spatial/contextual information from the vSUB and meanwhile communicate with the amygdala on the shock information via their intimate reciprocal connections (Dong, Petrovich, & Swanson, 2001; Swanson, 1976; Weller & Smith, 1982).

In conclusion, the present results show a critical role of cholinergic activity in the vSUB in the memory consolidation process for aversive learning. Moreover, influences of the vSUB on memory processing involve, and are possibly mediated by, activation of the glutamatergic and noradrenergic fibers innervating the BNST. In view of the evidence that both the vSUB and BNST were not necessary for retrieving memory in an inhibitory avoidance task or other forms of learning (Chen et al., 2004; Floresco et al., 1996; Govindaiah et al., 1997; Laxmi et al., 1999; Liang et al., 2001), these two brain regions may be part of a circuit that is normally activated by either stress or context cues of a learning task and modulates consolidation of memory elsewhere in the brain.

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