A Site of Alcohol Action in the Fourth Membrane-associated Domain of the N-Methyl-d-aspartate Receptor*

Received for publication, February 27, 2003, and in revised form, September 18, 2003 Published, JBC Papers in Press, September 23, 2003, DOI 10.1074/jbc.M302097200

Hong Ren, Yumiko Honse, and Robert W. Peoples‡
From the Unit on Cellular Neuropharmacology, Laboratory of Molecular and Cellular Neurobiology, National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland 20892-8203

The N-methyl-d-aspartate (NMDA) subtype of ionotropic glutamate receptor is an important mediator of the behavioral effects of ethanol in the central nervous system. Although ethanol is known to inhibit NMDA receptors by influencing ion-channel gating, its molecular site of action and the mechanism underlying this effect have not been established. We have previously identified a conserved methionine residue in the fourth membrane-associated domain of the NMDA receptor NR2A subunit (Met823) that influences desensitization and gating of the ion channel. Here we report that this residue plays an important role in mediating the effect of ethanol on the NMDA receptor. Ethanol IC50 values among functional substitution mutants at this position varied over the range —130–225 μM. There was a weak correlation between IC50 and mean open time of NR2A(Met823) mutants that was dependent on inclusion of the value for the tryptophan mutant. In the absence of this value, there was no trend toward a correlation among the remaining mutants. Desensitization appeared to influence the action of ethanol, because ethanol IC50 of the mutants was correlated with the steady-state to peak current ratio. With the exception of tryptophan, ethanol sensitivity was significantly related to the molecular volume and hydrophobicity of the substituent. The relation between ethanol sensitivity and the molecular volume and hydrophobicity at this position suggests that this residue interacts with or forms part of a site of ethanol action and that the presence of a tryptophan residue in this site disrupts its ability to interact with ethanol.

Ethyl alcohol or ethanol, one of the oldest and most widely abused drugs, produces a well known spectrum of behavioral effects primarily through actions on ion channels in the nervous system. The N-methyl-d-aspartate (NMDA) receptor, a subtype of receptor for the major excitatory neurotransmitter glutamate, is thought to be of particular importance in mediating the effects of alcohols in the mammalian brain. Ethanol inhibits NMDA-activated current in central neurons (1, 2) as well as NMDA-evoked Ca2+ flux, cyclic GMP production, and neurotransmitter release (3–6). Studies using in vivo electrophysiological techniques have also reported ethanol inhibition of NMDA receptors at relevant concentrations (7). Ethanol appears to interact with a novel allosteric site, which is independent of the recognition site for the agonist glutamate or coagonist glycine (6, 8–12), and reduces the mean open time and opening frequency of the channel (13, 14).

Presumed alcohol binding sites have been identified on a small number of receptors and ion channels, but the location and nature of these sites vary considerably. Sites of alcohol interaction have been reported to be located in the ion-channel lumen of nicotinic acetylcholine receptors from muscle (15) in a cytoplasmic loop of a Drosophila potassium channel (16), in the cytoplasmic C terminus of G-protein-coupled inwardly rectifying potassium channels (17), and in transmembrane domains of the GABAA and glycine receptors (18–20). The identity of alcohol binding sites is also variable among alcohol-sensitive proteins. No consensus sequence or structure has yet been defined for an alcohol binding site. A recent study has demonstrated that a phenylalanine residue in the third membrane-associated domain (M3) of the NR1 subunit influences ethanol sensitivity (21), but the magnitude of the variation in ethanol sensitivity among mutants at this site suggests that it is not the sole site of alcohol action. Previous work in our laboratory has shown that the site of alcohol action on the NMDA receptor is located on a region of the protein that is accessible only from the extracellular environment (22). We hypothesized that there may be an additional site or sites of alcohol action in one of the membrane-associated domains that participates in the regulation of ion-channel gating and that is accessible from the extracellular environment. We have previously identified a methionine residue in M4 of the NR2A subunit (Met823), which has a predicted location close to the extracellular face of the membrane and which exerts a powerful influence on NMDA receptor ion-channel gating (23). We report here that this residue influences NMDA receptor alcohol sensitivity in a manner that is related both to desensitization of the ion channel and to the molecular volume and hydrophobicity of the substituent amino acid.

