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Droperidol Inhibits $GABA_A$ and Neuronal Nicotinic Receptor Activation

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Background: **Droperidol is used in neuroleptanesthesia and as an antiemetic. Although its antiemetic effect is thought to be caused by dopaminergic inhibition, the mechanism of droperidol's anesthetic action is unknown. Because γ-aminobutyric acid type A ($GABA_A$) and neuronal nicotinic acetylcholine receptors (nAChRs) have been implicated as putative targets of other general anesthetic drugs, the authors tested the ability of droperidol to modulate these receptors.**

Methods: **γ-Aminobutyric acid type A $\alpha_1\beta_1\gamma_2$ receptor, α_7 and $\alpha_4\beta_2$ nAChRs were expressed in *Xenopus* oocytes and studied with two-electrode voltage clamp recording. The authors tested the ability of droperidol at concentrations from 1 nM to 100 μM to modulate activation of these receptors by their native agonists.**

Results: **Droperidol inhibited the GABA response by a maximum of 24.7 ± 3.0%. The IC_{50} for inhibition was 12.6 ± 0.47 nM droperidol. At high concentrations, droperidol (100 μM) activates the $GABA_A$ receptor in the absence of GABA. Inhibition of the GABA response is significantly greater at hyperpolarized membrane potentials. The activation of the α_7 nAChR is also inhibited by droperidol, with an IC_{50} of 5.8 ± 0.53 μM. The Hill coefficient is 0.95 ± 0.1. Inhibition is noncompetitive, and membrane voltage dependence is insignificant.**

Conclusions: **Droperidol inhibits activation of both the $GABA_A$ $\alpha_1\beta_1\gamma_2$ and α_7 nAChR. The submaximal GABA inhibition occurs within a concentration range such that it might be responsible for the anxiety, dysphoria, and restlessness that limit the clinical utility of high-dose droperidol anesthesia. Inhibition of the α_7 nAChR might be responsible for the anesthetic action of droperidol.**

LABORIT and Huguenard[1] pioneered neuroleptanesthesia in the 1950s in an attempt to produce "artificial hibernation" that did not cause circulatory and respiratory depression. Droperidol is a buterophenone derivative synthesized by Jansen that is used in combination with fentanyl for neuroleptanesthesia. It has both anesthetic and antiemetic properties. At droperidol concentrations used for anesthesia (0.125 mg/kg), plasma concentration reaches a peak of 2 μM.[2] When 90% protein binding is taken into account, free plasma concentration of droperidol during surgical conditions is approximately 0.2 μM.[3] The antiemetic effects of droperidol occur at low nanomolar concentrations and are thought to be caused by dopaminergic antagonism.[4]

The mechanism by which droperidol causes anesthesia is unknown. One hypothesis is that general anesthetics act to inhibit synaptic transmission by modulating ligand-gated ion channels.[5] γ-Aminobutyric acid type A ($GABA_A$) receptors and neuronal nicotinic acetylcholine receptors (nAChRs) have been implicated in the mechanism of action of both intravenous and gaseous general anesthetics.[5,6] Every general anesthetic used today modulates the $GABA_A$ or nAChR within its clinically relevant concentration range. Volatile anesthetics inhibit heteromeric nAChRs more potently than homomeric receptors composed of the α_7 subunit,[7,8] whereas thiopental and ketamine inhibit both types of nAChRs approximately equipotently.[9–15] Modulation of $GABA_A$ receptors by general anesthetics is not particularly dependent on subunit composition.[16] As such, we tested the rat $\alpha_1\beta_1\gamma_2$ $GABA_A$ receptor and the human α_7 and $\alpha_4\beta_2$ nAChRs, expressed in *Xenopus* oocytes, for modulation by droperidol.

Methods

Molecular Biology

The expression vectors for receptor subtype cDNAs were as follows: pSP64 for the human α_4 and β_2 type nAChR, pMXT for the α_7 type nAChR, pGEMHE for the rat GABA α_1 and γ_2, and pGEMVE for the rat GABA β_1. The restriction enzymes used to linearize the plasmids were *XbaI* for the α_7-type nAChR, *AseI* for the α_4 nAChR, *PvuII* for the β_2 nAChR, and *nhe1* for all of the $GABA_A$ subunits. Using a standard protocol, the SP6 RNA polymerase was used to make cRNA from the nACh subunits, and the T7 RNA polymerase was used to make cRNA from the $GABA_A$ subunits.

