MANUSCRIPT REVIEW BOARD INFORMATION SHEET

MANUSCRIPT TITLE: Studies on the Effects of Intraventricular Infusions of (-)-Nicotine on Behavior Maintained under Fixed Ratio Schedules (FR)

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ABSTRACT

Acute intraventricular infusion of (-)-nicotine is known to produce a prostration-immobilization syndrome, the duration of which is 0.5-2.0 min. Behavioral recovery occurs 10-12 min. prior to recovery in amplitude and frequency changes in EEG recorded from dorsal hippocampus. This prostration syndrome can be prevented or antagonized by intraventricular pretreatment with N-benzyl and N-p-nitrophenylazido derivatives of nicotine or piperidine but not by acetylcholine or anticholinergic drugs (Abood et al, 1978, 1979). The present studies were designed to investigate: 1) the effect of intraventricular infusion of (-)-nicotine on behavior maintained under FR schedules of food reinforcement, 2) possible changes in prostration with repeated but spaced (5 days apart) infusions of (-)-nicotine and, 3) the effect of nicotinic-cholinergic antagonists on the rate suppressing effects of intraventricularly administered nicotine.

Food deprived male albino rats each implanted with stainless steel cannula into the left lateral ventrical were shaped to lever press in a standard operant chamber for food reinforcement. During experiment one the rats (N=12) were maintained under an FR 16 whereas during the second (N=7), and the third experiment (N=4), the rats were maintained under an FR 32. Daily sessions consisted of two successive 15-min. periods with a 5-min. time-out after the first 15 min. Intraventricular infusions occurred during the 5 min. time-out when lever pressing under the FR schedules was stable (less than 10% variance in the response rate for 5 days). The rats were first infused with saline (5 µℓ of 0.9% saline) and placed immediately back in the operant chamber. Repetitive 15 min. sessions were run until: 1) response rate returned to previous levels or, 2) the rat stopped eating due to satiation. Following re-stabilization of lever pressing (usually within 7 days) the rats were infused as previously described with 5µg of (-)-nicotine in 5 µℓ. In all three experiments the latency to complete the first ratio and the percent change in response rate following infusions were recorded. In Exp. 2, lever pressing was maintained under FR 32 and the effect of repeated but spaced infusions of (-)-nicotine (5µg in 5 µℓ every 5th day) was investigated. In Exp. 3, lever pressing was stabilized under FR 32, and the rats were tested as follows: 1) saline (5 µℓ of 0.9%), 2) (-)-nicotine (10µg in 5µℓ), 3) another (-)-nicotine infusion (10µg 5µℓ), 4) (-)-nicotine (10µg in 5µℓ) with a pre-injection (s.c.) of

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mecamylamine (1.5 *mg/kg*) or hexamethonium (1.0*mg/kg*) 5 min. prior to the infusion and, 5) saline and pre-injection (s.c.) of the antagonists. Infusions were separated by 7 days.

The results of Exp. 1 showed that latency to the first completed ratio following an infusion of (-)-nicotine was $\bar{X}$=10.94 min. (S.E. 1.56) whereas the latency following a saline infusion was $\bar{X}$=0.76 min. (S.E. 0.02). Observations of the rats via a one way mirror revealed that the prostration-immobilization syndrome appeared complete within 3-5 min. post-infusion. The mean latency to complete the first ratio in this study (10.94 min.) coincides with recovery time of EEG activity recorded for the dorsal hippocampus (Abood, et al 1978, 1979). In Exp. 2, the effect of repeated infusions was to decrease the latency for the first completed ratio. After the second infusion the latency for the first completed ratio decreased 45% ($\bar{X}$=7.71 min. (1.5 SE) to $\bar{X}$-4.23 (1.48 SE). Subsequent decreases were not observed. Saline infusions had little or no effect (latency= 0.83 sec. SE 0.31 sec.). There were no apparent effects of saline infusion, with or without pre-injections of mecamylamine or hexamethonium on latency to complete the first ratio. However, the pre-injection of mecamylamine partially antagonized the effects of the (-)-nicotine infusion whereas the hexamethonium had no effect. These results suggest that: 1) the duration of the behavioral effects produced by intraventricular infusion of (-)-nicotine extend far beyond the observed prostration-immobilization syndrome, 2) there was a diminished effect with repeated but spaced infusions, and 3) the fact that mecamylamine but not hexamethonium partially antagonized the effects on FR responding suggest that at least part of the prostration syndrome may be mediated by noncholinergic sites of nicotine's action.