Stereoselectivity of Channel Inhibition by Secondary Alkanol Enantiomers at Nicotinic Acetylcholine Receptors

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Background: At the nicotinic acetylcholine receptor, long chain alkanols reduce, whereas short chain alkanols augment endplate currents. Using the enantiomers of five members of a homologous series of secondary alkanols (2-butanol through 2-octanol), we tested the hypothesis that these actions occur at a single hydrophobic site in the lumen of the channel. Small alkanols would bind to this site without blocking the channel, stabilizing the open state and enhancing the apparent affinity of the agonist for channel opening. Long chain alkanols would bind the same site and simply inhibit without affecting the agonist's apparent affinity.

Methods: Agonist-stimulated ⁸⁶Rb⁺ efflux from acetylcholine receptor-rich vesicles from Torpedo nobiliana was studied by adding agonist and allowing efflux to proceed for 10 s before termination by filtration.

Results: All of the 2-alkanols inhibited ⁸⁶Rb⁺ efflux elicited by a maximally stimulating concentration of agonist. Inhibitory potency increased logarithmically with the number of carbon atoms in the hydrocarbon chain of the alkanol. The inhibitory potency of the enantiomers of 2-butanol differed twofold, but the other enantiomers exhibited no stereoselectivity. The enantiomers of 2-octanol caused a concentration-dependent depression of carbamylcholine-stimulated ⁸⁶Rb⁺ efflux without significantly altering the agonist's apparent dissociation constant. In contrast, the enantiomers of 2-butanol caused: (1) a nonstereoselective decrease in carbamylcholine's apparent dissociation constant and (2) the expected stereoselective decrease in maximal carbamylcholine-stimulated ⁸⁶Rb⁺ efflux.

Conclusions: The alkanol site that modulates the apparent agonist affinity for channel opening is distinct from the site that results in inhibition of cation flux through the channel. (Key words: Receptors; acetylcholine. Stereoselectivity; secondary alcohols.)

ALKANOLS, as a class of compounds, exert a variety of effects on excitable membranes and on synaptic transmission. Both short and long chain alkanols are capable of inducing general anesthesia.¹ ² However, their effects on postsynaptic membranes differ in that long chain alkanols reduce,³ whereas the short chain alkanols augment, neuromuscular endplate currents.⁴ At postsynaptic nicotinic acetylcholine receptor (AcChR)-rich membranes, pentanol and longer alkanols simply inhibit the channel in an insurmountable fashion; methanol and ethanol shift the agonist concentration response curve to the left without inhibiting; and intermediate length alkanols exhibit both effects.⁵ ⁷

It has been proposed that the site of action of the 1-alkanols at AcChR is a "hydrophobic patch" within the ion channel⁸ and that both short and long chain alkanols act at this site to produce channel inhibition and changes in agonist affinity. In this model, the short chain alkanols bind to the hydrophobic patch without blocking the channel because of their small size.⁹ In an alternative proposal, the sites of action that mediate alterations in agonist affinity and channel inhibition are different, thus explaining the different actions of the short and long chain alkanols.⁹

One strategy for obtaining more information on the nature of the sites of actions of short and long chain alkanols is to study the effects of optical isomers of secondary alkanols on AcChR function. Whereas the pharmacologic actions of 1-alkanols on AcChR-rich membranes were examined in detail recently,⁷ the pharmacology of the secondary alkanols has not been explored. Accordingly, we studied the effects of a homologous series of optical isomers of secondary alkanols on postsynaptic membranes containing AcChR,
isolated from *Torpedo nobiliana*, with the objective of using stereoselectivity to distinguish between the one- or two-site model.

**Methods and Materials**

Electric organs from freshly killed *T. nobiliana* (Biofish, Georgetown, MA) were homogenized, and AcChoR-rich membranes were isolated by differential and sucrose density centrifugation as previously described. Membranes were suspended in *Torpedo* physiologic saline (250 mM NaCl, 5 mM KCl, 3 mM CaCl<sub>2</sub>, 2 mM MgCl<sub>2</sub>, 5 mM Na<sub>2</sub>HPO<sub>4</sub>, 0.02% NaN<sub>3</sub>, pH 7.0) Purified membranes typically contained between 0.5 and 1.5 µM [³H]-acetylcholine sites per gram of protein. [³H]-Acetylcholine binding sites were measured as previously described. Protein concentrations were determined by the method of Lowry using bovine serum albumin as a standard. The membranes were stored under liquid nitrogen until used.

