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Nicotine improves Morris water task performance in rats given medial frontal cortex lesions

Russell W. Brown*, Claudia L.R. Gonzalez, Bryan Kolb

Department of Psychology and Neuroscience, University of Lethbridge, 4401 University Drive, Lethbridge, AB, Canada T1K 3M4

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Abstract

The object of this study was to investigate whether nicotine would improve cognitive impairments produced by medial frontal cortex lesions in rats behaviorally tested on the Morris water task (MWT). Rats were assigned to either a lesion or sham group. In the lesion group, animals were given vehicle (peanut oil) treatment or treatment with nicotine for 11 consecutive days before, after, or before and after a medial frontal cortex lesion. Additionally, a sham group was included that was given vehicle both before and after the lesion. Results showed that lesioned rats receiving pre- or post-operative nicotine treatment demonstrated improved Morris task acquisition performance relative to the lesioned group given the vehicle, although a deficit was shown relative to shams. On the probe trial, rats that received a pre- and post-treatment of nicotine demonstrated performance equivalent to shams and had significantly better performance than rats that received nicotine treatment before the lesion and lesioned animals treated with the vehicle. These results demonstrate that nicotine has therapeutic effects in rats that have received cortical injury.

Keywords: Morris water task; Spatial memory; Frontal cortex; Lesions; Nicotine

The central cholinergic system has been found to play an important role in learning and memory functioning. The majority of research on the cholinergic system has been on the muscarinic acetylcholine receptor subtype. There is an abundance of data that have shown that muscarinic antagonists, such as scopolamine and atropine, impair performance on different learning and memory tasks [17,21,30]. However, less research attention has been focused on the nicotinic cholinergic system. Acute or chronic administration of the nicotinic agonist nicotine has been shown to produce an up-regulation of nicotinic receptors in several areas of the brain, as well as augment cognitive functioning on a variety of behavioral tasks [1,2,8,9,13,14,16,17,19]. In addition to producing nicotinic receptor up-regulation, nicotine also increases the release of several neurotransmitters [32]. If nicotine enhances cognitive performance, then this drug may also be therapeutic in subjects given acute brain damage that produces cognitive deficits. The object of this study was to investigate whether nicotine would improve cognitive impairments produced by medial frontal cortex lesions in rats behaviorally tested on the Morris water task (MWT).

Research on humans has shown that nicotine improves memory, and studies have demonstrated that nicotine given to Alzheimer's patients improved attentional processes [24,31], and nicotine given to normal human subjects, either before or after behavioral training, has produced an improvement in cognitive function [23,28]. It is known that current drugs used to treat individuals afflicted with Alzheimer's disease (AD), such as the cholinesterase inhibitor donezepil (Aricept), produces an increase in the number of nicotinic receptors in several areas of the brain [29]. More recently, the nicotinic agonist ABT-418 was shown to produce significant improvement in AD patients on several verbal and nonverbal learning tasks [19]. Thus, drugs that stimulate central nicotinic receptors have been shown to produce acute cognitive benefit in AD patients.

Although central nicotinic stimulation produces cognitive improvement in normal and AD human patients, there is

* Corresponding author. Tel.: +1-403-329-2406; fax: +1-403-329-2555.

E-mail address: russell.brown@uleth.ca (R.W. Brown).

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little information concerning whether stimulation of nicotinic receptors may improve recovery of function after brain injury. In the animal literature, nicotine has been shown to improve performance in rats given lesions to the basal forebrain cholinergic system on the working memory version, as well as a two-platform discrimination version of the MWT [6,8,20,21]. Additionally, the enhanced performance produced by nicotine is maintained in rats subsequently tested up to 15 days later without additional drug treatment, implying that nicotine's cognitive enhancing effects in brain-lesioned rats are not transient [6,15]. However, in these previous studies, nicotine was given immediately before training and thus, the animal was under the influence of the drug during training.

