N/OFQ and CRF systems dysregulation in Marchigian Sardinian (msP) rats underlies their innate sensitivity to stress and alcohol preference

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Drugs of abuse produce powerful emotions such as a pronounced euphoria or a series of negative emotional states that create a break in the homeostasis and an “allostatic hedonic state” which represents the key to the etiology and maintenance of the pathophysiology of addiction (Koob, 2015). It has been largely debated the hypothesis that the brain has specific neurochemical circuitry implied in the hedonic extremes of pleasant and unpleasant emotions. In this context, through the study of opponent systems it has been demonstrated that the nociceptin/orphanin FQ (N/OFQ) system attenuates stress-like responses (Martin-Fardon et al., 2010), whereas the corticotropin-releasing factor (CRF) is recruited in the aversive and stress-like states (Koob and Le Moal, 2001); both systems represent two important neurobiological player in ethanol (EtOH) dependence. Genetically selected marchigian sardinian Preferring (msP) rats show innate EtOH preference together with an anxious phenotype that ameliorates following EtOH drinking (Ciccocioppo et al., 2006). Latest 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 (Koob, 2003). We aimed to evaluate innate or EtOH-induced differences of N/OFQ and CRF systems gene expression in the AM and BNST of Wistar and msP rats. Animals were exposed to vehicle or chronic intermittent 10% EtOH (v/v) in a two-bottle choice paradigm; after 30 days rats were sacrificed.

Real-time qPCR analysis showed a significant increase of pN/OFQ mRNA basal levels in the AM and in the BNST of msP rats compared to Wistar. As expected, EtOH intake caused a significant decrease of pN/OFQ gene expression in both investigated regions of msP animals only. In addition, higher basal expression levels of nociceptin/orphanin FQ receptor (NOP) mRNA were observed in AM and BNST of msP compared to Wistar. Following EtOH exposure we observed the decrease of NOP mRNA levels in the AM and the NOP gene expression increase in the BNST of msP only.

Further analysis showed that the CRF mRNA basal levels of msP rats were higher compared to Wistar in the AM and EtOH intake caused a significant decrease of gene expression levels. Likewise, CRF basal levels of msP were higher compared to Wistar rats in the BNST; however, ETOH intake caused a further increase of CRF gene expression. In this area, the CRF1 receptor analysis showed higher gene expression levels in msP compared to Wistar rats whereas EtOH intake caused a further increase in the BNST of msP rats only.

Present findings indicate that the EtOH effects in the extended amygdala are totally dependent on the genotype, since no alterations were observed in Wistar rats following EtOH exposure. In addition, it is known that alcohol intake may allow the recovery from negative mood states acting through opioid system (Ciccocioppo et al., 2003) and our data obtained in the AM of msP

confirmed this evidence corroborating the hypothesis that the interactions between CRF-N/OFQ systems may be functionally relevant to control stress-related addictive behaviour. However, the further increase of CRF, CRF1 and NOP mRNA in the BNST following EtOH intake suggest that these mediators may play specific roles depending on the brain structure, thus mediating the relapse phenomena. In conclusion, our results contribute to define the peculiar gene expression arrangement of msP rats in which an innate preference for alcohol has been co-segregated with an anxious and depression-like phenotype.

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