**Agonist-induced Flux Assay**

Agonist-stimulated <sup>86</sup>Rb<sup>+</sup> efflux from sealed AcChoR-containing vesicles was measured after a 10-s exposure to agonist as follows. Vesicles were incubated overnight (4°C) with <sup>86</sup>RbCl (100–200 µCi/ml; Amersham, Arlington Heights, IL) and stoichiometric amounts of α-bungarotoxin (Sigma Chemical, St. Louis, MO) to remove spare receptors, which must be removed to prevent the vesicles from emptying before termination of the assay. Provided the vesicles do not empty and sufficient response remains for accurate determination, the exact amount of α-bungarotoxin can be varied between experiments without changing the resultant inhibition constants (IC<sub>50</sub>; fig. 3).

Extravesicular <sup>86</sup>Rb<sup>+</sup> was removed by exclusion chromatography (Sephadex G-50, Pharmacia, Piscataway, NJ, 0.5 cm × 20 cm). Vesicles were equilibrated for 20 min and then rapidly passed over a cation exchange column (Dowex 50W, Bio-Rad, Richmond, CA, 20–50 mesh) to remove extravesicular <sup>86</sup>Rb<sup>+</sup> from rapidly leaking vesicles. Efflux experiments were performed by adding an aliquot of vesicles loaded with <sup>86</sup>Rb<sup>+</sup> to a test tube containing *Torpedo* physiologic saline, with or without 5 mM carbamylcholine (Sigma) and/or alkanol, and vortexing the mixture. After 10 s, the contents of the test tube (1 ml) were filtered (Whatman GF/F, Whatman International, Maidstone, England) through a vacuum manifold (Millipore, Bedford, MA). The filtrate (0.5 ml) was added to liquid scintillation cocktail (Poly-fluor, Packard, Downers Grove, IL) and counted (Tri-carb Liquid Scintillation Counter, Packard).

Carbamylcholine-stimulated efflux was corrected for a slow time-dependent leakage of <sup>86</sup>Rb<sup>+</sup> from sealed vesicles that was linear over 45 min, during which the percentage of external counts doubled. The percentage of external counts initially was 20–25% and an experiment took 15–20 min. Passive release of <sup>86</sup>Rb<sup>+</sup> was fitted as a function of time by linear regression analysis to obtain an estimate of the leak at a given time. Total counts were measured in the unfiltered vesicle suspension. Agonist-stimulated, time-independent efflux (*F<sub>A</sub>*) is reported as the percentage of agonist-released <sup>86</sup>Rb<sup>+</sup> counts:

$$F_A = \frac{cpm(Ag,t) - cpm(leak,t)}{cpm(total) - cpm(leak,t)} \times 100,$$

where cpm(*Ag*,t) is carbamylcholine-stimulated efflux of <sup>86</sup>Rb<sup>+</sup> at time *t*, cpm(*leak*,t) is an estimate of the leak at a given time, and cpm(total) is the total count.

When alkanols were present, their effect on the passive release of <sup>86</sup>Rb<sup>+</sup> was ascertained. The degree of inhibition as a function of alkanol concentration was fitted to a logistic function using a nonlinear least squares fitting routine. Concentrations that produced 50% inhibition of agonist-stimulated <sup>86</sup>Rb<sup>+</sup> efflux (IC<sub>50</sub>) were determined. The estimated variance in the IC<sub>50</sub> for each isomeric pair was calculated from the standard error; the sum of these yielded the estimated variance of the difference in the IC<sub>50</sub> between the (+) and (−) isomers. The ratio of this difference to its standard error was referred to a standard normal distribution. The problem of multiplicity in comparing the slopes of the log concentration-inhibition curve was addressed using Bonferroni correction to maintain the overall significance level at 0.05.

