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PHILIP MORRIS U. S. A.

INTER-OFFICE CORRESPONDENCE

RICHMOND, VIRGINIA

To: . Dr. J. L. Charles

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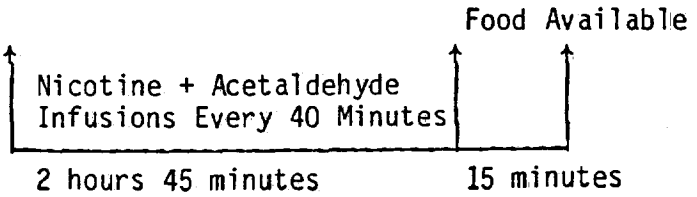
From: . V. J. DeNoble and P. C. Mele

Subject: . Behavioral Effects of Termination of Chronically Administered Nicotine- Acetaldehyde Combinations on Lever Pressing Maintained Under a Fixed Ratio Schedule of Food Presentation in Rats

A considerable amount of effort has been directed towards developing a behavioral profile of nicotine and acetaldehyde. Some major findings can be summarized as follows: 1) Both nicotine and acetaldehyde function as positive reinforcers for rats; 2) combinations of nicotine and acetaldehyde produce supraadditive effects when self-administered; 3) termination of chronically administered nicotine or acetaldehyde does not result in a physiological dependence.

The purpose of the present investigation was to extend the above findings by determining if termination of chronically administered combinations of nicotine and acetaldehyde results in a physiological dependence syndrome. Chronic administration of a variety of psychoactive agents results in physical (physiological) dependence. Physical dependence is generally characterized by abstinence signs when drug intake is abruptly terminated or when an antagonist is administered and behaviors maintained under several schedules of reinforcement have been shown to be sensitive to these effects.

Two rats were trained to lever press under a fixed ratio 22 (FR 22) schedule for a single delivery of a 45 mg food pellet. When response rates were stable (no increasing or decreasing trends in the number of responses/ second) the animals were surgically prepared with an indweling venous catheter. Following a 7 day recovery period the rats were placed in operant chambers in which sessions lasted 24 hours. Nicotine and acetaldehyde were infused intravenously every 40 minutes. Food was available under and FR 22 schedule for 15 minutes every 2 hours and 45 minutes (see below).



Food availability was signalled by a 1.0 second tone followed by the illumination of two lights above the response lever. At the end of the 15 minute food access period the lever lights were extinguished and the house light was illuminated for 2 hours and 45 minutes. This sequence was repeated 8 times each day. This procedure allows multiple samples of behavior to be collected within a 24 hour period and has been previously shown to be sensitive to drug withdrawal.

The results are summarized in Table 1. Analysis of the pattern of food delivery over the 24 hour sessions, (the eight, 15 minute food access periods) did not show any systematic changes between food access periods, therefore, we have combined the data within 24 hour periods for both rats.

Table 1

Mean food responses, total responses and food deliveries are shown as a function of saline or nicotine-acetaldehyde dosing conditions.

Dosing Condition (μg/kg/infusion)	Number of Days	Total Daily Dose (mg/kg) Nicotine-Acetaldehyde	Food Responses in 24 Hours	Total Responses in 24 Hours	Food Deliveries in 24 Hours
Saline	5	0	10,103 ± 445	10,155 ± 463	459 ± 20
Nicotine + 64 Acetaldehyde 32	6	2.30 1.15	8,735 ± 820	9,482 ± 370	397 ± 14
Nicotine + 64 Acetaldehyde 128	2	2.3 4.6	8,518 ± 582	9,422 ± 501	387 ± 33
Nicotine + 64 Acetaldehyde 256	6	2.3 9.2	9,170 ± 844	10,045 ± 407	416 ± 25
Nicotine + 64 Acetaldehyde 1024	5	2.3 36.9	9,681 ± 333	9,699 ± 335	440 ± 13
Saline	7	0	8,449 ± 387	8,469 ± 421	384 ± 17
Nicotine + 64 Acetaldehyde 2048	16	2.3 73.7	8,417 ± 332	8,610 ± 297	382 ± 21
Nicotine + 64 Acetaldehyde 4096	10	2.3 147.9	8,853 ± 520	9,101 ± 480	402 ± 19
Saline	5	0	9,001 ± 396	9,201 ± 399	409 ± 16

± SEM

The left column in Table 1 shows the dosing regimen beginning with the saline condition. After five days of saline infusions nicotine acetaldehyde combinations were infused every 40 minutes. The nicotine dose was held constant at 64 μg/kg/infusion throughout the experiment. During the initial exposure period the acetaldehyde dose increased from 32 μg/kg/infusion to 1024 μg/infusion. There were no consistent changes in either the number of lever presses or food intake throughout this period (Table 1). Subsequent saline substitution also failed to alter the lever pressing behavior. Following saline substitution the acetaldehyde dose was increased to 2048 μg/infusion

for 16 days, immediately followed by an acetaldehyde dose of 4096 µg/infusion for 10 days. Finally a second saline substitution did not result in any changes in the food maintained lever pressing.

The failure to find any disruption in food reinforced lever pressing when chronic nicotine-acetaldehyde administration was terminated across several doses and across several dosing schedules is strong evidence that chronic exposure to the combination of compounds does not result in a physiological dependence.

VD/PM/mps

cc: Dr. T. S. Osdene