ACTIVATION OF TRANSIENT RECEPTOR POTENTIAL VANILLOID TYPE 1 (TRPV1) BY ETHANOL: ROLE OF ENDOGENOUS LIPID MEDIATORS

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Background We have recently showed that ethanol (EtOH) stimulates a subpopulation of sensory nerves by activation of the Transient Receptor Potential Vanilloid 1 (TRPV1). A large and heterogeneous group of stimuli operates the TRPV1, including protons, capsaicin, low pH and others. Furthermore, three different classes of endogenous lipids have been reported to activate TRPV1. These are unsaturated N-acyldopamines, lipoxygenase products of arachidonic acid and the anandamide and N-arachidonoyl-dopamine. Many studies have demonstrated the ability of EtOH to destabilizes the neuronal plasma membrane and to release biological active lipids within the cytoplasm. The aim of the present work was to investigate whether the effect of EtOH on TRPV1 was mediated, at least in part, by lipid mediators. ***Methods*** The role of EtOH to modulate intracellular calcium concentration ($[Ca^{2+}]_i$) in cultured newborn rat trigeminal ganglion neurons was investigated by using a Nikon eclipse TE300 microscope, the ionophore Fura-2-AM-ester and a dynamic image analysis system (Laboratory Automation 2.0, RCS, Florence, Italy). ***Results***. EtOH (3%) produced a significant mobilization of $[Ca^{2+}]_i$ in primary sensory neurons (32 ± 5% of ionomycin, n=12) if compared to that of its vehicle (2 ± 1% of ionomycin, n=18). An effect that being inhibited by two diverse TRPV1 antagonists, capsazepine and iodo-resiniferatoxin, was ascribed to the channel activation. Pretreatment of cultured neurons with the phospholypase A_2 (PLA_2) inhibitor, OBAA (10μM), and the phospholypase C (PLC) inhibitor, U73122 (10μM), produced a significant reduction of the neuronal excitatory response to EtOH (15 ± 3% of ionomycin n=15 and U73122 12 ± 4% of ionomycin n=15, respectively). Furthermore, a significant reduction in EtOH-induced neuronal excitation was observed when cultured neurons were pretreated with the cytochrome P450 monoxygenase inhibitor, 17-ODYA, 10μM (~ 50% of inhibition). In contrast, no inhibitory effect was observed by blocking the lypoxygenase and cycloxygenase pathways. ***Conclusions.*** The TRPV1-dependent excitatory effect of EtOH on capsaicin-sensitive primary sensory neurons is mediated, in part, by the involvement of diverse intracellular lipidic pathways. Particularly, EtOH-induced effect is mediated by products of PLA_2 and PLC and CytP450. These results may suggest an indirect modulatory effect of EtOH on the neuronal TRPV1 channel. The intriguing hypothesis that the pungency and pain-like activity of the alcohol when applied to wounds or mucosal surfaces is mediated by one or more of these lipids must be scrutinized in the future.