EXPERIMENTAL PROCEDURES

Mutagenesis—Plasmids containing NR1-1a and NR2A subunit cDNA were kindly provided by Drs. D. R. Lynch (University of Pennsylvania) and D. M. Lovinger (National Institute on Alcohol Abuse and Alcoholism). Site-directed mutagenesis was performed using the QuickChange kit (Stratagene, La Jolla, CA), and all of the mutations were verified by DNA sequencing.

Cell Culture and Transfection—Human embryonic kidney (HEK 293) cells obtained from the American Type Culture Collection (Manassas, VA) were cultured in minimum essential medium containing 2 mM L-glutamine, Earle’s balanced salt solution, 0.1 mM non-essential amino acids, 1.0 mM sodium pyruvate, and 10% heat-inactivated horse serum at 37 °C in 5% CO2 and 95% air. Cells were plated at a density of 104
cells/ml in 35-mm dishes and allowed to grow to 70–95% confluence prior to transient transfection using LipofectAMINE 2000 or calcium phosphate (both from Invitrogen). The cDNA plasmid ratio for NR1 and NR2A subunits and green fluorescent protein (pGreen Lantern, Invitrogen) was 2:2:1 (total amount of DNA, 2.5–6 μg). During and after the transfection, 100 μM ketamine and 200 μM N-2-amino-5-phosphonovalerionic acid were added to the culture medium to enhance survival of transfected cells. Within 18–22 h following transfection, cells were mechanically dissociated and plated at a low density in 35-mm dishes for use in experiments.

Electrophysiological Recording—Whole-cell patch clamp recording was performed using an Axopatch 1D or 200B (Axon Instruments Inc., Union City, CA) amplifier at room temperature. Electrodes with open tip resistances of 1–5 megohms were used. After establishing whole-cell mode, series resistances of 2–10 megohms were compensated by 80%. Cells were voltage-clamped at −50 mV and superfused in an extracellular solution containing 150 mM NaCl, 5 mM KCl, 0.2 mM CaCl₂, 10 mM HEPES, and 10 mM glucose. pH was titrated to 7.4 with NaOH, and osmolality was adjusted to 340 mmol/kg with sucrose. Low Ca⁺ was used to minimize NMDA receptor inactivation (24). The intracellular (patch pipette) solution contained 140 mM CsCl, 2 mM Mg_ATP, 10 mM β-APTA, and 10 mM HEPES. pH was titrated to 7.4 with CsOH, and osmolality was adjusted to 310 mmol/kg with sucrose. Data were filtered at 2 kHz (low pass, 8-pole Bessel) and acquired at 5–10 kHz on a computer using a DigiData interface and pClamp8 software (Axon Instruments).

Drug Application—Solutions of agonists and ethanol were applied to cells by using a stepper motor-driven rapid solution exchange apparatus (Fast-step, Warner Instrument Co., used without the metallic manifolds supplied by the manufacturer) and 600-μm-inner diameter square glass tubing. Drugs were prepared daily in extracellular solution. Ethanol (95%, prepared from grain) was obtained from Pharmco Products (Brookfield, CT), and all of the other chemicals were obtained from Sigma.

Calculation of Physicochemical Properties of Amino Acids—Molecular (van der Waals) volumes of amino acids were calculated using Spartan Pro (Wavefunction, Inc., Irvine, CA) following structural optimization using the AM1 semi-empirical parameters. Values used for amino acid hydropathy, hydrophilicity, and polarity were reported previously (25–27).

Data Analysis—Values reported for IC₅₀ (half-maximal inhibitory concentration) and n (slope factor) were obtained from nonlinear curve fitting (Origin, OriginLab Corp., Northampton, MA) of data to Equation 1,

\[ y = E_{max} \left[1 + \left(\frac{IC_{50}}{[x]}\right)^n\right] \]  

(Eq. 1)

where \( y \) is the percent inhibition and \( E_{max} \) is the maximal inhibition. IC₅₀ values for inhibition of steady-state current were used because these did not differ significantly from those for peak current in mutants exhibiting substantial desensitization. Logarithmically transformed IC₅₀ values obtained from fitting concentration-response data from individual cells were statistically compared using analysis of variance (ANOVA) followed by the Fisher’s protected least significant difference (PLSD) test. In fluctuation analysis experiments, the data were filtered at 1 kHz (low pass 8-pole, Butterworth) and 25–60 traces, 600 or 800 ms in length, were acquired at 5 kHz. Background spectra were subtracted, and averaged spectra were fitted with a Lorentzian function of the form as shown in Equation 2,

\[ S_j = S_{0j} \left[1 + (f/c)^2\right] \]  

(Eq. 2)

where \( S_j \) is the spectral density at frequency \( f \) (in Hz), \( S_{0j} \) is the zero-frequency asymptote, and \( c \) is the corner frequency. Time constants (\( \tau \)) were obtained from the relationship \( \tau = 1/(2f_c) \). ANOVA, PLSD test, correlation analysis, and linear regression analysis were performed using the program StatView (SAS Institute, Inc., Cary, NC).

