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A Novel Alcohol-Sensitive Position in the M3 Domain of the NMDA Receptor GluN2B Subunit

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A Novel Alcohol-Sensitive Position in the M3 Domain of the Nmda Receptor Glun2b Subunit

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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. Previous studies in our lab have identified and characterized positions in the third and fourth membrane-associated (M) domains of the NMDA receptor GluN2A subunit that influence both channel gating and alcohol sensitivity. Although the GluN2A subunit predominates in the mammalian brain, a number of studies point to a major role for the GluN2B subunit in the action of alcohol. In the present study, we investigated positions in M3 and M4 of the GluN2B subunit

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corresponding to previously identified positions in GluN2A. Using site-directed mutagenesis and whole-cell patch-clamp recording, we have found a position in M3 of the Glun2B subunit, F637, which significantly influences ethanol sensitivity, glutamate potency and ion channel gating. Tryptophan substitution at F637 significantly increased the ethanol IC50, decreased both peak and steady-state glutamate EC50, and altered agonist deactivation and apparent desensitization. A series of mutants at this site all showed significantly altered glutamate potency and steady-state: peak current ratio. However, only a small number of mutants showed significantly decreased ethanol sensitivity. Interestingly, we have previously found that the cognate position in the GluN2A subunit, F636, can also influence alcohol action and glutamate potency, but the characteristics of this regulation differ from that in the GluN2B subunit. Given our previous findings that GluN2A(F636) interacts with GluN1(M818) to influence the kinetics and ethanol sensitivity of the receptor, these findings suggest that GluN2B(F637) may interact with the GluN1 subunit in a different way to alter the alcohol sensitivity and receptor kinetics. These studies were supported by grants R01 AA015203-01A1 and AA015203-06A1 from the NIAAA to R.W.P.