ETHANOL CAUSES NEUROGENIC VASODILATATION BY TRPV1 ACTIVATION AND CGRP RELEASE IN THE TRIGEMINOVASCULAR SYSTEM OF THE GUINEA PIG

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Ethanol (EtOH) has been recently found to stimulate primary sensory neurons by activation of the transient receptor potential vanilloid 1 (TRPV1) channel (Trevisani et al. 2002). By this mechanism EtOH releases sensory neuropeptides, including the calcitonin gene-related peptide (CGRP), thereby inducing neurogenic inflammation and, particularly, dilatation of cardiac or gastric arterial vessels (Gazzieri el al, 2006). Drinking alcoholic beverages is a common trigger of migraine attacks and activation of trigeminal neurons and CGRP release are considered to play a role in migraine mechanism. Thus, we have investigated in guinea pigs whether EtOH causes neurogenic inflammatory responses by activation of the trigeminovascular system by TRPV1 stimulation and sensory neuropeptide release. EtOH (0.3-3%) induced a concentration-related release of substance P (SP) and CGRP from slices of trigeminal ganglia or transverse and sagittal sinuses with attached dura mater (DMVS). This response was reduced in all cases by more than 80% in a Ca2+-free medium, by capsaicin pretreatment and by the TRPV1 antagonist, capsazepine. Administration of EtOH (280 µl/kg, i.p. or 1 ml/kg, intragastric) increased the baseline Evans blue dye extravasation in DMVS by 140±4% and 163±3% (n=6 each), respectively. The increased plasma extravasation induced by EtOH was abolished by capsazepine and by the NK1 receptor antagonist, SR140333. Finally, EtOH administration by intragastric route evoked a slowly developing and sustained increase in blood flow in the guinea pig dura mater (measured by a laser Doppler flowmeter) that averaged 234.1±42.7% over baseline (n=6). The EtOH-induced increase in blood flow induced of in the meningeal blood vessels of the dura mater was abated by capsazepine and by the CGRP receptor antagonist, BIBN4096BS. These two pharmacological interventions did not affect the modest increase in blood flow evoked by local application of acetylcholine (127±1.8% over baseline, n =6), thus indicating selectivity. We conclude that EtOH administration, *via* TRPV1 activation and SP/CGRP release, causes neurogenic inflammatory responses in the guinea pig dura mater. Ingestion of alcoholic beverages may cause TRPV1-depepndent trigeminal stimulation that directly or indirectly though a CGRP-mediated vasodilatation may contribute the headache and the other symptoms of the migraine attack. CGRP receptor antagonists, currently under scrutiny as abortive drugs for the migraine attack, may be useful in the treatment of alcohol-induced headache.

Trevisani et al, Nat Neurosci, 2002, 5: 546-51.
Gazzieri et al, Cardiovasc Res, 2006, 70:589-99.