All of the data values are expressed as the mean ± S.E.

RESULTS

Mutations at NR2A(Met²²³) Alter Ethanol Sensitivity—We have previously identified a site in the M4 region of the NR2A subunit, NR2A(Met²²³), that regulates NMDA receptor ion-channel gating (Fig. 1) (23). To test whether this site might participate in ethanol inhibition of NMDA receptors, we examined ethanol sensitivity of substitution mutants at this site. As we have reported previously, a number of amino acid substitu-


ditions at this site yielded nonfunctional receptors (23). All of the functional NR2A(Met²²³) substitution mutant receptors tested were inhibited by ethanol in a concentration-dependent manner (Fig. 2). The slope factors of the ethanol concentration-response curves did not differ significantly among the various mutants. However, the values for ethanol IC₅₀ varied significantly among the mutants, ranging from 131 to 224 mM (ANOVA, \( p < 0.0001 \)). Expression of the mutant subunits NR2A(M823C), NR2A(M823S), or NR2A(M823W) with NR1 subunits produced receptors with the lowest sensitivity to ethanol, and coexpression of NR1 subunits with NR2A(M823F), NR2A(M823L), or NR2A(M823Y) mutant subunits resulted in receptors with the highest sensitivity to ethanol.

Ethanol Decreases Mean Open Time in NR2A(Met²²³) Substitution Mutant Receptors—To verify that the mutations did not produce a fundamental change in the mechanism of action of ethanol on the receptor, we used fluctuation analysis to obtain approximate mean open times in NMDA receptors containing selected mutant subunits in the absence and the presence of 100 mM ethanol. Fig. 3 shows plots of power density spectra for NMDA-activated current in cells expressing NR1/NR2A(M823I) and NR1/NR2A(M823L) mutant receptors. As we have observed previously (23), time constants derived from fitting of Lorentzian functions to power density spectra revealed that the mean open time of NR1/NR2A(M823I) NMDA receptors was markedly reduced compared with that in wild type receptors. Nevertheless, ethanol produced a decrease in the mean open time in these receptors similar to that observed in wild type receptors. On average, 100 mM ethanol inhibited mean open time by 25 ± 1.9% in receptors containing NR2A(M823I) subunits (0.82 ± 0.034 versus 0.62 ± 0.024 ms in the absence and presence of ethanol, respectively, Student’s paired t test, \( p < 0.0005 \)). Similar results were obtained in cells expressing NR1/NR2A(M823L) mutant subunits (27 ± 1.4% inhibition of mean open time, 2.2 ± 0.19 versus 1.6 ± 0.13 ms in the absence and presence of ethanol, respectively, Student’s paired t test, \( p < 0.01 \)). These observations are similar to results obtained for wild type receptors in native neurons in a previous study (14). In addition, a variance analysis of NMDA-activated current indicated that the unitary conductance of the ion channel was not changed in the presence of ethanol in receptors containing NR2A(M823I) or NR2A(M823L) mutant subunits (data not shown).

Relation of Ethanol Sensitivity to Glycine Sensitivity—Because the inhibitory potencies of ethanol on the NMDA receptor

![Fig. 1. Location of Met²²³ in M4 of the NMDA receptor NR2A subunit. Topological model of the NR2A subunit showing the membrane-associated domains (M1–M4), ligand binding domains (S1–S5, bold lines), and presumed position of Met²²³ (filled circle).](http://www.jbc.org/)
may be linked to sensitivity to the coagonist glycine under some conditions (21, 28), we tested whether representative mutations that altered ethanol sensitivity could alter the glycine concentration-response relationship. We found no significant differences in EC50 values of glycine for activation of peak and steady-state current in cells expressing wild type, NR2A-(M823C), NR2A-(M823F), NR2A-(M823W), and NR2A-(M823Y) subunits (Table I).