Oocyte Extraction and Injection

Xenopus laevis oocytes were extracted from anesthetized females and placed in ND-96 medium (96 mM NaCl, 2 mM KCl, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$ H_2O, 5 mM HEPES, 2.5 mM Na-pyruvate, 0.5 mM theophylline, and 10 mg/l gentamicin, adjusted to pH 7.5). The oocyte clusters were incubated in 0.2% collagenase (type IA, Sigma-Aldrich, St. Louis, MO) in ND-96 medium for defolliculation. Oocytes were agitated at 18.5°C for 4 h and afterward were rinsed with Barth medium (88 mM NaCl, 1 mM KCl, 2.4 mM $NaHCO_3$, 15 mM HEPES, pH 7.6). The oocytes were left to recover for 24 h in L-15 oocyte medium (Specialty Media, Phillipsburg, NJ) before injection of cRNA. L-15 oocyte media was obtained from Specialty Media.

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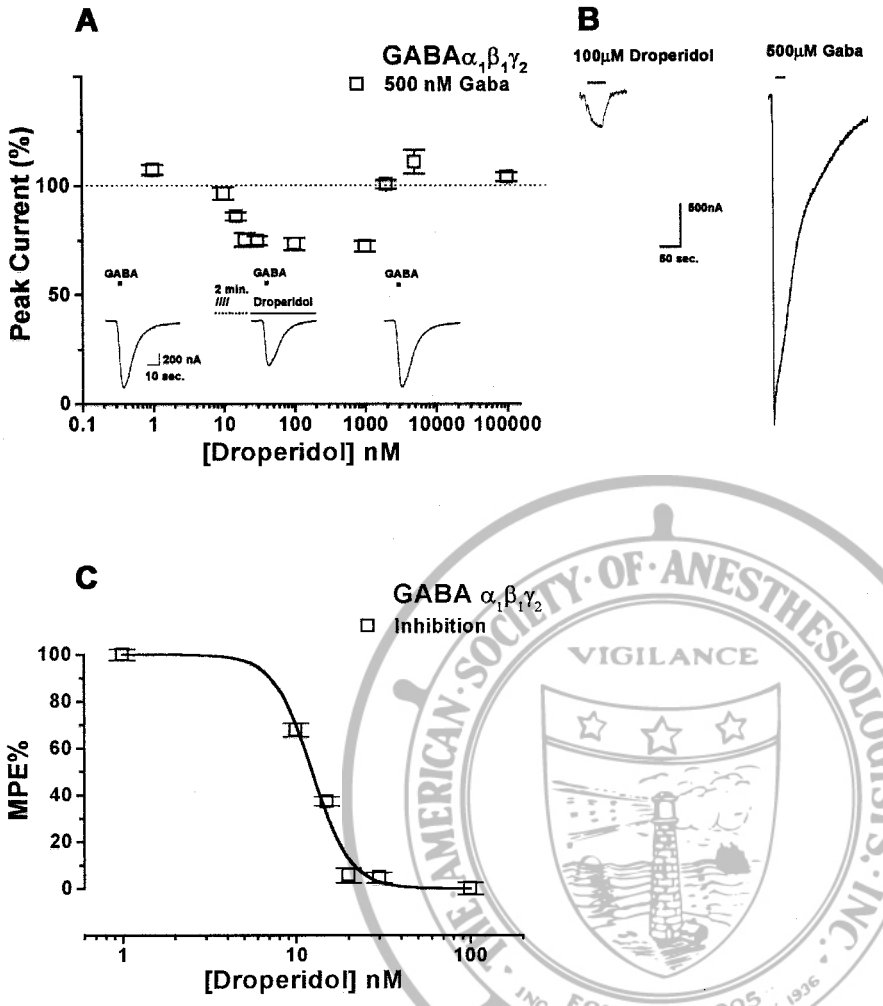

