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INTER-OFFICE CORRESPONDENCE

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To: Dr. W. L. Dunn Date: April 24, 1980

From: V. J. DeNoble

Subject: Nicotine Program - Behavioral Research Laboratory

An outline of the behavioral testing program is discussed on the following pages.

Discrimination Testing

The discrimination task has proven to be effective for screening nicotine analogues. We do not feel that any major changes in the method should be made, however, additional data collection techniques will provide us with more detailed information. For example, each compound tested should be subjected to a dose-response function. This will provide us with a measure of the relative behavioral potency of each compound tested. A more refined analysis of individual data is necessary; e.g., if a rat on a test day is given a nicotine analogue and emits 8 "saline" responses then 10 "nicotine" responses, the test day is scored as "nicotine" or "nicotine-like." If that same rat is given a different analogue and presses exclusively on the nicotine lever, that too is scored as a "nicotine-like" response; however, the two test days are clearly different. Therefore, in addition to the absolute choice data, a relative response frequency measure should be used to elucidate the data. In addition, we are now using cumulative records to look at the temporal distribution of responses.

Four of eight rats tested with 0.6 mg/kg of (-)-nicotine had imcomplete tests; that is, one in which the rats did not complete a ratio run on either lever within the 5-minute period. We are now retesting these rats and will be administering blockers (mecamylamine and hexamethonium) to determine the role of peripheral vs. central receptor sites in the rats' debilitation.

Prostration Syndrome

The laboratory has been able to demonstrate the prostration syndrome reliably with both (-)-nicotine and (+)-nicotine, with the latter being about 1/10 to 1/20 as active. The increase in reliability of the data from this laboratory can be attributed to the refinement of techniques by Dr. Levy. Having gained a reliable data base with both (-)-nicotine and (+)-nicotine it is now essential to examine relative potency of the nicotine analogues, most importantly analogues that have shown to be nicotine-like in the discrimination tests.

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An interoffice correspondence (Oct. 8, 1979, from C. J. Levy, K. Young and L. Carron) described the results of a study that investigated the effect of mecamylamine hydrochloride (a nicotinic cholinergic antagonist) and hexamethonium chloride (a nicotinic cholinergic antagonist which penetrates the blood-brain barriers in only small amounts) on the prostration syndrome in rats. Briefly, pretreating the rats with mecamylamine hydrochloride reduced the severity of the response while pretreatment with hexamethonium chloride did not. This work should be replicated using the nicotine analogues. In addition, studies should be undertaken to locate sites of action and to determine the extent of the behavioral prostration. Even without detailed knowledge of the underlying physiological mechanisms, the use of behavioral measures will provide important information about the sites of action in the brain. We are currently undertaking a study that will examine the effects of nicotine and nicotine analogues injected into the lateral ventricles of rats that are engaged in scheduled controlled behavior. Operant techniques have been shown to be highly sensitive to physiological manipulation and the resulting behavioral change can be site specific.

In collaboration with Dr. Gullotta we will begin a series of electrophysiological recording studies to locate sites of action in the brain.

Nicotine Self-Administration

The development of self-administration procedures in our laboratory will add considerably to our testing facilities. Self-administration techniques not only demonstrate the reinforcing properties of a compound but can be used to investigate tolerance factors, discrimination between compounds, and can be used to evaluate the effects of agonists and antagonists on nicotine's behavioral actions.

The self-administration technique also provides a chronic data base from which many investigations can begin. We plan to explore both intravenous and intracerebral routes of administration.

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