Relation of Ethanol Sensitivity to Desensitization and Mean Open Time—For mutant subunits exhibiting marked desensitization, no differences were observed for ethanol inhibitory potency of peak versus steady-state current (data not shown). Because the mean open time and steady-state-to-peak current ratio varied widely among mutants (Fig. 4), we tested whether either of these parameters could be related to the observed differences in ethanol sensitivity. Ethanol IC50 was significantly correlated with steady-state-to-peak current ratio (Fig. 4A, R2 = 0.445; p < 0.05). There was also a significant correlation between ethanol sensitivity and mean open time (Fig. 4B, R2 = 0.465; p < 0.05) for the series of NR2A-(Met823) mutants. However, this latter correlation was entirely dependent on the long mean open time observed in the tryptophan mutant because the correlation disappeared when this mutant was excluded from the analysis (R2 = 0.0298; p > 0.05), despite the fact that both mean open time and ethanol IC50 varied significantly among the remaining mutants.

Ethanol Sensitivity Depends upon Hydrophilicity and Molecular Volume of the Substituent at NR2A-(Met823)—If the observed changes in ethanol sensitivity among the NR2A-(Met823) mutant subunits were due to a direct interaction of ethanol with this site, one would predict that this would be reflected in a significant linear relation of ethanol sensitivity with one or more physicochemical parameters of the amino acid substituent at the site. To evaluate the relative contribution of the physicochemical parameters of the amino acid residue at this site to alcohol sensitivity, we performed linear regression analysis of alcohol sensitivity versus hydropathy, hydrophilicity, hydrogen bonding, molecular volume, and polarity of the substituent (Fig. 5). When all of the substitution mutants were included in the analysis, there was no significant linear relation observed between ethanol IC50 and hydropathy (R2 =
Fig. 4. Correlation between NMDA receptor ion-channel gating properties and ethanol inhibition. A, graph plots IC$_{50}$ values for ethanol versus maximal steady-state:peak ratio (Iss:Ip) of current activated by 1000 μM NMDA and 10 μM glycine in the various NR2A(M823) mutant subunits. The line shown is the least-squares fit to the data. Ethanol IC$_{50}$ and $I_p(I_s/I_p)$ were significantly correlated (p < 0.05). The data point labeled W was obtained in cells expressing the tryptophan substitution mutant receptor. B, graph plots ethanol IC$_{50}$ versus mean open time of NMDA receptors activated by 5 or 10 μM NMDA and 10 μM glycine in the various NR2A(M823) mutant subunits. These values were significantly correlated when all of the mutants tested were included (p < 0.05; solid line) but not when the tryptophan mutant was excluded from the analysis (p > 0.05; dashed line). The lines shown are least-squares fits to the data.

Discussion

The results of the present study demonstrate that mutations at the conserved methionine (Met823) in the fourth membrane-associated domain of the NR2A subunit influence sensitivity of the NMDA receptor-ion channel to ethanol. The range over which ethanol IC$_{50}$ values varied among the mutants is greater than the range we have previously observed among wild type NR2 subunits (results not shown). Although it is not possible at present to demonstrate conclusively that the fundamental mechanism of action of ethanol was not different among the various mutants, the observation that substitutions at this position did not alter either the slope factor of the ethanol concentration-response curve or the extent of inhibition by ethanol of mean open time is consistent with this idea.

We previously reported that both the rate and extent of desensitization as well as mean open time differed significantly among the various mutants at NR2A(Met823), indicating an important role for this residue in the regulation of ion channel gating (23). A recent report has also shown a role for the M4 domain in regulating desensitization (29). Although ethanol inhibits the NMDA receptor largely by decreasing mean open time of the ion channel, there was only a weak correlation in the present study between ethanol sensitivity and mean open time of NR2A(Met823) mutants that was entirely dependent on the inclusion of the value for the tryptophan mutant. When this value was excluded from the analysis, there was no trend toward a correlation of ethanol sensitivity with mean open time.
among the remaining mutants, despite the fact that there were still significant differences among these mutants in both ethanol IC50 and mean open time. In contrast, ethanol sensitivity among the various NR2A(Met823) mutants in the present study was correlated with the steady-state to peak current ratio, a measure of the extent of macroscopic desensitization, such that the greater the desensitization in a given mutant, the lower its ethanol sensitivity. A possible explanation for this latter observation could be that NR2A(Met823) influences ethanol potency indirectly via changes in desensitization. However, this explanation is not supported by results of studies in wild type NMDA receptors in which ethanol potency is not reduced at high, desensitizing agonist concentrations (6, 8, 11). This observation could instead indicate that ethanol acts in part by increasing NMDA receptor desensitization (14), but no increase in macroscopic apparent desensitization in the presence of ethanol was observed in any of the mutant receptors tested in the present study. Furthermore, from inspection of the plot of steady-state to peak ratio versus ethanol IC50, it is apparent that there is not an absolute dependence of ethanol sensitivity on desensitization. For example, the steady-state to peak ratios of the alanine and tyrosine substitution mutants were similar, but the ethanol IC50 values of these mutant subunits differed considerably. Although the results of the present study cannot exclude a role for desensitization in the action of ethanol, a more probable explanation for these observations may be that similar molecular forces at NR2A(Met823) influence both changes in desensitization and changes in alcohol sensitivity.