Fig. 1. Droperidol causes biphasic response in the rat γ-aminobutyric acid type A ($GABA_A$) $\alpha_1\beta_1\gamma_2$. Additionally, droperidol activates the $GABA_A$ receptor alone at high concentrations. (*A*) Concentration–response curve for droperidol in the presence of 500 nM GABA ($GABA\ EC_{20}$). Inhibition occurs between concentrations of 10 nM and 1 μM droperidol, (number of oocytes for each data point, n = 5–12). (*Insert*) A current activated by 500 nM GABA before (*left*), with 100 nM droperidol (*middle*), and after droperidol washout (*right*). (*B*) $GABA_A$ $\alpha_1\beta_1\gamma_2$ current trace activated by 100 μM droperidol alone (*left*) and by saturating GABA (500 μM) (*right*). (*C*) The inhibitory portion of the concentration–response curve for droperidol in the $GABA_A$ $\alpha_1\beta_1\gamma_2$ receptor, plotted as maximal possible effect (MPE). Low concentrations of droperidol inhibits a current response activated by 500 nM GABA. IC_{50} is 12.6 ± 0.5 nM with a Hill coefficient of 4 ± 0.57.

Approximately 10 ng of α_7 nAChR cRNA, 10 ng of a 1:1 ratio of α_4 to β_2 nAChR cRNA, or 10 ng of a 1:1:1 ratio of α_1 to β_1 to γ_2 GABA cRNA were injected into individual oocytes in volumes of approximately 100 nl using an automatic injector (Nanoject; Drummond Scientific, Broomall, PA). The oocytes were incubated at 17°C for 2–5 days in ND-96 medium before electrophysiologic recording.

Electrophysiology

Current recordings were made from whole oocytes at room temperature (19–23°C) using a Gene-Clamp 500 two-microelectrode voltage clamp amplifier with an active ground circuit (Axon Instruments, Inc., Foster City, CA). The recording electrodes were pulled from glass capillary tubing (Drummond) to obtain a resistance between 1 and 5 MΩ and then filled with 3 M KCl. The Ringer solution (115 mM NaCl, 2.5 mM KCl, 1.8 mM $BaCl_2$, 10 mM HEPES, 1 μM atropine, pH 7.4) used for recordings contained atropine to prevent muscarinic receptor stimulation and barium in place of calcium to avoid current amplification by calcium-activated chloride currents. Oocytes were clamped at a holding potential of −60 mV unless otherwise indicated and held in a 125-μl cylindrical channel. Perfusion was applied at a flow rate of 4 ml/min.

γ-Aminobutyric acid, acetylcholine, and other chemicals used were obtained from Sigma-Aldrich (St. Louis, MO). Droperidol was obtained from Abbott Laboratories (North Chicago, IL). Droperidol was made as a stock solution and serially diluted to the appropriate concentration on the day of the experiment. A saturating concentration of 1 mM acetylcholine was used in all experiments with α_7 and $\alpha_4\beta_2$ nAChRs unless otherwise indicated. A concentration of GABA that was approximately EC_{20} (500 nM GABA) was used in all experiments for the $GABA_A$ $\alpha_1\beta_1\gamma_2$ receptor, unless otherwise noted. The oocytes were preequilibrated with droperidol for 2 min before a 2-s coapplication with the agonist. Activation reached its peak during agonist application. To minimize the contribution of nAChR desensitization, 5 min passed between acetylcholine applications. Three minutes passed between GABA applications. Using these time intervals, steady state recordings could be obtained in control experiments. A baseline control response to the agonist was measured before and after each agonist–

