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MANUSCRIPT REVIEW BOARD INFORMATION SHEET

MANUSCRIPT TITLE: Influence of Behavioral Factors in the Development of Tolerance to (-)-Nicotine.

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ABSTRACT

Tolerance to a substance is defined as a diminished effect with repeated administration. Tolerance may be a result of factors which alter the effective concentration of the active agent at the receptor. These factors include altered absorption, distribution, degradation or elimination mechanisms. Tolerance may also result from a decreased sensitivity of the receptor even though the concentration of the active agent at the receptor is unchanged.

There are several studies indicating that the development of tolerance to a number of compounds may also be influenced by certain behavioral (i.e. learning or performance) factors. Thus, the development of tolerance to the behavioral effects of a compound may depend on the behavior in question and/or the specific behavioral alterations produced. "Behavioral" tolerance, then, exists when such relationships can be identified. One factor that influences the development of tolerance is whether or not a compound disrupts ongoing behavior in such a way as to alter the frequency or rate of reinforcer delivery. If a compound produces a loss of reinforcement, then tolerance is more likely to occur (or at least occur more rapidly) than when reinforcement frequency is not altered. That tolerance occurs to some of the behavioral effects of nicotine in animals following repeated administration is well documented. Whether behavioral factors are important in the development of tolerance to nicotine is unknown.

To address this question, fourteen rats were trained to respond under a fixed ratio 32 (FR 32) schedule of food pellet presentation. (-)-Nicotine (.05, .1, .2, .4, .8 mg/kg) disrupted FR behavior in a dose-dependent manner following acute (once per week) injections. Response rates and the number of food pellets delivered were decreased and the latency to complete the first ratio was increased as a function of (-)-nicotine dose. Maximal effects occurred early in the session with the highest dose typically eliminating all responding for the first 6-12 minutes of the 30 minute session. Recovery of responding was rapid with performance approximating control values by the end of the session.

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Four weeks after the completion of the acute dose-effect determinations, the rats were divided into two equal sized groups matched for response rate. Saline was injected twice per day, once before and once after the session for five days, as a control for the repeated administration of nicotine. For the next 30 consecutive days, one group of rats (the Before group) received .8 mg/kg of nicotine before and saline after the session, while the other group of rats (the After group) received saline before and nicotine after the session.

With the Before-After paradigm both groups of rats receive exactly the same quantity of nicotine on a day-to-day basis. What varies, however, are the nicotine-induced behavioral alterations experienced by the two groups of animals. The Before group experiences nicotine-induced disruptions of FR performance, including loss of reinforcement, while the After group does not. If loss of reinforcement is a critical factor in the development of tolerance to nicotine, then the After group is not expected to show tolerance when, or at least to the degree that, the Before group does.

Over the 30 day period of chronic nicotine administration, the Before group showed a gradually decreasing disruption of FR performance by nicotine, i.e., tolerance. For example, on day 1 of chronic nicotine administration the total number of food pellets obtained by the Before group was reduced to 48.6 ± 9.3% (mean ± SE) of saline control; on day 31 the number of food pellets had recovered to 90.5 ± 9.8% of control. The FR responding of the After group did not differ from control values during the first 30 days of chronic nicotine administration. On day 31 the After group received nicotine before the session as a test for tolerance in this group. On day 31 the performance of the After group was severely disrupted by the presession injection of nicotine. Comparison between the Before and After groups showed that the After group was altered to a significantly greater degree on all measures of responding by nicotine. These findings indicate that the development of tolerance to nicotine may be dependent on certain behavioral factors, such as the nicotine-induced reduction in reinforcement, in addition to the mere repeated administration of nicotine. Subsequently, the acute nicotine dose-effect functions were redetermined in all rats while chronic nicotine administration was continued; additional higher doses (1.2 and 1.6 mg/kg) were included. Results showed that the dose-effect functions were shifted to the right, providing additional confirmation for the development of tolerance to chronic nicotine administration.