

inside the terminal, probably activates presynaptic dopamine autoreceptors, reducing stimulus-induced DA release.

LITERATURE CITED

1. E. V. Volina, "Reverse trans-synaptic regulation of catecholamine synthesis and uptake," Author's Abstract of Candidate's Dissertation, Moscow (1977).
2. O. V. Godukhin and A. D. Zharikova, *Fiziol. Zh. SSSR*, No. 1, 141 (1979).
3. S. M. Antelman, D. J. Edwards, and M. Lin, *Brain Res.*, 127, 317 (1977).
4. G. B. Baker, M. Raiteri, A. Bertollini, et al., *J. Pharm. Pharmacol.*, 28, 456 (1976).
5. F. Cerrito, G. Casazza, G. Levi, et al., *Neurochem. Res.*, 5, 115 (1980).
6. D. J. Diamond and R. L. Borison, *Pharmacology*, 17, 210 (1978).
7. D. A. Durden, S. R. Phillips, and A. A. Boulton, *Can. J. Biochem.*, 51, 995 (1973).
8. K. Fuxe, H. Brobecker, and J. Jonsson, *Eur. J. Pharmacol.*, 2, 202 (1967).
9. M. F. Giorgiueff, M. L. Le Floch, J. Glowinski, et al., *Brain Res.*, 106, 117 (1976).
10. J. C. Miller and A. J. Friedhoff, *Biochem. Pharmacol.*, 28, 688 (1979).
11. T. Nakajima, Y. Kakimoto, and I. Sano, *J. Pharmacol. Exp. Ther.*, 143, 319 (1964).
12. A. Nieoullon, A. Cheramy, and J. Glowinski, *J. Neurochem.*, 28, 819 (1977).
13. M. Raiteri, F. Cerrito, A. M. Cervoni, et al., *J. Pharmacol. Exp. Ther.*, 208, 195 (1979).
14. S. B. Ross and A. L. Renyi, *Acta Pharmacol.*, 24, 297 (1966).
15. H. C. Sabelli, R. L. Borison, B. I. Diamond, et al., in: *Noncatecholic Phenylethylamines. Part I. Phenylethylamine: Biological Mechanisms and Clinical Aspects*, New York (1978), p. 345.

FORMATION OF ADDICTION TO NICOTINE IN NONINBRED ALBINO RATS

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KEY WORDS: nicotine; addiction; rats.

Tobacco smoking is currently the most widespread type of toxicomania, which is based on the pharmacologic effects of nicotine [3-6].

The search for drugs for the treatment of tobacco smoking, which has not yet proved very effective, is made more difficult by the absence of a pathogenetically based experimental model of this toxicomania. The aim of the present investigation was accordingly to study the possibility of formation of addiction to nicotine in laboratory rats and to create an experimental model of nicotine toxicomania on this basis.

EXPERIMENTAL METHOD

The formation of addiction to nicotine was studied on 56 male rats weighing 190 to 210 g. The rats were kept in individual cages measuring 40 × 12 × 15 cm, equipped with a feeding bowl (food was provided *ad lib.*) and with two graduated vessels containing water and 0.005% nicotine solution for a period which ranged from 2 months (26 rats) to 4 months (30 rats). The quantity of water and of nicotine solution drunk per day by each rat was recorded and preference of each animal for a particular liquid was calculated. The results were subjected to statistical analysis with calculation of the significance of differences between fractions [1].

EXPERIMENTAL RESULTS

Rats kept in individual cages with choice allowed between water and 0.005% nicotine solution could be divided after the first day into three groups on the basis of preference for one or other fluid (Table 1).

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TABLE 1. Distribution of Rats by Preference for Water and 0.005% Nicotine Solution

Duration of experiment	Number of rats, per cent		
	preferring water	preferring nicotine solution	with no preference for either fluid
1 day	64	32	4
1 week	35,5	46	18,5
2 weeks	52	44	4
3 "	47	35	18
4 "	65	35	—
5 "	70	26	4
6 "	69	27	4
7 "	68	28	4
8 "	68	28	4

TABLE 2. Quantity of Nicotine Consumed by Rats Per Day (in mg/kg)

Quantity of nicotine consumed	Duration of experiment, weeks								Daily average ($\bar{M} \pm m$)
	1	2	3	4	5	6	7	8	
Small	1,8	1,42	1,2728	1,27	0,92	0,9827	0,92	1,47	1,226 \pm 0,1
Large	1,447	1,266	1,7578	1,522857	1,99	2,169	1,987	2,169	1,788 \pm 0,1

TABLE 3. Quantity of 0.02% Cocaine Solution Consumed Daily by Rats (in ml/kg)

Group of animals	Time of experiment, weeks					
	9 weeks			16 weeks		
	1-st	2-nd	3-rd	1-st	2-nd	3-rd
Rats consuming small quantity of nicotine	7,3	6,5	5,6	34,6	45,6	46
Rats consuming large quantity of nicotine	54,1	57,6	76,7	—	—	—

After one day 32% of the animals preferred nicotine solution, 64% preferred water, and 4% had no preference for either fluid.