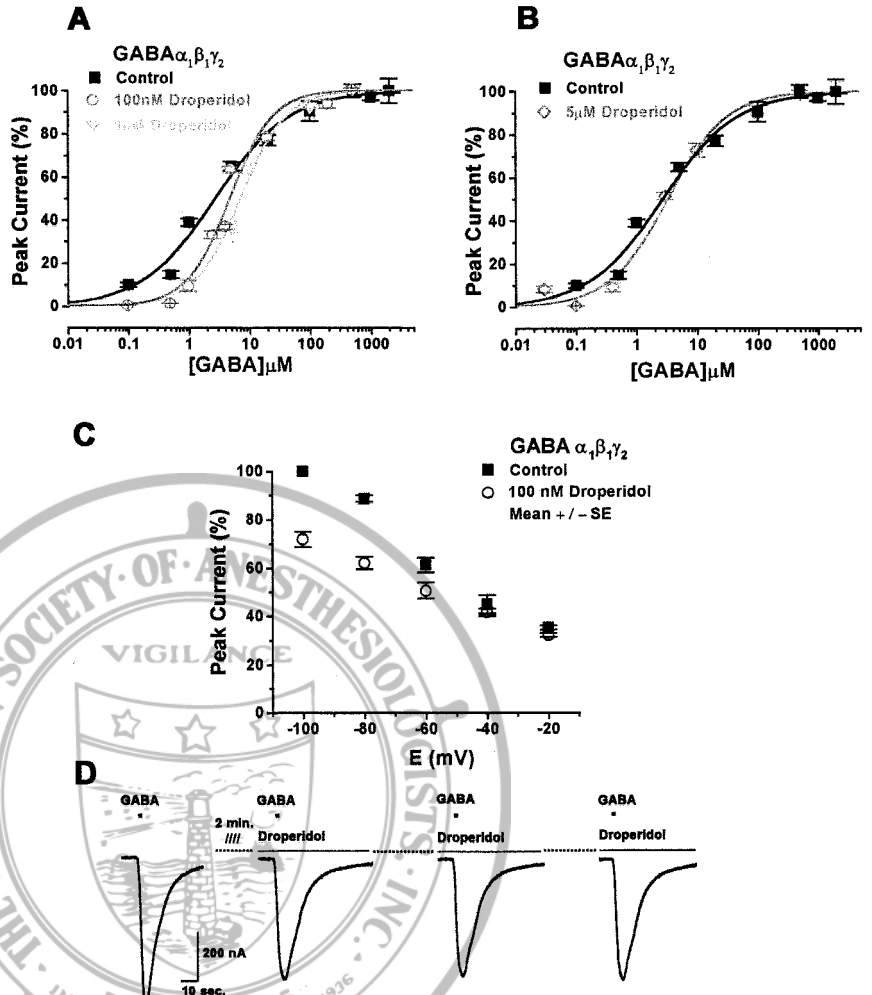

Fig. 2. Droperidol inhibition and voltage dependence of γ-aminobutyric acid type A ($GABA_A$) responses. (*A*) A dose–response curve for the activation by GABA of the rat $GABA_A$ $\alpha_1\beta_1\gamma_2$ receptor in the absence and presence of two inhibitory concentrations of droperidol (1 μM or 100 nM). Membrane potential was held at −60 mV (n = 5–13). For the control curve, GABA EC_{50} is 2.6 ± 0.7 μM, and the Hill coefficient is 0.7 ± 0.1. In the presence of 100 nM droperidol, the GABA EC_{50} is increased to 4.9 ± 0.6 μM, and the Hill coefficient is increased to 1.2 ± 0.2. In the presence of 1 μM droperidol, the GABA EC_{50} is further increased to 7.1 ± 0.6 μM, and the Hill coefficient is 1.2 ± 0.1. (*B*) A dose–response curve for GABA activation in the absence and presence of droperidol at a concentration at which inhibition is relieved (5 μM). The control values are as in (*A*). In the presence of 5 μM droperidol, GABA EC_{50} is 3.3 ± 0.5 μM, and the Hill coefficient is 0.9 ± 0.1. Membrane potential was held at −60 mV (n = 7–11). (*C*) Voltage–response relation for the $GABA_A$ receptor activated by 500 nM GABA in the presence and absence of 100 nM droperidol. All values are normalized to the maximal mean control response (−100 mV). Points are mean ± SE (n = 5–7). (*D*) Repeated application of 0.5 μM GABA in the continued presence of 300 nM droperidol did not result in significantly increased inhibition.

antagonist coapplication. Responses that did not return to within 80% of baseline values were rejected for analysis. Clampex 7 (Axon Instruments, Inc.) was used for data acquisition, and Microcal Origin 5.0 (Microcal, Northampton, MA) was used for graphics and statistical calculation.

Statistical Analysis

Concentration–response curves for acetylcholine and GABA were fitted to a modified Hill equation:

$$y = y_{max}\, x^n/(EC_{50}{}^n + x^n),$$

where IC_{50} is the concentration of agonist that elicited 50% of the maximal response, y_{max} is the maximal current elicited by the agonist, n is the Hill coefficient, and x is the concentration of agonist. Concentration–response relations for the inhibition were constructed by calculating the current recorded in the presence of antagonist as a percentage of that elicited by the agonist alone. Agonist dose–response curves were normalized to a saturating concentration of agonist, 1 mM acetylcholine or 500 μM GABA, in the absence of droperidol. The data points obtained at each antagonist concentration were averaged, and the calculated mean and SE were fit to a modified Hill equation:

$$y = y_{max}/(1 + (x/IC_{50})^n$$

where IC_{50} is the concentration of antagonist at which 50% of the response is inhibited, and x and n have the same meanings as above. In studies with multiple agonist applications, the peak current after the first agonist application was compared with that resulting from further applications of agonist with a Student *t* test. A Woodhull analysis was performed where the mean current inhibition was plotted on a semilogarithmic scale *versus* membrane potential and fit with a linear equation. The resulting equation was compared with the fit equation with a zero slope with an analysis of variance.[17,18] $P < 0.05$ was considered significant, and data were represented as mean ± SEM.

