Effect of chronic ethanol consumption on the contraction induced by endothelin-1 in rat corpus cavernosum: role of NAD(P) oxidase and MAP Kinase

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Endothelin 1 (ET-1) is a peptide with vasoconstrictor action that controls the tonus of cavernosal muscle contributing to maintain the flaccid state of penis. In addition to its effects in vasoconstriction, the ET-1 activates other pathways, such as mitogen-activated protein kinase (MAPK), metalloproteinases (MMPs) and increases the production of reactive oxygen species (ROS). The increase of ET-1 has been associated with erectile dysfunction (ED) of different etiologies, including the ED caused by chronic ethanol consumption. The aim of this study was to assess the effects of chronic ethanol consumption on the endothelinergic system and intracellular pathways activated by ET-1 in cavernosal tissue.

All protocols were approved by the local Ethics Committee (12.1.317.53.9). Male Wistar rats were divided in two groups: ethanol group– treated with ethanol (20% vol/vol) for 6 weeks; control group– water for 6 weeks. Cumulative concentration-response curves for ET-1 were performed on isolated cavernosal tissues on the presence or absence of apocynin (APO) (100µmol/L), an inhibitor of NAD(P)H oxidase, and SP600125 (100µmol/L), an inhibitor of MAPK SAPK/JNK. Antioxidant activity and MMP-9 and MMP-2 levels were measured in plasma. mRNA levels of p38MAPK, SAPK/JNK, ERK1/2, AKT, MMP-9 and MMP-2 were assessed by RQ-PCR in cavernosal tissue.

ET-1-induced contraction was higher in ethanol-treated rats (36.1 ± 2.7% KCl 120mM; n=5) compared to control group (20.7 ± 0.9% KCl 120mM; n=5) (P<0.05, Student’s T test). In ethanol group, the contraction induced by ET-1 was significantly reduced in the presence of APO (25.2 ± 2.2% KCl 120mM; n=3) and SP600125 (25.4 ± 3.3% KCl 120mM; n=5) (P<0.05, Student’s T test). The antioxidant activity and MMP-9 and MMP-2 plasma levels were increased in ethanol group when compared to control group (P<0.05, Student’s T test). It was not found alteration in mRNA level of MAPKs, MMPs and AKT when control was compared to ethanol group.

Fig1 – Cumulative concentration-response curves for ET-1 on the presence of (A) APO and (B) SP600125
These results show that the chronic ethanol consumption increases the ET-1-induced contraction and APO and SP600125 revert this response. Furthermore, the chronic ethanol consumption increases the antioxidant activity and plasma levels of MMP-9 and MMP-2. Therefore, the chronic ethanol consumption affects intracellular pathways activated by ET-1 in cavernosal tissue, which can lead to ED.