Other investigators have presented evidence that alcohols and anesthetics are able to bind to a site formed by residues in the M2 and M3 domains of GABA_A and glycine receptors and regulate channel function in a manner that is dependent upon volume occupation of the site (18, 20, 30, 31). In this study, we did not initially observe a relation between ethanol sensitivity and molecular volume of the substitution at NR2A(Met823). However, when the value for the tryptophan mutant was excluded from the analysis, there was a highly significant linear relation of ethanol sensitivity with molecular volume. Because tryptophan is the largest naturally occurring amino acid, this finding may indicate that the action of ethanol involves filling a critical volume in a cavity formed in part by this site in the receptor and that the presence of a bulky tryptophan residue in the cavity severely disrupts its ability to interact with ethanol. In addition, in this study we observed that ethanol sensitivity of the mutants, with the exception of tryptophan, was related to the hydrophilicity at this position. A number of previous studies have demonstrated that the action of alcohols on NMDA receptors largely depends upon hydrophobic interactions (1, 32–35). The observation of a relation between ethanol sensitivity and hydrophilicity of the substituent at NR2A(Met823) in this study suggests that ethanol interacts with this site in a manner that involves hydrophobic binding.

The observations of this study are consistent with a role of NR2A(Met823) in mediating part of the inhibitory effect of ethanol on the NMDA receptor. In particular, the observations that ethanol sensitivity was significantly related to the molecular volume and hydrophobicity of the substituent fulfill part of the criteria for a putative site of alcohol action. Previous studies on other alcohol-sensitive ion channels have reported correlations between the molecular volume of various alcohols and anesthetics and their potency for ion-channel modulation (31, 36, 37). In addition, in one of these studies, the anesthetic molecular volume above which ion-channel modulatory potency is lost (“cutoff” point) was dependent upon the molecular volume of the substituent at a proposed site of alcohol action (31, 36, 37). Although similar results might be expected for this site on the NMDA receptor based on the previous observation of a cutoff (34), we have recently shown that the cutoff phenomenon for alcohol inhibition of the NMDA receptor is not dependent upon the molecular volume of the alcohol (35). Thus, in light of our previous results, we consider that the results of the present paper are most consistent with a model in which NR2A(Met823) forms part of a site of alcohol action that is better represented as a long groove rather than a spherical pocket. In this scheme, alcohols bind in the long axis of the groove and NR2A(Met823) is in a critical region that is perpendicular to the long axis of the groove. The correlation with molecular volume of the amino acid at this site observed in the present paper suggests that part of the alcohol molecule interacts with NR2A(Met823) to influence channel function. According to this model, increases in the size of the amino acid side chain would extend perpendicular to the axis of the groove, whereas changes in alcohol chain length would extend parallel to it so that changes in the molecular volume of the amino acid or the alcohol would produce disparate effects. If this interpretation is correct, it would imply that changes in the molecular volume of amino acids at positions adjacent to NR2A(Met823) along the binding groove would probably alter the potency of alcohols with different carbon chain lengths. Future experiments should address this possibility.

The importance of NR2A(Met823) in regulation of normal ion-channel function (23) is in contrast to the view that mutations at a site of ethanol action on a protein should not disrupt its function. In light of the fact that ethanol produces its effects at concentrations in the millimolar range, however, for any ethanol-sensitive protein, ethanol undoubtedly interacts with low affinity with multiple sites and one or more of these sites that are important in normal regulation of function could constitute the sites of ethanol action. This appears to be true of putative alcohol and anesthetic binding sites on glycine and GABA_A receptors (18–20), because a recent study has reported that a mutation in at least one of these sites alters ion-channel gating (38). It should be noted that NR2A(Met823) does not appear to be able to account completely for ethanol inhibition, because ethanol sensitivity was not eliminated in any of the mutants tested. Because both NR1 and NR2 subunit activation is required for NMDA receptor-ion-channel opening, it is possible that sites of ethanol action are located on both subunit types. In this regard, an ethanol-sensitive site in the third membrane-associated domain (M3) of the NR1 subunit has been reported recently (21). Interestingly, mutations at this site in M3 can influence glycine potency (21) and appear to alter ion-channel gating as well. Ethanol may thus inhibit the NMDA receptor by acting in concert at multiple sites, including NR2A(Met823), that are important in the regulation of NMDA receptor function. Future experiments should allow assessment of the magnitude of the contribution of each of these sites in the NR1 and NR2 subunits to the overall alcohol sensitivity of the NMDA receptor.

