chronotropic effect. However, the sensitivity to bradykinin varied considerably since 15 out of 45 hearts remained unaffected up to a concentration of 10^{-6} M; these hearts are not included in the statistical evaluation of the figure. In 'sensitive' hearts, the maximum decrease in rate obtained upon the infusion of bradykinin (3×10^{-7} M) was reached within about 3 min and amounted to 21 $\pm$ 6% (N = 4); any further increase of the dose did not result in a stronger response. Moreover, pronounced tachyphylaxis was observed; soon after the maximum decrease, heart rate returned to normal. When the infusion was discontinued, this refractory state was reversible; about 15 min later, the negative chronotropic effect could be reproduced by a second infusion of the same dose.

The right-hand columns of the figure show that pretreatment with atropine completely antagonized the retardation induced by bradykinin and frequently even reversed it into a slight but significant acceleration; the latter was also subject to a distinct tachyphylaxis, but was not further analysed. The negative chronotropic effect of bradykinin was equally suppressed by 10^{-9} M (not shown) or 10^{-8} M tetrodotoxin. On the other hand, it remained unchanged in the presence of hexamethonium (10^{-5} M); this concentration of hexamethonium reduced the bradycardic effect of 10^{-4} M nicotine by about 90% (N = 3; not shown).

10^{-4} M nicotine transiently decreased the heart rate by 25 $\pm$ 3% (N = 4). In some experiments, 3×10^{-7} M bradykinin was added during continuous infusion of nicotine (10^{-4} M) both immediately after complete development of nicotine tachyphylaxis and 30 min later. In either case, the effect of bradykinin was abolished (N = 4; not shown).

Discussion. It has previously been shown that 10^{-7} M bradykinin lowers the heart rate of the isolated rabbit heart[7]. The present results show that the effect is concentration-dependent. Moreover, several findings suggest that it is mediated through the parasympathetic innervation of the heart. 1. The bradykinin-induced decrease was prevented by atropine, thus demonstrating an involvement of muscarine receptors. 2. It was also abolished by tetrodotoxin, which blocks the propagation of nerve action potentials by interfering with the rapid sodium inward current[8]. This makes excitation by bradykinin of a proximal (ganglionic or preganglionic) site most likely, from whence impulses are carried down to the postganglionic parasympathetic nerve endings. On the other hand, a tetrodotoxin-sensitive direct depolarization of the postganglionic nerve endings cannot be entirely ruled out (cf. the interaction of tetrodotoxin and nicotine on postganglionic sympathetic axon terminals[9]). 3. The effect of bradykinin was not changed by hexamethonium. This observation excludes the possibility that the decrease in heart rate was due to stimulation of preganglionic vagal fibres, and confines possible sites of action to the ganglion cells. Moreover, the lack of antagonism by hexamethonium indicates that the ganglionic receptors are distinct from nicotine receptors. 4. In sympathetic ganglia, the effect of non-nicotinic stimulants such as angiotensin is abolished during the early, depolarizing phase of the block produced by nicotine; during the late, non-depolarizing phase, the effect is facilitated[5]. Only block, but no subsequent facilitation was observed in the present experiments. It should be noted, however, that even in sympathetic ganglia the effect of bradykinin differs from that of other non-nicotinic stimulants in that it recovers only to a very small extent after prolonged exposure to nicotine[5].

In conclusion, our results are consistent with the view that bradykinin excites not only sympathetic, but also some parasympathetic ganglion cells. In the rabbit isolated heart, only $^2/_3$ of all preparations tested were found to be responsive. As in sympathetic ganglia, the effect can be classified as non-nicotine-like.

8 C. Y. Kao, Pharmac. Rev. *18*, 997 (1966).
9 K. Starke, Rev. Physiol. Biochem. Pharmac. *77*, 1 (1977).

Efficacy of ethanol as a discriminative stimulus in ethanol-preferring and ethanol-nonpreferring rats

J. L. York[1]

New York State Department of Mental Hygiene, Research Institute on Alcoholism, 1021 Main Street, Buffalo (New York 14203, USA), 17 May 1977

Summary. Rats which exhibited a preference for drinking a 6% w/v solution of ethanol in a free choice situation did not differ in their sensitivity to ethanol from animals exhibiting an aversion for ethanol, as measured by learning rates in a T-maze task in which ethanol served as a discriminative stimulus.

