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Metabolic tolerance as related to initial rates of ethanol metabolism

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It is well known that the rate of ethanol metabolism varies markedly in individuals of the same species [1, 2]. However, the within-group interindividual variance becomes less marked when one studies the rate of ethanol metabolism in inbred lines of experimental animals and in humans of the same ethnic group. American Indians and Orientals appear to have higher rates of ethanol metabolism than Caucasians [3]. It is also known that chronic ethanol consumption leads to metabolic tolerance in humans and experimental animals [4, 5], and the question arises whether tolerance develops to the same extent in individuals with different initial rates of ethanol metabolism.

We have examined this aspect in two rat lines inbred for their different central nervous system sensitivities to the motor-impairing effects of ethanol [6]. The MA (most affected) line is more sensitive than the LA (least affected) line. Apart from their different CNS sensitivities to ethanol, we have also found a sex/line difference in their initial ethanol metabolic rates (EMR), viz. the MA males had a 40–45% lower EMR compared to the other three groups of animals. Therefore, these animals offered a model to investigate the problem of extent of metabolic tolerance.

MA and LA rats used for this study were 60-day-old (at the start of experiment) offspring of the twenty-second generation. The origin stock (generation 19) was kindly provided by Dr. D. Lester of the Center of Alcohol Studies, Rutgers University, and then maintained by inbreeding in our own animal quarters. Animals for this experiment were housed individually and allowed continuous *ad lib.* access to standard rat chow and tap water. Food and water were withheld on days of measurement of EMR.

The ethanol metabolic rates for all four groups were determined before and after chronic ethanol treatment, following the i.p. injection of a test dose of ethanol [2.5 g/kg as a 12.5% (w/v) solution]. Samples of capillary blood (0.05 ml) from the cut tip of the tail of each animal were taken every hour for 7–8 hr after ethanol injection. Each sample was deproteinized, and ethanol was measured by the enzymatic method as described previously [7]. The disappearance rates of blood ethanol were calculated from the slope of the linear descending portion of each curve, and the rates of ethanol metabolism in mg per kg per hr were calculated as described previously [8]. Chronic ethanol treatment consisted of single daily ethanol (5 g/kg) intubations for up to 6 weeks for the males and 4 weeks for the females.

The initial body weights for the males were MA = 257 ± 10 and LA = 268 ± 9 g; for the females MA = 170 ± 4 and LA = 176 ± 4 g. Although body weights of males and females were different, no line difference was observed. While initial EMR values for the MA and LA females as well as LA males were similar, the MA males had a significantly lower EMR (40–45%). Following chronic ethanol treatment, all four groups showed significant increases in EMR, but the sex/line difference had disappeared (Table 1). As shown in Fig. 1, the increase in ethanol metabolism in the male LA animals occurred progressively over the first 3 weeks. On the other hand, a sharp increase in EMR occurred between 1 and 2 weeks of ethanol treatment in the male MA animals. While the same maximum value of ethanol metabolism was reached in both lines, after 6 weeks of chronic ethanol treatment, the temporal differences in the activation of ethanol metabolism in the two strains may represent two different mechanisms of metabolic tolerance.

The results indicate that the extent of metabolic tolerance is markedly dependent on the initial rates of metabolism which, in these rates lines, appear to be sex/line dependent. It is of interest to note that, despite differences in the initial (naive) rates of ethanol metabolism, the rates of metabolism after chronic ethanol treatment were virtually identical in all groups.

In another line of rats, a similar situation is seen when comparing males and females. Adult males of the spontaneously hypertensive line, which metabolize ethanol at

Table 1. Rates of ethanol metabolism in MA and LA rats before and after chronic ethanol treatment*

	Initial EMR ($mg \cdot kg^{-1} \cdot hr^{-1}$)	Final EMR ($mg \cdot kg^{-1} \cdot hr^{-1}$)	Increase (%)
Females			
LA	399 ± 21	473 ± 7	20
MA	388 ± 21	465 ± 7	20
Males			
LA	361 ± 15	455 ± 13	26
MA	244 ± 16	462 ± 5	89

* Values are means ± S.E.M.; N = six to ten animals per group.

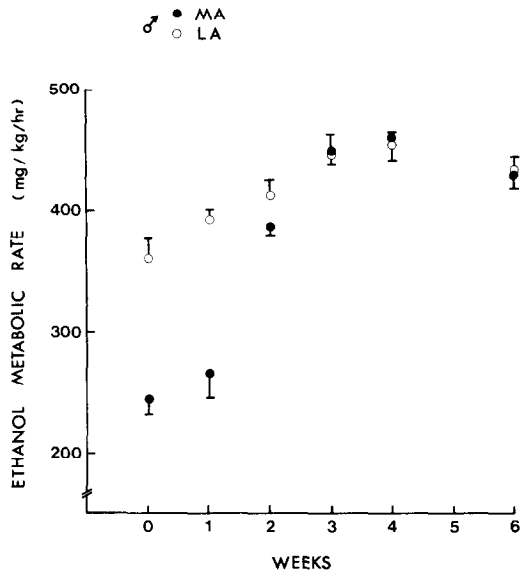

Fig. 1. Ethanol metabolic rates for MA and LA male rats determined during the course of chronic ethanol treatment. Each point represents mean ± S.E.M.; N = six to eight animals per group.

low rates, show a marked metabolic tolerance (80–100%) of the order of that reported here for MA animals [9]. However, females of the same line have high initial EMR values and show only a modest increase (30–40%) as also reported here for the LA and MA females [10].

In the spontaneously hypertensive male rats [9] and in the male Sprague–Dawley [11, 12] rates of ethanol metabolism in mature naive animals are associated with a low alcohol dehydrogenase (ADH) activity, an enzyme that, in these lines, is repressed by testosterone. It has been shown that chronic alcohol consumption leads to a reduction in testosterone levels with an associated increase in ADH activity and in the rate of ethanol metabolism. A low ADH activity has also been shown in MA males as compared to MA females by Lester *et al.* [13]. Thus, it is conceivable that the mechanism leading to a greater relative metabolic tolerance in the males of the MA line following chronic ethanol consumption may also be sex hormone dependent.

The findings reported may explain the marked differences in metabolic tolerance following chronic ethanol consumption reported by many investigators both in experimental animals and humans.

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Effects of morphine on norepinephrine turnover in various functional regions of rat spinal cord

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The locus coeruleus (LC), the A5 pontine nucleus and the A1/A2 catecholaminergic nuclei provide the major noradrenergic innervation to the ventral horn, the zona intermedia, and the dorsal horn, respectively, of the spinal cord [1–4]. Recently, a number of reports have implicated spinal norepinephrine (NE) in the antinociceptive effects of morphine administered either systemically [5, 6] or into discrete brain nuclei [7]. Moreoever, NE, when administered intrathecally to the spinal cord, causes analgesia [8, 9]. On the basis of the above neuroanatomical and pharmacological considerations, one would predict that the most likely site for the interaction of morphine with spinal noradrenergic transmission would be the dorsal horn. We now report, on the basis of a detailed investigation, that