To determine whether the anesthetic alcohols inhibited agonist-stimulated efflux or merely altered the apparent affinity of the agonist for its binding site, carbamylcholine concentration-response curves (concentration range 0.1 µM–0.05 M) were determined in the presence and absence of alkanols. These curves were fitted by nonlinear least squares to a logistic function to yield the concentration of carbamylcholine causing half maximal response (EC<sub>50</sub>) and the Hill coefficient (*n*<sub>H</sub>). Optical isomers of secondary alcohols (Norse Laboratories, Newbury Park, CA) had chemical purity greater than 98%, which was confirmed in our laboratory by gas chromatography (Beckman GC72, Pora-
pak "P" column packing, Waters, Milford, MA; column temperatures 120–215°C). Optical purity, which was determined by optical rotatory dispersion by the manufacturer for each numbered batch, was greater than 96%. Racemic 2-butanol was purchased from Sigma. Fresh solutions of alkanol were prepared daily by vortexing weighed aliquots of the isomers of each compound in *Torpedo* physiologic saline at 4°C for up to 10 min.

**Results**

All secondary alkanol isomers inhibited agonist-stimulated $^{86}$Rb$^+$ efflux in a concentration-dependent manner. Log [alkanol]-inhibition curves were sigmoidal and steep (figs. 1a and 1b) with $n_H$ ranging between 1.3 and 2.0 for individual experiments. These slopes were not statistically different from each other ($P > 0.2$), and therefore, the IC$_{50s}$ provide a satisfactory measure of relative potency.

The half inhibitory concentrations (IC$_{50s}$) and their standard deviations are shown in table 1. The (+) isomer of 2-butanol was approximately twice as potent as the (−) isomer ($P < 0.05$), whereas the racemate had a potency that was intermediate to that of the (+) and (−) isomers. In contrast to this, there was no significant difference in the IC$_{50s}$ between any other pair of isomers.

Stereoactivity can be expressed as a ratio of potencies for members of each pair of enantiomers.$^{15}$ In the present study, potency ratios for channel inhibition calculated as (−)-IC$_{50}$/(+)-IC$_{50}$ for paired experiments, each performed simultaneously on a single vesicle preparation, were averaged, and are shown in table 1. Only the potency ratio for the 2-butenols significantly differed from unity ($P < 0.01$).

There was a systematic increase in potency in the series from 2-butanol through 2-octanol, such that the enantiomers of 2-octanol were about 900 times more potent in inhibiting the channel than was (+)-2-butanol and about 1,800 times more potent than (−)-2-butanol. The addition of each methylene group resulted in an approximately fivefold increase in potency. The relationship between potency and the number of carbon atoms in the hydrocarbon chain of the alkanol was logarithmic, such that a linear least-squares fit of log [(+)-IC$_{50}$] versus chain length produced a slope of $-0.74 \pm 0.013$ and a correlation coefficient of 0.9996 (fig. 2). The relationship between log [(-)-IC$_{50}$] and chain length (excluding the IC$_{50}$ value of (−)-2-butanol) was obtained with a linear least squares fit and produced a line that had a slope of $-0.71 \pm 0.045$ and a correlation coefficient of 0.9995. These two relationships predict IC$_{50}$ values for (−)-2-butanol of 72 and 58 nm, respectively. Thus, it is apparent that (−)-2-butanol is less potent than predicted, and (+)-2-butanol has the expected potency. Therefore, the observed deviation

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**Fig. 1.** Typical concentration-inhibition curves of $^{86}$Rb$^+$ efflux from AcChoR-rich vesicles from *Torpedo* stimulated by 5 μm carbachololine. (A) The effect of (+)- and (−)-2-butanol. The (+)-enantiomer is represented by X and a dashed line while the (−) enantiomer is represented by O and a solid line. Each point is the average of duplicate determinations during a single experiment. Curves were fitted as described in Methods and Materials. For this experiment, the IC$_{50}$ (±SE) for (+)-2-butanol is $83 \pm 4.1$ nm with $n_H$ of 1.9 ± 0.19, while the IC$_{50}$ for (−)-2-butanol is $166 \pm 23$ nm with $n_H$ of 1.9 ± 0.35. (B) The effect of (+)- and (−)-2-octanol. The enantiomers are distinguished as above. For this experiment, the IC$_{50}$ (±SE) for (+)-2-octanol is $86 \pm 6.3$ μm with $n_H$ of 1.3 ± 0.12, and the IC$_{50}$ for (−)-2-octanol is $71 \pm 5$ μm with $n_H$ of 1.7 ± 0.18.
Table 1. Inhibitory Potencies of Enantiomers of Secondary Alkanols on Carbachol-stimulated Cation Flux from Acetylcholine Receptor-rich Vesicles