One interesting issue concerning nicotine's behavioral effects in animals is whether nicotine can produce cognitive enhancement through chronic administration before behavioral training. A pre-injury nicotine-treatment group would test whether the physiological changes produced by nicotine are sufficient to produce cognitive enhancement without the drug present in the system during behavioral training. Buccafusco and Jackson [5] have demonstrated that nicotine infused 24 h before monkeys were placed on a delayed matching-to-sample task improved performance in both young and aged animals. Additionally, Abdulla et al. [2] have shown that chronic administration of nicotine before training on the MWT in non-brain lesioned rats produced facilitation in the rate of acquisition of the task. Based on the findings of Abdulla et al., if nicotine can produce facilitation of MWT performance given before training in rats not given brain trauma, then it is possible that nicotine would produce facilitation in recovery of function in rats given brain lesions.

Research has shown that medial frontal cortex lesions produce a significant spatial memory impairment on the MWT [11,12,27], as well as other spatial tasks [10]. The medial frontal cortex is the recipient of direct projections from the hippocampus and parahippocampus cortical regions, brain areas that have been found to be important in spatial memory function [7,18]. Additionally, there are cholinergic fibers of passage through the medial frontal cortex from the basal forebrain [32]. With the important role that the medial frontal cortex may play in memory functioning, it is surprising that there is little information relative to different pharmacological treatments that may improve cognitive deficits produced by injury to this brain region. In this study, we utilized a chronic administration paradigm in which animals were given a chronic treatment of nicotine before behavioral training on the MWT. As in previous studies [1,2,5], nicotine administration ceased 24 h before behavioral training and the drug was not present during acquisition training. We predicted that lesioned animals given nicotine treatment, regardless of whether nicotine was given before or after the lesion, would demonstrate a significant improvement on the MWT relative to lesioned animals given only the vehicle.

1. Methods

1.1. Subjects

Subjects used in this study were 30 male Long–Evans rats. Animals were housed in group cages and kept in a climate-controlled vivarium with a 12-h on/12-h off light/dark cycle. All rats weighed 275–325 g at the beginning of drug treatment. Food and water were available ad libitum.

1.2. Groups and drug administration

Rats were divided into five treatment groups. All rats received two subcutaneous (sc) injections of either drug or vehicle daily for 11 consecutive days before and 11 consecutive days after the medial frontal cortex lesion. The nicotine dose used was 0.3 mg/kg and was made from a 98% pure nicotine solution and dissolved in peanut oil. All injections were given in the volume 1 ml/kg. Rats were given one injection in the morning and one injection in the afternoon, and were administered the drug or vehicle (peanut oil) according to group assignment. In Group PRE, rats were administered nicotine before surgery, and the vehicle after surgery. In Group POST, rats were given the vehicle before surgery, and nicotine after surgery. In Group PRE/POST, animals were given nicotine both before and after surgery. In addition to the three nicotine groups, there was a no treatment lesion group (Group NT) and a sham group (Group SHAM), each of which were given the vehicle for 11 days both before and after the lesion. There were no injections given the day after surgery due to surgical stress, and all injections ceased 24 h before behavioral testing.

1.3. Apparatus

The maze consisted of a circular pool 1.5 m in diameter and 45 cm in height. The inside of the pool was painted white and filled to a height of approximately 25 cm with water that was 19–21°C. A clear Plexiglas platform (11 × 12 cm) was placed centrally in the southwest quadrant and remained there throughout training. Its top surface was approximately 1 cm below the surface of the water. Powdered milk was dissolved in the water so that the platform was not able to be seen by the swimming rat.

1.4. Behavioral testing

Behavioral testing on the MWT began approximately 24 h after the last injection. Animals were run in squads of seven animals each. All animals were given eight trials a day for 3 consecutive days, were tested at the same time each day, and all conditions were represented in each squad of rats tested. The intertrial interval for each trial was approximately 4–5 min and acquisition latency was recorded on each training trial. Rats were released twice from each of four release locations (N, W, S, E) in each trial

block, and were allowed 60 s to reach the platform. The platform remained stationary throughout training. If the animal did not locate the platform on a particular trial, it was placed there by the experimenter. All animals spent the last 10 s of each trial on the platform, regardless of whether the animal reached the platform of their own volition or it was placed there by the experimenter. Immediately after the last training trial on the third day of training, rats were given a 60-s probe trial. On this trial, the platform was removed and the animal was allowed to swim freely with the subject's swim patterns recorded by a videocamera that was mounted above the pool. These swim patterns were later analyzed on videotape by an observer blind to treatment conditions.

