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BRIEF COMMUNICATION

Effects of Chronically Administered Nicotine and Saline on Motor Activity in Rats[1]

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CRONAN, T., J. CONRAD AND R. BRYSON. *Effects of chronically administered nicotine and saline on motor activity in rats.* PHARMACOL BIOCHEM BEHAV 22(5) 897–899, 1985.—This study investigated the differential effects of chronically administered nicotine and saline on motor activity in the rat. Nicotine was administered via a subcutaneously implanted osmotic minipump to effect an 8 hour off, 16 hour on, flow. Subjects were 48 male and 48 female albino rats, each about 165 days old. Activity was monitored every hour for 192 consecutive hours. Results indicated that the female animals were more active than the males, and that animals receiving nicotine were significantly more active on the first two days of drug administration than control animals; however, by the fourth day there were no significant differences between the activity levels of animals that received nicotine and those of control animals.

Nicotine Motor activity Rats

NICOTINE may stimulate or depress spontaneous motor activity in rodents, depending upon the dosage employed, sex of the animal, duration of exposure to the drug, and the method of drug administration. In general, small doses of nicotine have a stimulating effect on activity, while large doses have a depressing effect [11].

Females are often affected more than males by nicotine [47]. Doses of 0.4 mg/kg nicotine significantly increased spontaneous motor activity in female rats, but not in males [10]. It has been suggested that higher androgen levels in males inhibit the metabolism of nicotine, producing the smaller increases in activity levels [5]. However, the time courses of activity changes following nicotine injection in castrates, males, and females are very similar [2].

In one tolerance study, daily injections of small amounts of nicotine (0.3 mg/kg) increased both EEG and behavioral activity until the sixth day of nicotine administration [8]. In another study the elevated activity levels associated with a 0.2 mg/kg bw daily dosage persisted for twelve days [1]. Single injections of nicotine produced maximal activity after 2 hours, with no effect of nicotine after 8 hours. Repeated doses of nicotine (three times daily for eight days) produced chronic tolerance, which persisted for at least 90 days [13]. Another experiment tested the effects of three vehicles for drug administration: IP injections, reservoirs implanted subcutaneously, or the rats' drinking water. Larger doses of nicotine were required to induce tolerance by the latter two methods [12].

All of these methods of nicotine administration have deficiencies. Injections provide very large instantaneous bursts of nicotine; reservoir dosage is continuous throughout the day/night cycle; dosage with drinking water is not controlled. In the present study, general activity level was assessed in male and female rats over an eight day period. Nicotine was infused via osmotic minipumps according to an alternating 16 hours on, 8 hours off schedule.

METHOD

Subjects

The subjects were 48 female and 48 male experimentally naive Sprague-Dawley-derived rats bred at Simonsen Laboratories in Gilroy, CA. Male and female animals were housed in separate rooms in individual wire mesh cages with free access to food and water. Experimental observations were begun when animals were 5½ months old, at which time the range of weights for females were 223–347 grams and for males 321–538 grams. Animals were run in four squads of 24, with an equal number of males and females in each.

Apparatus

Twenty-four electric photocell chambers (40 cm long × 20 cm wide × 25 cm high) constructed of unfinished wood with a wire mesh floor 2.4 cm above the base platform, and with a

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hinged wire mesh lid, were used. One photocell and two mirrors were used to create two parallel beams located 7 cm from either side and 5 cm from the mesh floor. All chambers were interfaced with an Apple II computer, which recorded the number of light beam interruptions within each one-hour period for a total of 192 hours.

Alzet Osmotic Minipumps, model 2002, with adaptor ends attached to fine coiled polyethylene (PE) tubing were used for the administration of nicotine. The tubing was filled with nicotine (dissolved in physiological saline) stratified with air to effect an 8 hour off, 16 hour on flow, such that animals would receive a nicotine dosage of 1 mg/kg per day. This dosage and schedule were chosen in an attempt to approximate the dosage pattern of a human smoker who smokes two packages of cigarettes per day. Pumps for control animals were prepared similarly, alternating strata of physiological saline with air. Prior to implantation, each pump was primed for 5 hours at 37°C (rats' body temperature) in physiological saline.