<table>
<thead>
<tr>
<th>Alkanol</th>
<th>n</th>
<th>IC₅₀ (mM)</th>
<th>n₁</th>
<th>Potency Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-2-Butanol</td>
<td>5</td>
<td>147 ± 17.2</td>
<td>1.7 ± 0.46</td>
<td>2.04 ± 0.33†</td>
</tr>
<tr>
<td>(+)-2-Butanol</td>
<td>5</td>
<td>72 ± 14.3</td>
<td>1.6 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>(-)-2-Pentanol</td>
<td>3</td>
<td>10.9 ± 0.93</td>
<td>1.4 ± 0.15</td>
<td>0.79 ± 0.68</td>
</tr>
<tr>
<td>(+)-2-Pentanol</td>
<td>3</td>
<td>14 ± 2.5</td>
<td>1.6 ± 0.51</td>
<td></td>
</tr>
<tr>
<td>(-)-2-Hexanol</td>
<td>3</td>
<td>2.3 ± 0.26</td>
<td>1.7 ± 0.05</td>
<td>1.10 ± 0.22</td>
</tr>
<tr>
<td>(+)-2-Hexanol</td>
<td>3</td>
<td>2.1 ± 0.35</td>
<td>1.7 ± 0.32</td>
<td></td>
</tr>
<tr>
<td>(-)-2-Heptanol</td>
<td>3</td>
<td>0.48 ± 0.078</td>
<td>1.8 ± 0.12</td>
<td>1.04 ± 0.24</td>
</tr>
<tr>
<td>(+)-2-Heptanol</td>
<td>3</td>
<td>0.46 ± 0.075</td>
<td>1.6 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>(-)-2-Octanol</td>
<td>4</td>
<td>0.082 ± 0.015</td>
<td>1.4 ± 0.41</td>
<td>1.03 ± 0.25</td>
</tr>
<tr>
<td>(+)-2-Octanol</td>
<td>4</td>
<td>0.080 ± 0.013</td>
<td>1.2 ± 0.21</td>
<td></td>
</tr>
</tbody>
</table>

n = number of paired determinations of the IC₅₀; n₁ = Hill coefficient. The IC₅₀ are the mean ± SD of these n individual determinations. Paired experiments were performed simultaneously on a single vesicle preparation.

* Mean ± SD of ratios of (−)-IC₅₀/(+)IC₅₀ from individual paired determinations.
† The ratio is significantly different from unity, P < 0.05.

of the IC₅₀ for (−)-2-butanol from its predicted value cannot be attributed to a more potent contaminant.

To quantify stereoselective effects on the apparent affinity of carbachol for receptor sites, the effects of fixed concentrations of the enantiomers of 2-octanol and 2-butanol on carbachol concentration-flux curves were studied. In these experiments, to maintain sufficient stimulated ⁶⁸Rb⁺ efflux, less α-bungarotoxin was used than in the concentration-inhibition experiments. Thus, an IC₅₀ concentration of an alkanol appears not to produce 50% inhibition when compared to the control because fewer of the receptors are blocked with α-bungarotoxin (figs. 3 and 4). This will not affect the value of C₅₀ as long as the maximal flux response is well below 100%. Either the 2-octanol enantiomers caused significant change in the C₅₀ for carbachol (fig. 3). In contrast, both enantiomers of 2-butanol resulted in a significant alteration of the carbachol concentration-response curve such that the C₅₀ was decreased by a factor of approximately three (fig. 4). The experiment was repeated in quadruplicate, and the mean value of C₅₀ for carbachol was reduced from 74 ± 17 μM to 29 ± 5 μM and 33 ± 11 μM for the (−) and (+) isomers, respectively, at a concentration of 70 mM. Thus, this effect is nonstereoselective as both enantiomers are equally effective at shifting C₅₀ to lower values. Furthermore, no difference was seen when the ratios of the C₅₀s, obtained from individual paired experiments with the enantiomers, were compared (P < 0.01). The maxi-

![Fig. 2. Relationship between log IC₅₀ and the number of carbon atoms in the secondary alkanol enantiomers. (+)-Enantiomers are represented by X and (−)-enantiomers are represented by O. The results of the (+)- and (−)-enantiomers were analyzed separately by linear regression analysis. In the case of the (−)-enantiomers, 2-butanol was excluded from the linear regression analysis. The equations for the graphs are y = (−0.71 ± 0.016)X + 4.58 ± 0.510 for the (−)-enantiomers (solid line) and y = (−0.74 ± 0.012)X + 4.81 ± 0.076 for the (+)-enantiomers (dashed line).](image)