On the probe trial, we used the dependent measure referred to as the mean zone difference (MZD) score [3]. This score was used to circumvent some of the problems with other probe trial dependent measures. For example, search time in the quadrant of the former platform location, a common probe trial measure, is a measure of the general accuracy of the animal's memory for the former platform location, but does not measure exact accuracy for the former location of the platform. Visits to the former platform location does not take into account other areas of the pool, thus, an animal could demonstrate a high number of visits for the former platform location without demonstrating a strong spatial bias. The MZD score takes into account accuracy for the exact former platform location, as well as spatial bias relative to the other three quadrants of the pool.

For the MZD score, the number of visits to each of three nontarget zones that are equal in size to the platform (A, B, and C) are separately subtracted from the number of visits to the exact former platform location (referred to as D) and divided by 3 (the total number of nontarget zones). The three nontarget zones are located centrally in the northwest (referred to as A), northeast (referred to as B), and southeast (referred to as C) quadrants. The formula for this score is as follows:

$$\frac{(D-A)+(D-B)+(D-C)}{3}$$

For example, if an animal visits the former platform location (D) eight times, and the other three zones three times a piece, the MZD will yield a score of 5. The higher the MZD score, the stronger the spatial bias to the former platform location.

1.5. Lesion procedure

For surgery, animals were anesthetized with somnitol (65 mg/kg) and atropine methyl nitrate (5 mg/kg) and placed into a stereotaxic apparatus. A midline incision was made and two drill holes were made on the surface of the skull in each hemisphere at the following coordinates relative to bregma: 1.3 mm anterior, 1.5 mm lateral, and 3.6 mm ventral; 1.5 mm anterior, 0.5 mm lateral, and 3.3 mm ventral. The lesion was made by passing a 2.0 mA cathodal current for 40 s through an electrode placed at these two lesion sites in each hemisphere. Sham rats received anesthesia and a midline incision.

1.6. Histological procedure

At the completion of behavioral testing, all animals were deeply anesthetized and perfused with saline followed by formalin. Brains were removed and stored in a paraformaldehyde solution for 48 h, removed, and then stored in a 30% sucrose–formalin solution. Brains were cut in 40-μm sections on a cryostat with every fifth section saved and stained with Cresyl violet and every sixth section saved and stained for acetylcholinesterase (AChE).

A densitometry analysis was performed on brain sections stained for AChE to analyze both whether the frontal lesions affected cholinergic projections to remaining cortical area. This measure is used to analyze density (light/darkness) of AChE staining, and was performed using an NIH scion image analysis system that was connected to a Zeiss (Germany) light microscope. Sections were visualized at magnification $2.5\times$, and the size of the sample was 3.07×10^5 square pixels. The posterior parietal cortex was selected for measurement because this region is known to be important for spatial processing and it is an area that receives a significant input from the medial frontal cortex. In this analysis, only Groups PRE/POST, NT, and SHAM were included. One tissue section was chosen for each animal and this section was located in the posterior parietal area (area P1) directly dorsal to the hippocampus. There were three non-overlapping samples taken for each hemisphere, and a mean of stain density was taken for each sample.

2. Results

2.1. Histological results

A drawing representation of the lesion site is presented in Fig. 1. All lesioned animals had significant, but not complete, damage to the Cg1, Cg2, and Cg3 areas of the frontal cortex. There was no damage to the striatum in any case. Two cases had bilateral damage to the septal region, and these animals were dropped from the study. Thus, for all behavioral analyses, there were six animals in Groups PRE, POST, and NT, and five animals in Groups PRE/POST and SHAM.

