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Nicotine Program

To: V. J. DeNoble

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Subject: Discrimination Studies

As part of the ongoing nicotine discrimination program, we have completed initial testing on a series of additional compounds. These compounds included various dialkylaminomethylpyridines, metanicotine, its dihydro derivative, and several isomeric nicotines. See Table I. All compounds were prepared and injected in the same manner as previously described in the memo to W. L. Dunn, from C. J. Levy and L. Carron, entitled Nicotine Discrimination Studies.

TABLE I

	Dose (mg/kg)	Total Number of Responses		
		Saline	Nicotine	Incomplete Test*
3-dimethylamino-methylpyridine	4.0	4	6	1
	8.0	0	4	3
2-dimethylamino-methylpyridine	4.0	14	0	0
4-dimethylamino-methylpyridine	4.0	8	0	0
	8.0	6	0	0
dihydrometanicotine	4.0	8	0	0
	8.0	9	0	0
metanicotine	4.0	3	4	0
	8.0	0	9	0
3,3'isonicotine	1.0	6	10	0
	2.0	2	9	0
2,3'isonicotine	2.0	8	0	0

*An incomplete test is one in which the rat does not complete 10 responses on either the saline correct or nicotine correct lever within 5 minutes.

Addition of the dimethylaminomethyl substituent to the pyridine ring in the 3 position produced "nicotine-like" responses from the animals whereas the isomeric 2- and 4- substituted compounds gave no indication of activity. The 3-pyridyl derivatives yielded "nicotine" responses in 55% of the animals at a 4.0 mg/kg dose. (This level represents 10x that of the training dose used in the nicotine discrimination task.) When the dose was increased to 8.0 mg/kg, 4 animals responded on the nicotine correct lever and 3 animals

gave incomplete tests. Presently, we are decreasing the dose of the 3-dimethylaminomethylpyridine to try to obtain a dose level at which the animals that responded with an incomplete result will give a nicotine response. It has been our experience in the past (memo to W. L. Dunn, from C. J. Levy and L. Carron, entitled Nicotine Discrimination Studies) that incomplete tests are indicative of a dose level that is debilitating to the rat.

Metanicotine, unlike its dihydro derivative, showed nicotinic activity in the animals tested. Apparently, the unsaturation in the side chain, in this compound, is necessary to produce activity, since metanicotine at a dose of 4.0 mg/kg produced nicotine cues in approximately half of the animals. When the dose was increased to 8.0 mg/kg, 100% of the animals responded on the nicotine correct lever.

Of the isonicotine derivatives, the 3,3'substituted N-methylpyrrolidine showed activity while the 2,3'isonicotine did not. At a dose only 5x that of the normal discrimination training dose of (-)-nicotine (2.0 mg/kg), the 3,3'isonicotine was active in 9 out of 11 animals. When the dose was reduced to 1.0 mg/kg, 63% of the animals tested responded with the nicotine correct lever. We are now testing the 3,3'isonicotine in conjunction with both the peripheral and central nicotinic blockers [hexamethonium HCl (1.0 mg/kg) and mecamylamine HCl (1.5 mg/kg)].

These blockers have been used in the past with the (-)-nicotine in the nicotine discrimination task. It is of importance to determine if the nicotine-discrimination animals will show the same differential response, when tested with the 3,3'isonicotine and the nicotine blockers.

It is interesting to note that with the 3-dimethylaminomethylpyridine, metanicotine, and 3,3'isonicotine a difference in performance was observed between two groups of our animals. These two groups were trained at different times and differed in age as well as body weight. Consistently, the older group of rats (approximately 2 years old) were able to discriminate active analogues at a dose about one-half that of the one used with the younger rats (approximately 1 year old). Yet both groups of animals were performing to criterion. The difference may be attributed to the fact that the older rats are more experienced with nicotine and have developed a better ability to generalize the specific cues associated with the nicotine and the nicotine analogues. Another less likely explanation is that in administering doses in mg/kg of body weight, the older heavier rats are receiving more nicotine. However, the relative brain size between the two groups is basically the same and, therefore, it is possible that the older rats are receiving more nicotine in the brain. If this difference in responding continues to occur, it would be important to investigate the potential differences in the amount of nicotine reaching the brain as a function of the amount of nicotine injected (mg/kg/body wt.).

jh

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