![Fig. 3. Effect of enantiomers of 2-octanol on the carbachol concentration-response relationship. The uppermost curve (open triangles) is the control carbachol concentration-response relationship. X and O represent the percentage of maximal flux responses obtained in the presence of (+)- and (−)-2-octanol, respectively. Upper curve, 80 μM; lower curve, 140 μM. The concentration-response curves shown were obtained by fitting data from the (+)- and (−)-enantiomers. The C₅₀ (±SE) of the control curve was 91 ± 7 μM, and those in the presence of alkanols did not differ significantly from this value (P > 0.05). The alkanol samples were pre-blocked with less α-bungarotoxin than the controls to increase the maximum observed flux and enhance the accuracy with which C₅₀ may be determined (see Methods and Materials).](image)
Fig. 4. Effect of enantiomers of 2-butanol on the carbachol concentration-response relationship. The uppermost curve (open triangles) is the control carbachol concentration-response relationship. X and O represent the percentage of maximal flux responses obtained in the presence of 70 mM (+)- and (−)-2-butanol, respectively. The $C_{50}$ (±SE) of the control curve was 92 ± 10 µM, significantly higher than that for (−)-butanol (31 ± 2 µM) and (+)-2-butanol (25 ± 2 µM). The alkanol samples were preblocked with less α-bungarotoxin than the controls to increase the maximum observed flux.

maximum flux achieved in the presence of the (−)-2-butanol was, however, always greater than that in the presence of (+)-2-butanol ($P < 0.01$). $n_{ii}$ ranged from 1.5 to 1.25 and did not differ significantly.

Discussion

Do Alkanols Act at One or Two Sites?

As discussed, 1-alkanols exert two actions on the ion channel activated by acetylcholine. The short chain alkanols augment agonist affinity without inhibiting the channel, whereas the longer chain alkanols inhibit the channel in an insurmountable fashion. Intermediate chain length 1-alkanols (propanol and butanol) exhibit both effects. The results presented here show that 2-alkanols also exhibit both effects, although a pure affinity augmenting effect was not observed. The main aim of this work was to use stereoselectivity as a probe of the underlying mechanism(s) of these effects.

Results for the 1-alkanols have been subjected to at least two different mechanistic interpretations. One is that the alkanols could bind to a single hydrophobic site within the ion channel. The short chain alkanols could bind to this site either without occluding or only partially occluding the channel, but in either case, stabilize the open state, resulting in an increase in apparent affinity for the agonist. The longer chain alkanols, in contrast, could bind to the same site but would be of sufficient size to block the channel. Alternatively, separate sites could be involved in mediating these different effects. That is, the enhancement of agonist affinity could be mediated through a site separate and distinct from the site of channel inhibition.

Our present findings, that the enantiomers of 2-butanol cause a weak stereoselective channel inhibition but that they nonstereoselectively decrease the apparent affinity of the agonist, suggest a dual- rather than a single-site model. A two-site model also was proposed in a study of the 1-alkanols, based on the observation that their potency for altering the $C_{50}$ of an agonist had a shallower dependence on acyl chain length than that for channel inhibition.

What Is the Nature of the Alkanol Sites?

The stereoselectivity of the ion channel inhibition site suggests that it involves a more specific interaction with the alkanol than does the site responsible for alterations in agonist affinity. That is, the former site must interact with 2-butanol through three points of attachment. One possible explanation for the lack of stereoselective inhibition with the more potent longer chain enantiomeric pairs is that these three points of attachment consist of the ethyl, hydroxyl, and hydrogen moieties rather than the methyl, hydroxyl, and acyl chain groups and that there exists a high degree of specificity for the ethyl group. An alternative explanation is that the site of inhibition for the 2-butanol differs from that of the other secondary alkanols studied, but this seems improbable.

That the site of channel inhibition is stereoselective suggests that it is on a protein, although an action on lipids cannot be ruled out. Both the glycerol backbone of the phospholipids and the ring system of cholesterol are chiral, and there are a number of examples of weakly stereoselective drug interactions with lipid bilayers. For example, adsorption of morphine to phosphatidylinerine bilayers is stereoselective, and the enantiomers of $\Delta^1$-tetrahydrocannabinol selectively disorder spin-labeled lecithin/cholesterol liposomes.

