Title

Acute activation of hemichannels by ethanol leads to Ca2+-dependent gliotransmitter release in astrocytes

Abstract

Multiple studies have demonstrated that acute ethanol consumption alters brain function and cognition. Nevertheless, the mechanisms underlying this phenomenon remain poorly understood. Astrocyte-mediated gliotransmission is crucial for hippocampal plasticity, and recently, the opening of hemichannels has been found to play a relevant role in this process. Hemichannels are plasma membrane channels composed of six connexins or seven pannexins, respectively, that oligomerize around a central pore. They serve as ionic and molecular exchange conduits between the cytoplasm and extracellular milieu, allowing the release of various paracrine substances, such as ATP, D-serine, and glutamate, and the entry of ions and other substances, such as Ca2+ and glucose. The persistent and exacerbated opening of hemichannels has been associated with the pathogenesis and progression of several brain diseases for at least three mechanisms. The uncontrolled activity of these channels could favor the collapse of ionic gradients and osmotic balance, the release of toxic levels of ATP or glutamate, cell swelling and plasma membrane breakdown and intracellular Ca2+ overload. Here, we evaluated whether acute ethanol exposure affects the activity of astrocyte hemichannels and the possible repercussions of this phenomenon on cytoplasmatic Ca2+ signaling and gliotransmitter release. Acute ethanol exposure triggered the rapid activation of connexin43 and pannexin1 hemichannels in astrocytes, as measured by time-lapse recordings of ethidium uptake. This heightened activity derived from a rapid rise in [Ca2+]i linked to extracellular Ca2+ influx and IP3-evoked Ca2+ release from intracellular Ca2+ stores. Relevantly, the acute ethanol-induced activation of hemichannels contributed to a persistent secondary

increase in [Ca2+]i. The [Ca2+]i-dependent activation of hemichannels elicited by ethanol caused the increased release of ATP and glutamate in astroglial cultures and brain slices. Our findings offer fresh perspectives on the potential mechanisms behind acute alcohol-induced brain abnormalities and propose targeting connexin43 and pannexin1 hemichannels in astrocytes as a promising avenue to prevent deleterious consequences of alcohol consumption. Copyright © 2024 Gómez, García-Rodríguez, Marillán, Vergara, Alvear, Farias-Pasten, Sáez, Retamal, Rovegno, Ortiz and Orellana.

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