Under some circumstances, the consumption of alcoholic beverages in man may be partially determined by inherited characteristics[2–5]. Alcohol drinking behavior in some strains of laboratory mice and rats has also been reported to be an inherited characteristic[6–9]. Studies on such strains may yield valuable information concerning the inherited characteristics which predispose some individuals to the excessive consumption of beverages containing ethyl alcohol. It has been reported, for example, that animals that prefer ethanol are less sensitive to the hypnotic and depressant effects of ethanol than are ethanol-nonpreferring animals[10–14]. Whether such differences in sensitivity to the effects of ethanol play a role in the self-selection of solutions of ethanol remains a major, unanswered question. However, implicit in such an inquiry, is the premise that conscious animals n a free choice situation are capable of gaining information concerning the effects of injested ethanol and may titrate drinking behavior accordingly. Drug discrimination procedures have proved to be useful for determining the extent to which animals are aware of the effects produced by specific drugs[15]. The present study employed a drug discrimination task to determine if ethanol-preferring rats differ from ethanol-nonpreferring rats with respect to the magnitude of the internal stimulus produced by a moderate dose of ethanol.

Subjects and methods. 105 female, Wistar rats (Woodlyn Laboratories, Guelph, Ontario, Canada) about 4 months of age and approximately the same weight were housed individually in transparent plastic cages (18″ l × 8″ w × 9″

h) with beddings of wood shavings. Each cage was provided with 2 bottles of drinking fluid, one containing tap water, and the other containing a 6% w/v solution of ethanol. Food pellets were available ad libitum. The consumption of fluid from each bottle was determined at weekly intervals and the position of the bottles was then switched to control for position preferences. At the end of 4 weeks, 2 experimental groups were formed: an 'ethanol-preferring' group (n = 10) which had derived 57–67% of its total fluid requirements from the bottle containing 6% ethanol, and an 'ethanol-nonpreferring' group (n = 10) which derived only 18–22% of its total fluid requirements from the bottle containing ethanol (figure 1).

To determine if the 2 groups differed in their sensitivity to the effects of ethanol, the animals were tested for the rate at which they learned a drug descrimination based upon the internal effects of ethanol (780 mg/kg, i.p. in 10% solution, 20 min latency) versus saline, the underying premise being that any difference in learning rates could be attributed to a difference in the internal cue produced by ethanol in the 2 groups of rats. The dose of ethanol employed was expected to be only moderately descriminable from saline[16] and, thus, was expected to allow for the detection of differences in the discriminative capacities

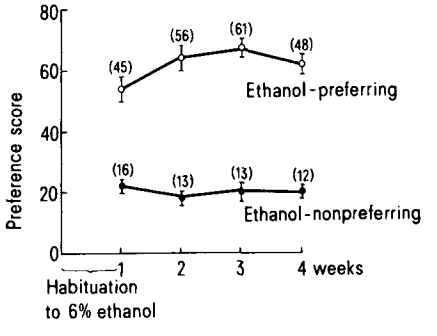

Fig. 1. Consumption of ethanol by ethanol-preferring rats and ethanol-nonpreferring rats. For the 1st week the rats were given only 6% w/v ethanol to drink. Thereafter, they were given a free choice between 6% w/v ethanol and tap water. The preference score (ordinate) refers to the amount of 6% ethanol consumed expressed as a percent of the total fluid consumed from both bottles. Determinations were made at weekly intervals. Brackets indicate SE (n = 10). For reference, the mean intake of ethanol in g/kg/week is indicated in parentheses.

