

PROPOSAL C

The Effects of Nicotine on Learning and Memory in Old and Young Rats

Many cognitive skills decline with age, including short and long-term memory (Smith 1996; Zornetzer, et al. 1982). In rats, these deficits appear to be associated with neurochemical changes in the brain such as reduced levels of acetylcholine (Perry et al. 1992) and a decrease in the number of nicotine receptors (Court and Clementi, 1995). Deficits similar to these have been reported in patients suffering from Alzheimer's disease (Coyle et al., 1983) and suggesting that drug treatments that increase the levels of acetylcholine in the brain (cholinergic agonists) may be an effective treatment for this disease. The two cholinergic agonists currently approved by the FDA (Donepezil and Tacrine) have a limited positive effect on memory and have serious side effects (Sahakian and Coull, 1993). There is a need for the development of new drug treatments that are effective in countering the effects of aging on memory.

One possible cholinergic agonist with promising effect is nicotine. Nicotine agonists produce memory deficits in rats (Levin et al. 1997) and impair the neurological functioning of healthy humans in ways that mimic the early stages of Alzheimer's disease (Newhouse et al., 1992). The evidence in support of nicotine as a treatment for memory deficits is mixed. Some studies have found improvements in short-term memory but not long-term memory in rats (Levin et al., 1993), while other have found the opposite (Arendash et al. 1995).

The goal of this study is to determine the effects of nicotine on memory performance in young and old rats. Rats are a particularly good model for memory deficits in humans because changes in brain anatomy and function in aged rats resemble those observed in aging humans (Coleman and Flood, 1986). However, nicotine has many deleterious side effects, so it is important that the beneficial effects of this drug be fully understood before any attempts to use it as a treatment for human disease.

Subjects will be 16 young (4 months of age) and 16 old (16 months of age) rats of the Fisher 344 strain. Rats will be housed individually and provided with food (Purina Rat Chow) and water ad libitum. Rats will be randomly assigned to one of 4 groups based on age and drug treatment regime (Table 1).

Table 1. Treatment groups

Group	Age	Treatment
1	Young	Nicotine
2	Young	Saline (control)
3	Old	Nicotine
4	Old	Saline (control)

Prior to behavioral testing, each rat will receive an intra-peritoneal injection of saline (0.20 mg/kg body weight) or nicotine (0.20 mg/kg body weight) in accordance with its assigned treatment. Behavioral testing will consist of three tests: an activity chamber, a rotating rod test, and the Morris water maze. The activity test consists of a 30 x 30 x 30 cm cubic box with a wood paneled flooring that allows for the continuous recording of animal movements within the box.

Activity of each rat will be measured in two 5-minute sessions conducted on consecutive days. The activity test will measure general the general stimulant effects of nicotine, which can occur independently of memory improvements. However, activity and memory effects of nicotine may be related in that the increased levels of arousal produced by nicotine may allow faster learning in some types of tasks. The rotating rod test consists of a horizontal pole (10 cm in diameter, 162 cm long) connected to a motor that enables it to be rotated at a rate of 5 turns per minute. The pole is covered with tape to provide traction and is held 85 cm above a layer of foam padding, which prevents injury to rats that slip off the pole. At the beginning of each trial, a rat will be placed on the rotating pole so that all four of its feet are securely on the pole. All slips (rat falls off the rod but manages to hold on for at least one full rotation of the pole) and falls (rat completely loses contact with the rod) will be counted for a 1-minute period. After each slip or fall the rat will be repositioned on the rod until the 1-minute trial is complete. The rotating rod test is a measure of general coordination, which also may be affected by nicotine without any necessary accompanying increase in memory. The Morris water maze consists of a circular (145 cm diameter) tank filled with warm water. Inside the tank is a submerged platform positioned 15 cm from the side of the tank. The platform is concealed from the rat's view by adding white non-toxin tempura paint to the water in the tank, rendering it opaque. Rats will be released at a single point in the maze on each of four successive days and the time it takes them to swim to the submerged platform will be measured. This is a measure of learning and memory, since rats initially have to find the platform through trial and error, then on successive days can reach the platform much more quickly if they remember its location relative to the release point.

It is expected that treatment with nicotine will result in increased motor activity (as assessed by the activity test) of both young and old rats relative to the saline controls. Motor coordination (as assessed by the rotating rod test) is predicted to improve with nicotine treatment in both young and old rats, relative to saline controls. Learning ability and memory (as assessed by the Morris water maze) is predicted to improve with nicotine treatment, and would be indicated by a shorter time interval and swimming distance before finding the submerged platform. It is further predicted that old rats will show impairment relative to young rats on one or more of these tests, and that nicotine treatment will restore their performance to levels near those achieved by young rats.

This study promises to provide important new information regarding the effects of nicotine (a cholinergic agonist) on age-related learning and memory capabilities. If nicotine administration can restore learning and memory in aging rats to levels comparable to those of young rats, then it may be a promising treatment for age- and disease-related impairments in human learning and memory.

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