That the site involved in alteration of the $C_{50}$ of the agonist is nonstereoselective reveals little. Although the core of the lipid bilayer is an attractive prospect for this nonselective site, this site also might be a nonselective protein site, because small optically active molecules can interact nonselectively with proteins.
STEREOSELECTIVITY OF SECONDARY ALKANOLS

For example, enantiomers of halothane induce conformational changes in hemoglobin nonstereospecifically. Thus, lack of stereoselectivity per se does not discriminate between protein versus lipid sites.

It should be kept in mind that studies, such as the current one, which use integrated flux measurements, do not distinguish at which kinetic step, or steps, these agents produce inhibition. More detailed kinetic studies will be required before a complete description may be obtained. Nonetheless, the IC₅₀ determined to date has proved reliable.

Stereoselective Inhibition

While many different pairs of enantiomers have been examined with respect to their effects at the postsynaptic AcChoR, stereoselective inhibition of channel activation is uncommon. In addition to our present results with 2-butanol, the enantiomers of pentobarbital demonstrate weak stereoselective inhibition of carbamylcholine-stimulated cation efflux with the (+)-enantio-

mer being 1.2–1.5 times more potent than its counterpart. Swanson et al. demonstrated stereoselective ion channel inhibition of AcChoR for the (+) and (−) isomers of N-methylcotinol using a patch clamping technique. (+)- and (−)-nicotine activate single channel currents and induce slow desensitization stereoselectively, although they are equipotent as ion-channel inhibitors. To our knowledge, there are no other known examples of stereoselective inhibition of AcChoR. For example, the enantiomers of chloramphenicol inhibit the acetylcholine gated ion channel from the motor end-plate of _Tobomphis sirtalis_ nonster-

eselectively. Likewise, the enantiomers of perhydrosodicotoxin are nonstereoselective in their in-

hibition of end-plate channels.

Another unusual facet of our finding of weak stereoselective channel inhibition by enantiomers of 2-butanol, but not 2-octanol, is that stereoselectivity is often a function of the potency of the ligand. For example, horse liver alcohol dehydrogenase does not show stereoselectivity in the metabolism of the isomers of 2-butanol, but the enzyme is stereoselective for 2-octanol, which has a higher apparent affinity. However, if an ethyl group is required as one point of attachment for channel inhibition, as suggested above, this anomaly would be rationalized.

Comparison with General Anesthesia

Previous studies have questioned the relationship between inhibition of the acetylcholine receptor's channel and general anesthesia on the basis that the normal alkanol chain length dependence of channel inhibitory potency is steeper than that for general anesthetic potency. The present study supports this conclusion in two ways. First, an examination of the dependence of the logarithm of IC₅₀ on acyl chain length for the secondary alkanols has a slope of 0.73 ± 0.010 (excluding (−)-2-butanol; fig. 2), whereas the slope of a similar plot of the anesthetic potency of the secondary alkanols in tadpoles is only 0.60 ± 0.013. Thus, the general anesthetic concentration for the 2-

butanols is 17 mm, four to nine times lower than for channel inhibition, while for the 2-octanols general anesthetic potency differs little from that for channel inhibition. Second, the weak stereoselectivity of the 2-

butanol enantiomers for channel inhibition is absent in general anesthesia. Thus, while some anesthetics act on the acetylcholine-activated channel at clinically relevant concentrations, the channel's pharmacology suggests it is not involved in causing general anesthesia. On this receptor, the desensitizing actions of general anesthetics have a better claim. Whether the channels of other members of the superfamily will prove so selective remains to be seen.

The enantiomers of secondary alkanols all inhibited agonist-stimulated efflux from nicotinic acetylcholine channels. In contrast to all the other agents, the enantiomers of 2-butanol demonstrated weak stereoselectivity with respect to channel inhibition. In addition, the enantiomers of 2-butanol caused a twofold enhancement of apparent agonist affinity for opening the channel; however, this effect was not stereoselective. These results suggest that the site of action for modulation of apparent agonist affinity is distinct from the site for channel inhibition. The weak stereoselectivity of channel inhibition by the enantiomers of 2-butanol is in direct contrast to the general anesthetic effects in vivo where no stereoselectivity is observed.

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