Results

Actions of Droperidol at the $GABA_A$ $\alpha_1\beta_1\gamma_2$ Receptor

Droperidol inhibited the activation of the $GABA_A$ $\alpha_1\beta_1\gamma_2$ receptor in a biphasic manner with concentra-

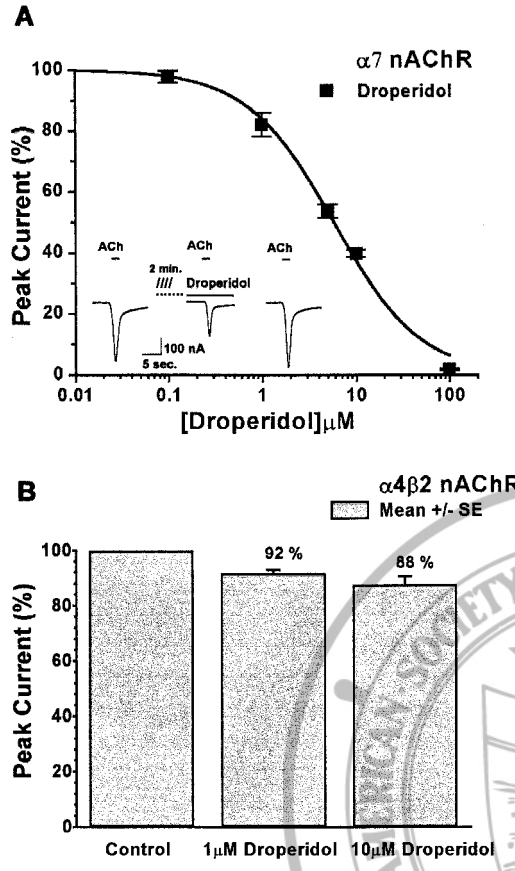

Fig. 3. Droperidol inhibits the acetylcholine (ACh) activation of the human α_7 neuronal nicotinic acetylcholine receptors (nAChRs) at possibly clinically relevant concentrations. (*A*) A concentration–response curve for droperidol inhibition of the activation of the α_7 nAChR. The IC_{50} is 5.8 ± 0.53, and the Hill coefficient is 0.95 ± 0.1 (n = 4–5). (*Inset*) A control current activated by 1 mM acetylcholine (saturating) from the α_7 nAChR before (*left*), during a 2-s acetylcholine application with 6 μM droperidol (*middle*), and after droperidol washout (*right*). (*B*) Activation of nicotinic receptors composed of α_4 and β_2 subunit, with 1 mM acetylcholine was not significantly inhibited by 1 or 10 μM droperidol ($P > 0.05$, *t* test). Shown as a bar graph (mean ± SE).

tion-dependent inhibition between 10 nM and 1 μM that was reversed at concentrations higher than 5 μM (fig. 1A). The maximal inhibition of the GABA response by droperidol was 24.7 ± 3.0% and occurred at concentrations between 20 nM and 1 μM droperidol. At high concentrations (100 μM), droperidol can activate the $GABA_A$ $\alpha_1\beta_1\gamma_2$ receptor in the absence of GABA (fig. 1B, *left*). There was no effect of droperidol 100 μM on uninjected oocytes. The inhibitory response to droperidol is shown in figure 1C as a percentage of the maximal possible effect. The IC_{50} concentration for droperidol is 12.6 ± 0.5 nM.