The number of rats preferring nicotine solution remained unchanged until the 5th week, when it fell to 26% ($P < 0.05$) and it remained at that level until the end of the experiment. The number of rats preferring water did not change significantly and remained basically stable throughout the eight weeks of contact with nicotine solution. The group of animals with no preference for either fluid was most variable: During the first 4 weeks marked fluctuations were observed in this parameter, basically with an increase in the number of rats preferring water. Starting from the 4th week of the experiment the number of animals in this group stabilized.

The results are evidence that among a population of laboratory albino rats there are individuals inclined *ab initio* to consume nicotine.

Further experiments were carried out in order to determine whether animals consuming nicotine may develop physical dependence, having regard to clinical and experimental data [2] showing that persons with established toxicomania, during a period of withdrawal of the primary substance, attempt to replace it by other pharmacologic agents which induced toxicomania. For this purpose the nicotine solution in the graduated vessels was replaced by a 0.02% solution of cocaine. The substitution was carried out in the 9th week for a period of 3 days. It was observed that rats which consumed larger quantities of nicotine solution switched immediately when it was withheld to consuming cocaine solution.

In rats which consumed small quantities of nicotine no switching to consumption of cocaine solution took place during this period. Switching of the animals of group 2 of this kind took place only after 4 months of consumption of nicotine solution (Tables 2 and 3).

Switching of the rats to drinking cocaine solution on withdrawal of the nicotine solution from them is evidence mainly that prolonged consumption of nicotine leads to the development of physical dependence, as takes place during consumption of other substances inducing toxicomania: The times of development of dependence were connected with the quantity of nicotine consumed daily. In the present experiments, in rats consuming a mean dose of 1.788 mg/kg nicotine daily, dependence developed after 8 weeks, whereas in rats with a daily consumption of nicotine of 1.226 mg/kg it developed after 16 weeks.

These data thus indicate that animals may in principle develop nicotine toxicomania by voluntary consumption of nicotine. Animals consuming nicotine can be used as an experimental model for the study of the pathogenetic mechanisms of development of nicotine toxicomania and preclinical evaluation of the effectiveness of new chemical compounds for use in the treatment of addiction to tobacco smoking.

LITERATURE CITED

1. N. A. Plokhinskii, Biometrics [in Russian], Moscow (1970).
2. I. N. Pyatnitskaya, Clinical Narcology [in Russian], Leningrad (1975).
3. M. A. H. Russell, in: Research Advances in Alcohol and Drug Problems, Vol. 3, New York (1976), pp. 1-49.
4. M. A. H. Russell, C. Wilson, C. Feyerabend, et al., Br. Med. J., 2, 391 (1976).
5. M. A. H. Russell, S. R. Sutton, C. Feyerabend, et al., Br. Med. J., 1, 1060 (1977).
6. M. Raw, in: Research Advances in Alcohol and Drug Problems, Vol. 4, New York (1978), pp. 441-485.

β -ENDORPHIN AND ENDOGENOUS ETHANOL BLOOD LEVELS IN PATIENTS WITH ALCOHOLISM

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A series of model experiments on rats has shown that animals predisposed to the development of ethanol dependence possess a number of particular behavioral, neurochemical, and biochemical features [1-3]. However, it is not yet clear which of these characteristics are of predominant importance in the formation of alcoholism. Since studies on animals have revealed the possible role of endogenous ethanol (EE) and of some neuropeptides in the development of experimental alcoholism [3, 5], it is of considerable interest to study these parameters in patients with chronic alcoholism.

The aim of this investigation was to study EE and β -endorphin (β -E) levels and their possible pathogenetic role in patients with chronic alcoholism.

EXPERIMENTAL METHOD

Altogether 58 men aged 25-42 years with stage II of chronic alcoholism were studied; their alcohol tolerance was high, and had remained constant during the last 3-6 years before the investigation. By depth and structure of the borderline psychopathological disorders which were observed in the patients outside the period of abstinence, the patients were divid-

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