2.2. AChE density

Overall, there was a decrease in AChE density in parietal cortex of rats with frontal lesions but no effect of nicotine treatment. A one-way ANOVA was performed on the AChE densitometry measure, and revealed a

Fig. 1. Drawings through serial sections of a representative medial frontal lesion. The midline frontal cortex is largely destroyed, and there is gliosis (marked by dots) both in cortex and striatum. Abbreviations: Zilles' parietal area 1 (Par 1); Zilles' frontal areas (Fr1, Fr2, Fr3); Zilles' forelimb area (FL).

significant main effect of group $F(2, 13) = 10.57$, $P < .01$. The number of rats per group, means/S.E.M. for the three groups were as follows: Group Sham ($N = 5$) = 149.9/1.14, Group NT($N = 6$) = 141.59/1.61, GroupPRE/POST ($N = 6$) = 139.62/1.12. Newman–Keuls post hoc tests revealed that the mean density for Group Sham was significantly higher than the mean densities for Groups PRE/POST and NT. Therefore, the medial frontal cortex lesion produced a decrease in AChE staining in this region, probably due to the severing of fibers arising from the nucleus basalis in the forebrain that pass through the medial frontal cortex on their way to the parietal cortex. However, nicotine did not significantly influence the density of AChE staining in the posterior parietal cortex, implying that nicotine did not alter cholinergic activity in this region relative to controls.

2.3. Behavioral results

Acquisition latencies are shown in Fig. 2. The overall result was that frontal lesions produced an acquisition deficit and this deficit was reduced by nicotine treatment. A two-way ANOVA revealed a significant main effect of trial block $F(5, 125) = 61.1$, $P < .01$ and a Group × Trial Block interaction $F(20, 125) = 1.79$, $P < .02$. Newman–Keuls post hoc tests revealed that the Group NT significantly differed from Group SHAM from trial blocks 1–5, and Group PRE/POST differed from Group NT at trial blocks 2, 4, and 5. Both Groups PRE and POST differed from Group NT at trial blocks 1,2, and 5. There were no significant differences between any of the groups at trial block 6. This result indicates that nicotine improved the performance of lesioned animals relative to the vehicle-treated lesion group and that all lesioned rats demonstrated a rate of acquisition impairment relative to shams.

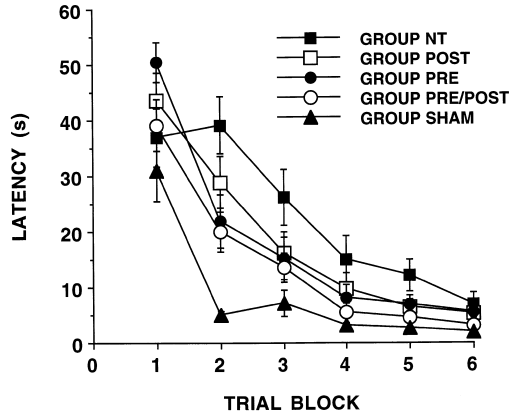

Fig. 2. Acquisition latency is represented as a function of trial block. Trial blocks consisted of four training trials each. All three groups receiving nicotine performed significantly better than Group NT on trial blocks 2–5, but all three nicotine groups had significantly higher latencies than the sham group on trial blocks 2–5. There were no group differences at trial block 6.

MZD scores are shown in Fig. 3. A one-way ANOVA revealed a significant group main effect $F(4, 23) = 4.45$, $P < .01$. Newman–Keuls post hoc tests showed that Groups PRE/POST and SHAM did not significantly differ, and both had significantly higher MZD scores than Group NT. There were no other significant differences between groups. Therefore, on the probe trial, animals that received both pre- and post-treatment of nicotine demonstrated equivalent perfor-

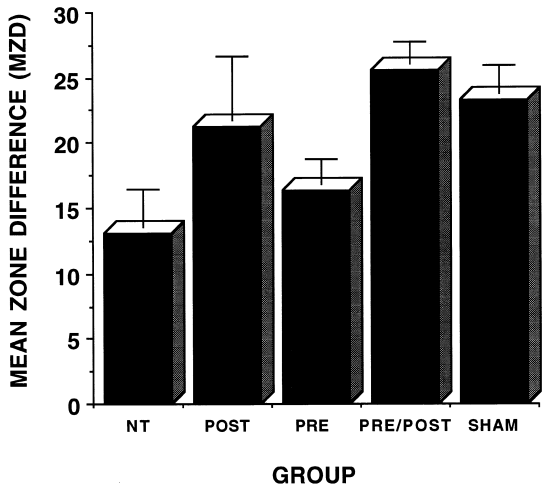

Fig. 3. MZD scores are represented as a function of group. The PRE/POST, POST, and SHAM groups did not significantly differ, and all three groups had significantly higher scores than Groups PRE and NT.

mance to shams and improvement over the vehicle-treated lesion group.