γ-Aminobutyric acid concentration–response curves were constructed in the presence and absence of two different inhibitory concentrations of droperidol (100 nM and 1 μM) and a higher concentration at which inhibition was no longer observed (5 μM). The GABA dose–response curves in the presence of 100 nM and 1 μM droperidol shifted the curve to the right at low concentrations of GABA, but at high agonist concentrations droperidol had no effect (fig. 2A). Droperidol at 5 μM had no significant effect on activation by GABA at any concentration (fig. 2B). To determine whether the inhibition of the $GABA_A$ $\alpha_1\beta_1\gamma_2$ receptor by droperidol was voltage-dependent, the percent inhibition by 100 nM droperidol, when 500 nM GABA activated the receptor, was determined at a range of holding potentials from −100 to −20 mV. Inhibition of the $GABA_A$ $\alpha_1\beta_1\gamma_2$ receptor activation increased with membrane hyperpolarization (fig. 2C). To determine whether inhibition by droperidol was dependent on channel activation, we measured peak current responses to repeated applications of GABA, at 3-min intervals, during a continuous application of droperidol at concentrations from 100 nM to 1 μM. There was no increment in the degree of inhibition of the $GABA_A$ $\alpha_1\beta_1\gamma_2$ receptor by droperidol with repeated agonist application (fig. 2D; $P > 0.05$, *t* test).

Actions of Droperidol at the Human α_7 and $\alpha_4\beta_2$ Neuronal Nicotinic Acetylcholine Receptors

When activated by 1 mM acetylcholine, droperidol inhibited the α_7 nAChR with an IC_{50} of 5.8 ± 0.5 μM (fig. 3A). Droperidol only slightly inhibited the activation of the $\alpha_4\beta_2$ nAChR at concentrations of 10 μM and greater. Droperidol at 1 μM did not inhibit the $\alpha_4\beta_2$ nAChR, and there was only 10–15% inhibition with 10 μM droperidol (fig. 3B).

Acetylcholine concentration–response curves were constructed in the presence and absence of droperidol at approximately its IC_{50} concentration (6 μM). The slope of the acetylcholine dose–response curve was shallower in the presence of droperidol, and the maximal current amplitude was reduced (fig. 4A). To determine whether the inhibition of the α_7 nAChR by droperidol was voltage-dependent, the percent inhibition by droperidol when the receptor was activated by 1 mM acetylcholine was determined at a range of holding potentials from −100 to −30 mV. Inhibition of the α_7 nAChR increased slightly with membrane hyperpolarization; however, the change was not statistically significant (fig. 4B; $P > 0.05$, analysis of variance). To determine whether inhibition by droperidol was dependent on channel activation, we measured peak current responses to repeated applications of acetylcholine, at 5-min intervals, during a continuous application of droperidol (fig. 4C). There was no increment in the degree of inhibition of the α_7 nAChR by droperidol with repeated agonist application ($P > 0.05$, *t* test).

Discussion

Droperidol's modulation of the $GABA_A$ receptor is distinct from other general anesthetics that have been stud-