Procedure

A pump with attached PE tubing was subcutaneously implanted just below the base of the neck in each rat while animals were anesthetized with ketamine hydrochloride (1 mg/kg bw). Eight hours after implantation each rat was placed in its photocell chamber, where it remained for 192 consecutive hours. Food and water were available continuously; the food was scattered on the floor.

Animals were maintained on a normal (12 hours light/12 hours dark) day-night cycle at 21°C. Prerecorded white noise was played continuously to control for ambient noise.

In six cases removal of the pumps at the end of the experiment revealed that connective tissue had grown over the opening of the osmotic pump, preventing the release of fluid or air. These cases, and two additional randomly chosen animals, were excluded to yield four equal treatment groups of 22 rats each.

RESULTS

A 2 (nicotine vs. saline) × 2 (male vs. female) × 4 (time in 2-day increments) mixed design analysis of variance was performed on the mean activity levels. Females were significantly more active than males, $F(1,84)=7.44$, $p<0.01$.

No significant main effect was found for drug or time. However, a significant drug by time interaction was found, $F(3,252)=4.06$, $p<0.01$. Figure 1 shows this interaction. A post hoc Neuman-Keuls revealed a significant difference between animals that received nicotine and those that received saline during the first two days. Animals receiving nicotine were more active. The saline animals were slightly more active during days 3–4 and 5–6, with groups virtually identical in activity on days 7–8. None of these differences were statistically significant. From Fig. 1 it appears that the implantation operation depressed activity levels for the first two postoperative days.

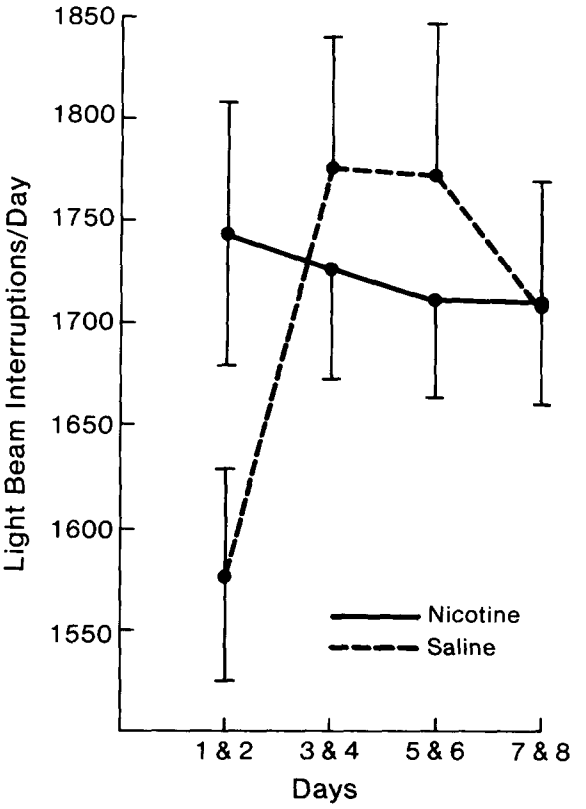

FIG. 1. Figure 1 shows the mean number of light beam interruptions for each two day period for males and females combined. Vertical bars indicate standard errors of means. Each animal received either 1 mg/kg per day of nicotine or saline without nicotine on an 8 hour off, 16 hour on flow through an Alzet Osmotic Minipump.

DISCUSSION

The present study is the first attempt to administer chronically and gradually moderate amounts of nicotine. Further, the method used shows promise; osmotic minipumps allow investigators to control both amount and rate of dosage. However, in the current experiment the off/on periods of nicotine administration were not monitored independently of the activity observations.

The fact that the females were more active than the males is consistent with previous findings [3, 6, 9]. The time course of development of apparent tolerance to the activity-enhancing effects of small dosages of nicotine is similar to the time course of large dosages of nicotine (see [13]). However, the time required for the activity levels of nicotine and saline animals to converge was less than that for animals receiving similar amounts of nicotine via injection [8].

Although females were more active than males, the expected sex differences in responsiveness to nicotine and in rate of convergence of activity levels were not obtained. The failure to find a sex by drug or sex by time interaction is consistent with some prior results [2]. This constitutes further indirect evidence that sex differences are not produced by differences in the rates of nicotine metabolism.

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