3. Discussion

The results of this study showed that: (1) rats with medial frontal lesions are impaired at acquisition of the MWT; (2) chronic administration of nicotine given for 11 consecutive days before, after, or before and after a medial frontal lesion improved rate of Morris task acquisition, although not to control levels; and (3) nicotine treatment both before and after the lesion improved probe trial performance to sham control levels. This is the first demonstration of nicotine improving post-operative functional recovery in animals given cortical lesions. Therefore, nicotine may have therapeutic effects for the treatment of cortical injury.

The mechanisms by which nicotine is able to produce its cognitive enhancing effects are diverse. For instance, administration of nicotine, either acutely or chronically, has been shown to produce an up-regulation of postsynaptic nicotinic receptors in the frontal cortex, posterior cingulate cortex, several midbrain structures, as well as the hippocampal formation [1,16]. Nicotinic receptor up-regulation also has been shown to result in increased tyrosine hydroxylase activity in the hippocampus [26], which indicates that there may be increased dopaminergic or noradrenergic activity in the hippocampus as a result of nicotinic receptor up-regulation. The hippocampus is a brain area known to be important in spatial memory, so it is possible that the enhanced recovery following nicotine treatment results from nicotine's actions on the hippocampus.

Another possible mechanism could be the effects of nicotine on the interaction of the glutamatergic and cholinergic systems. Shoaib et al. [25] have shown that MK-801, an NMDA antagonist, blocked not only behavioral sensitization to nicotine, but also the receptor up-regulation produced by nicotine, and there is an overabundance of data emphasizing the importance of the NMDA receptor in learning and memory function. This suggests that there may be an interaction of the glutamatergic system and nicotinic receptor up-regulation that may be playing a role in the facilitation in recovery of function after medial frontal lesions observed in this study. The exact nature of the interaction of these two systems is not known.

We have shown elsewhere that chronic administration of nicotine, similar to amphetamine and cocaine [22], leads to enhanced dendritic length and increased spine density in the nucleus accumbens and medial frontal cortex [4]. Therefore, it is possible that nicotine acts to stimulate recovery after cortical injury via changes in cerebral connectivity. Although we have not yet examined the hippocampus in animals treated with nicotine, it is quite possible that nicotine alters synaptic organization in other areas of the brain that could facilitate performance on tests of spatial cognition.

In the current study, we compared the effects of pre-, post-, and combined nicotine treatments on functional recovery. Although not entirely conclusive, the combined administration of pre- and post-lesion nicotine produces the more robust enhancement of MWT performance relative to the other nicotine groups, whereas pre- or post-lesion nicotine treatment alone enhanced acquisition compared to a lesion group given vehicle, but a pre- or post-lesion treatment of nicotine was not sufficient to improve probe trial performance. One complication in this result, however, is that the pre-treatment group was not given behavioral testing until 12 days following the cessation of nicotine administration, whereas the post- and pre- and post-treatment groups were given behavioral testing 24 h after the final nicotine injection. The pre-treatment group was designed to investigate whether nicotine would produce some type of neuroprotective effect for the medial frontal lesion, and, owing to the necessity of allowing these animals to recover from the acute effects of the surgery, it was not feasible to behaviorally test these animals at a short interval after surgery. Obviously, if these animals were tested more temporally proximal to the end of nicotine treatment, behavioral deficits could be due to the acute effects of the surgery rather than the lack of an effect of the pre-surgery treatment of nicotine. Therefore, the pre-treatment group was tested at the same time as the other nicotine treatment groups in order to investigate whether any neuroprotective effects of nicotine would endure. It appears that nicotine did not produce a neuroprotective effect relative to the size of the lesion or behavioral results shown in this study.

In summary, this study presents the novel finding that nicotine can act as a stimulant to facilitate recovery from cortical injury. Future studies in this laboratory will focus on both the mechanism of action and the generality of this result to other cerebral injuries.

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