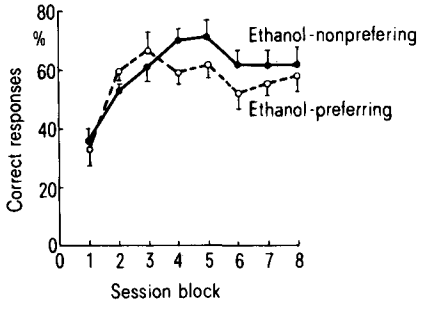

Fig. 2. Learning curves for ethanol-preferring and ethanol-nonpreferring rats. Animals were required to discriminate in a T-maze the internal effects produced by physiological saline and ethanol (780 mg/kg). See text for details. Each session block consists of 10 consecutive trials (days). The number of correct responses for the 10-day period was first determined in individual rats. The mean for the group of 10 rats was then calculated and plotted. Brackets indicate SE.

of rats. Training was initiated 16 weeks after the preference test had been conducted. The task required the animals to enter the safe goal compartment (left or right) in a T-maze under the ethanol condition or under saline. Access to the safe compartment was through a top-hinged door in either the left or right compartment of the maze. For half of the rats in each group the right door was unlatched under the ethanol condition and the left door was unlatched under the saline condition. The conditions were reversed for the remaining half of the rats in each group to balance for position preferences. A 0.4 ma scrambled current applied to the metal grid floor of the T-maze served as the motivating stimulus. Training of the drug discrimination was accomplished by alternating the drug condition and the corresponding safe goal compartment from day to day. 10 training trials were administered daily over a 10 min period. As the criterion for learning the drug discrimination, the rat was required to choose the correct box on the 1st trial on 8 of any 10 consecutive sessions (days).

Results and discussion. The data in figure 2 indicate that the rate of acquisition of the drug discrimination was similar in ethanol-preferring and ethanol-nonpreferring rats. In keeping with that interpretation, the mean number of trials (± SE) required to reach the criterion level of performance, i.e. 8 correct 1st trial responses on any 10 consecutive days, did not differ significantly between ethanol-preferring rats (29 ± 8) and ethanol-nonpreferring rats (25 ± 2). Furthermore, the mean number of correct responses over the 89-day duration of the experiment was similar in ethanol-preferring rats (50 ± 2) and ethanol-nonpreferring rats (54 ± 2).

These results are not in harmony with the hypothesis that ethanol-preferring animals differ from ethanol-nonpreferring animals in terms of their sensitivity to the effects of ethanol. Nor do these findings support the notion that drinking behavior in rats selected from a normal population is causally related to the magnitude of the drug experience drived from the effects of ethanol. Further studies will be required to determine the task, dose, and species dependency of this phenomenon. A similar experiment performed with strains of rats or mice selectively bred for their ethanol preference would be of interest.

1 The author is thankful to Miss Christine Currey for technical assistance.

2 C. Amark, Acta psychiat. neurol. scand. *70*, 1 (1951).
3 D. Goodwin, F. Schlusinger, L. Hermansen, S. B. Guze and G. Winokur, Arch. gen. Psychiat. *28*, 238 (1973).
4 L. Kaij, Alcoholism in Twins. Almqvist and Wiksell, Stockholm 1960.
5 J. Partanen, K. Bruun and T. Markkanen, Finn. Found. Alc. Stud. *14*, 159 (1966).
6 K. Eriksson, Science *159*, 739 (1968).
7 K. Eriksson, Ann. Zool. Fennici. *8*, 400 (1971).
8 J. Mardonnes, N. Segovia and A. Hederra, Q. J. Stud. Alcohol *14*, 1 (1953).
9 G. E. McClearn and D. A. Rodgers, Q. J. Stud. Alcohol *20*, 691 (1959).
10 R. Kakihana, D. Brown, G. McClearn and I. Tabershaw, Science *154*, 1574 (1966).
11 P. Nikander and L. Pekkanen, Psychopharmacology *51*, 219 (1977).
12 C. Randall and D. Lester, J. Pharmac. exp. Ther. *188*, 27 (1974).
13 M. Russi and K. Eriksson, Presented at the 3rd Biennal Symposium on Biomedical Research, Lausanne, Switzerland, 7–11 June 1976.
14 C. Schneider, P. Trzil and R. D'Andrea, Pharmac. Biochem. Behav. *2*, 549 (1974).
15 H. Barry, III, Fedn Proc. *33*, 1814 (1974).
16 D. Overton, in: The Biology of Alcoholism, vol. II. Ed. B. Kissin and H. Begleiter. Plenum Press, New York 1972.