4-METHYLPYRAZOLE INJECTION INTO THE PVTA IS ABLE TO PREVENT ETHANOL SELF-ADMINISTRATION BEHAVIOR IN RATS

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Introduction: The oxidative metabolism of ethanol into acetaldehyde involves several enzymes, including alcohol dehydrogenase (ADH) and catalase-H_2O_2. 4-methylpyrazole (4-MP) is renowned for the ADH inhibition, but little is known on its ability to interfere with fatty acid oxidation-mediated generation of H_2O_2in the liver, that may indirectly affect catalase whose enzymatic activity requires H_2O_2.

Aim: The aim of this investigation was to evaluate the effect of 4-MP after systemic or intra-p-VTA administration on ethanol self-administration in rats. We also extended our investigation to the effects of 4-MP on oral acetaldehyde and saccharin self-administration. Finally, additional experiments were carried out, to evaluate ex-vivo, the consequences of systemic 4-MP treatment on liver and brain catalase activity and on the levels of H_2O_2.

Materials and methods: Male Wistar rats were housed in Plexiglas cages with tap water and food available ad libitum. For the behavioral experiments rats (n= 50) were divided in 3groups, for ethanol, acetaldehyde and saccharin self administration, respectively. For the experiments on the maintenance phase and on the ethanol deprivation effect upon intra-p-VTA-administration of 4-MP, we tested the same rats under a random treatment order. The systemic doses of 4-MP were administrated 24h before self-administration experiments or before determination of brain catalase activity. Intra-p-VTA-administration of 4-MP took place immediately before the self-administration session. RESULTS: Experiments showed that the systemic, subchronic administration of a low dose of 4-MP compromised the maintenance of oral ethanol self-administration without interfering with that of oral acetaldehyde and saccharin, confirming the specificity of its action on this operant behavior related to ethanol. When the subchronic administration of 4-MP was discontinued, animals quickly resumed their previous phase of ethanol self-administration. Similar results in the maintenance phase were observed after acute systemic administration of higher doses of 4-MP. More, the effect of systemic 4-MP on the ethanol deprivation effect was also evaluated and obtaining that sub-chronic treatment with the low dose of 4-MP reduced this phase. Results of this study also revealed that the acute, bilateral application of 4-MP into the pVTA, immediately prior to allowing for operant behavior, was able to prevent ethanol but not saccharin self-administration, corroborating the idea about the specificity of the possible additional mechanism of action of 4-MP. In the ex-vivo experiment the results showed a reducing H_2O_2availability in the liver and brain following 4-MP systemic administration, 4-MP treatment could indirectly interfere with the formation of "compound I", necessary for catalase-mediated oxidation of ethanol into acetaldehyde. Nevertheless, 4-MP, by blocking ADH in the periphery, could result on one hand in less acetaldehyde reaching the brain, whereas, on the other hand, it could result in a greater availability of ethanol reaching the brain and exerting its effects.

Conclusions: Overall, these results indicate that 4-MP interferes with ethanol self-administration and suggest that its behavioral effects could be due to a decline in catalase- H_2O_2system activity as a result of a reduction of H_2O_2availability, thus highlighting the role of central catalase-mediated metabolism of ethanol and further supporting the key role of acetaldehyde in the reinforcing properties of ethanol.