Marchigian Sardinian alcohol-preferring (msP) and Wistar rats exhibit dynorphin system gene expression differences in response to voluntary ethanol intake in the Extended Amygdala

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The alcohol-preferring animal represent a suitable research models strategy to investigate genetic predisposition to high ethanol (EtOH) drinking. The marchigian sardinian alcohol-preferring (msP) rats are genetically selected to show a voluntary preference for alcohol, a spontaneous binge-type of drinking and a vulnerability to relapse. They exhibit differences in the gene expression of specific brain circuitries that may be crucial in shaping the vulnerability to alcoholism (1). Among multiple physiological systems involved in alcohol consumption, the endogenous opioids represent an important neurobiological player in EtOH intake and dependence (2). In particular, the dynorphin (DYN) system influences several aspects of alcohol response causing aversive dysphoric-like effects in animals and humans, and it has been hypothesized to mediate negative emotional states (3). Behavioral characterization of msP rats indicates that they are highly sensitive to stress and display anxious and depressive phenotype (4). Among the circuitries involved in the regulation of stress-induced drug-seeking behavior, recent evidence agree in identifying the extended amygdala as the site where addiction and stress interact sharing common neuronal pathways. This circuit comprises the bed nucleus of the stria terminalis (BNST), the central nucleus of the amygdala (AM) and the shell of the nucleus accumbens (5).
In this study we aimed to evaluate innate and EtOH-induced differences of DYN system gene expression in the AM and BNST of Wistar and msP rats. Animals (n=6/group) were exposed to chronic intermittent 10% alcohol (v/v) in a two-bottle choice (TBC) paradigm; after 30 days, rats were sacrificed, then AM and BNST were rapidly harvested and frozen.
Real-time qPCR analysis showed similar basal levels of prodynorphin (pDYN) gene expression in the AM and BNST of Wistar and msP rats. EtOH intake caused a down-regulation of pDYN mRNA level (0.45±0.09*vs.*msP vehicle 0.95±0.11, $p<0.05$; two-way ANOVA, Bonferroni's*post-hoc*test) in the AM of msP rats only, whereas no changes were observed in the BNST of both strains. A higher basal KOP gene expression was detected in the msP than in Wistar rats AM (1.26±0.05*vs.*1.00±0.10, $p<0.05$); the EtOH intake caused a KOP down-regulation in the msP AM (0.65±0.04*vs.*msP vehicle 1.26±0.05, $p<0.001$) and an up-regulation in the msP BNST (1.41±0.09*vs.*msP vehicle 0.88±0.04, $p<0.001$).
These findings suggest that in the extended amygdala, EtOH effect is totally dependent on the genotype, since no alterations were observed in the Wistar rats following alcohol intake.
Moreover, the pDYN/KOP system down-regulation observed in the AM of msP rats could be related to an attempt to self-medicate from negative emotional state. In this context, the higher KOP basal level in the msP rats match with the lower preference and alcohol consumption exhibited by KOP knock-out mice in TBC paradigm (6). On the other hand, data from BNST showed an up-regulation of KOP mRNA level following EtOH intake thus suggesting a differential regulation of pDYN/KOP system within the extended amygdala of msP rats.

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