Acknowledgments—We thank Julia Healey, Guoxiang Luo, and Robert Lipsky for technical advice and assistance.

REFERENCES

1. Lovinger, D. M., White, G., and Weight, F. F. (1989) Science 243, 1721–1724
2. Lovinger, D. M., White, G., and Weight, F. F. (1990) J. Neurosci. 10, 1372–1379
3. Dildy, J. P., and Leslie, S. W. (1989) Brain Res. 499, 383–387
4. Hoffman, P. L., Moses, F., and Tabakoff, B. (1989) Neuropharmacology 28, 1239–1243
5. Hoffman, P. L., Rube, C. S., Moses, F., and Tabakoff, B. (1989) J. Neurochem. 55, 1937–1940
6. Göthert, M., and Fink, K. (1989) Naunyn-Schmiedeberg’s Arch. Pharmacol. 340, 516–521
7. Simon, P. E., Cisewski, H. E., Johnson, K. B., Hicks, R. E., and Breeze, G. R.

*Y. Honse and R. W. Peoples, unpublished observations.
Alcohol Action and NMDA Receptor M4 Domain

Peoples, R. W., and Stewart, R. R. (2000) Neuropharmacology 39, 1681–1691

Ren, H., Houe, Y., Karp, B. J., Lipsky, R. H., and Peoples, R. W. (2003) J. Biol. Chem. 278, 276–283

Zilberter, Y., Utsei, V., Sokolova, S., and Khodorov, B. (1991) Mol. Pharmacol. 40, 337–341

Hopp, T. P., and Woods, K. R. (1981) Proc. Natl. Acad. Sci. U. S. A. 78, 3824–3828

Krye, J., and Doolittle, R. F. (1982) J. Mol. Biol. 157, 105–132

Zimmerman, J. M., Eliezer, N., and Simha, R. (1968) J. Theor. Biol. 21, 170–201

Buller, A. L., Larson, H. C., Morrisett, R. A., and Monaghan, D. T. (1995) Mol. Pharmacol. 48, 717–723

Schorge, S., and Colquhoun, D. (2003) J. Neurosci. 23, 1151–1158

Masica, M. P., Trudell, J. R., and Harris, R. A. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 9305–9310

Jenkins, A., Greenblatt, E. P., Faulkner, H. J., Bertaccini, E., Light, A., Lin, A., Andreessen, A., Viner, A., Trudell, J. R., and Harrison, N. L. (2001) J. Neurosci. 21, 1–4

Fink, K., and Gobbert, M. (1990) Eur. J. Pharmacol. 191, 225–229

Gonzales, R. A., Westbrook, S. L., and Bridges, L. T. (1991) Neuropharmacology 30, 441–446

Peoples, R. W., and Weight, F. F. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 2925–2929

Peoples, R. W., and Ren, H. (2002) Mol. Pharmacol. 61, 169–176

Godden, E. L., Harris, R. A., and Dunwiddie, T. V. (2001) J. Pharmacol. Exp. Ther. 296, 716–722

Krasowski, M. D., Nishikawa, K., Nikolaeva, N., Lin, A., and Harrison, N. L. (2001) Neuropharmacology 41, 952–964

Scheller, M., and Forman, S. A. (2002) J. Neurosci. 22, 8411–8421
A Site of Alcohol Action in the Fourth Membrane-associated Domain of the N-Methyl-D-aspartate Receptor
Hong Ren, Yumiko Honse and Robert W. Peoples

J. Biol. Chem. 2003, 278:48815-48820.
doi: 10.1074/jbc.M302097200 originally published online September 23, 2003

Access the most updated version of this article at doi: 10.1074/jbc.M302097200

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC’s e-mail alerts

This article cites 38 references, 18 of which can be accessed free at
http://www.jbc.org/content/278/49/48815.full.html#ref-list-1