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Identification of alcohol binding residues in brain proteins using electrospray ionization mass spectrometry

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Alcohols bind and regulate functions of many proteins in the human brain. To develop antagonists for the alcohol addiction and alcoholism, it is necessary to identify the site of action of alcohol in these proteins. We have investigated alcohol binding sites in protein kinase C (PKC) epsilon, a serine/threonine kinase and Munc13-1, a presynaptic protein expressed predominantly in the brain. To identify alcohol binding site(s), C1 domains of PKCε and Munc13-1 were photolabeled with the diazirine analogs of butanol and octanol, 3-azibutanol and 3-azioctanol, and the sites of photo-incorporation were identified by MS/MS analysis using electrospray ionization mode. Azialcohols labeled Tyr-176 of PKCεC1A, His-248 and Tyr-250 of PKCεC1B. In Munc13-1, Glu-582 is exclusively photo-labeled by the azialcohols. Azialcohols failed to photolabel these sites when these residues were mutated with alanine. Inspection of the model structure of PKCεC1 and Munc13-1C1 reveals that these residues forms groove where alcohol can bind. The present results provide evidence for the presence of alcohol-binding sites on PKCε and Munc13-1 and underscore the power of mass spectrometry in identifying sites of alcohol action in the brain.

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