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Sites of Alcohol Action at the GluN1/GluN2B NMDA Receptor M3-M4 Domain Intersubunit Interfaces

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Presentation Abstract

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Abstract: The N-methyl-D-aspartate (NMDA) receptor has been shown to be one of the most important target sites of alcohol in the central nervous system. We and others have identified positions in the third and fourth membrane-associated (M) domains of both GluN1 and GluN2A subunits that influence alcohol sensitivity. In the structural model of the NMDA receptor based upon the related GluA2 receptor, the outward face of the M3 domain of one subunit type is oriented toward the M4 domain of the other subunit type. We recently reported that four pairs of alcohol-sensitive amino acid positions in GluN1/GluN2A NMDA receptors interact at the M3-M4 intersubunit interfaces with respect to alcohol sensitivity and receptor kinetics. Because a number of studies point to a major role for the GluN2B subunit in the action of alcohol in the brain, in the present study we used site-directed mutagenesis and electrophysiological patch-clamp recording in transfected cells to investigate the sensitivity of cognate positions in the GluN2B subunit, as well as interactions between positions in the M3 and M4 domains of the GluN1 and GluN2B subunits affecting ethanol inhibition. Although the M3 and M4 domains of GluN2A and GluN2B are highly conserved, only one of four positions in GluN2B, F637, corresponding to alcohol-sensitive positions in GluN2A exhibited altered ethanol IC_{50} values in substitution mutants. However, we observed interactions with respect to ethanol sensitivity among three out of four pairs of positions (G638/M824, F639/L825, and M818/F637 in GluN1/GluN2B), even when single substitution mutations at one of the two positions in a pair (GluN1 M818; GluN2B M824, L825) had no effect on alcohol sensitivity. These results support the existence of sites of alcohol action formed by clusters of positions at the M3-M4 domain intersubunit interfaces of GluN1/GluN2B NMDA receptors, although they appear to differ from the corresponding sites in GluN1/GluN2A receptors reported previously.

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