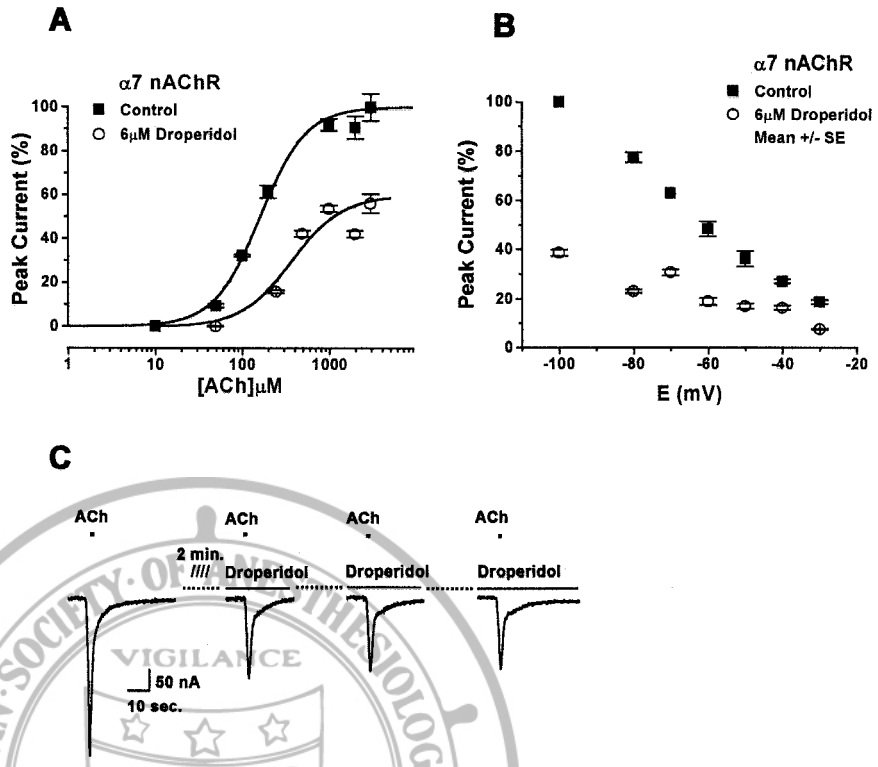

Fig. 4. Droperidol inhibition on acetylcholine (ACh) activation is noncompetitive at the α_7 nAChR. (*A*) A concentration–response curve for the activation of α_7 nAChR by varying acetylcholine concentrations in the absence and presence of 6 μM droperidol. During control conditions, the EC_{50} for acetylcholine was 160 ± 12 μM, and the Hill coefficient was 1.6 ± 0.2. In the presence of droperidol, the EC_{50} for acetylcholine was increased to 373 ± 11 μM, and the Hill coefficient was 1.5 ± 0.7. Membrane potential was held at −60 mV (n = 5). (*B*) Voltage–response relation for the α_7 nACh receptor activated by 1 mM acetylcholine in the presence and absence of 6 μM droperidol. All values are normalized to the maximal mean control response (−100 mV). Points are mean ± SE (n = 5). (*C*) Repeated application of 1 mM acetylcholine in the continued presence of 6 nM droperidol did not result in significantly increased inhibition ($P > 0.05$, *t* test).

ied. Droperidol has two actions on the $GABA_A$ receptor that appear to occur at different molecular sites with different affinities. At low droperidol concentrations, from 10 nM to 1 μM, droperidol inhibits the maximal GABA activation by approximately 25% (figs. 1A and C). Inhibition by droperidol is only seen when the receptor is activated by less than saturating concentrations of GABA (fig. 2A). Thus, there may be little effect of droperidol in the setting of classic synaptic activation by the transient application of a high concentration of agonist. However, there is evidence that $GABA_A$ receptors have important physiologic actions other than the mediation of synaptic transmission. There exists a persistent tonic background current as a result of activation of a pharmacologically and functionally distinct $GABA_A$ receptor that is preferentially potentiated by propofol.[19] It is possible that droperidol might inhibit such a current.

Inhibition is moderately voltage-dependent and was larger at negative potentials (fig. 2C). According to Woodhull,[17] blockade by positively charged particles can be considered as a Boltzmann distribution under a potential difference. Accordingly, the voltage dependence of blockade can be estimated with the following equation:

$$\ln((I_{max} - I)/I) = \ln(dBd + K_B(0)) - \delta zEF/RT$$

where I_{max} is the current amplitude in the absence of droperidol, B is the concentration of droperidol, K_B is the apparent dissociation constant at the reference potential of 0 mV, δ is the electrical distance from the outer mouth of the channel, z is the charge, and E, F, R, and T have their general meanings. When the mean current inhibition at various potentials is plotted as a semilog distribution (fig. 5A), the slope is −0.019. Using the Henderson Hasselbach equation to calculate the concentration of charged particles, droperidol has a charge of +0.635 at pH 7.4. According to equation 1, δ (z) is calculated to be 0.76 or 76% of the electrical distance. It is therefore likely that droperidol does not reduce GABA affinity by binding to the agonist site; rather, its inhibitory site may be within the membrane electric field. In contrast, figure the slope for the voltage dependence in figure 5B is not significantly different from 0, suggesting little effect of the membrane electric field in the α_7 nAChR.

At high concentrations (100 μM), droperidol can activate the $GABA_A$ receptor. Because of limitations in solubility, we were unable to determine if droperidol is capable of full activation of the $GABA_A$ receptor. Droperidol is not acting as a partial agonist at the $GABA_A$ receptor because, if this were the case, at low GABA concentrations larger currents would be expected in the combined presence of droperidol and agonist.

It has recently become clear that, unlike agonist binding at the nAChR, GABA binding is not diffusion-dependent.[20] Instead, agonist affinity could be predicted by binding rates that were much slower than would be predicted by diffusion. In the $GABA_A$ receptor, a conformational change in the binding site either precedes or accompanies binding. Droperidol could affect the free energy required for such a conformational change by acting anywhere within the channel. It might either

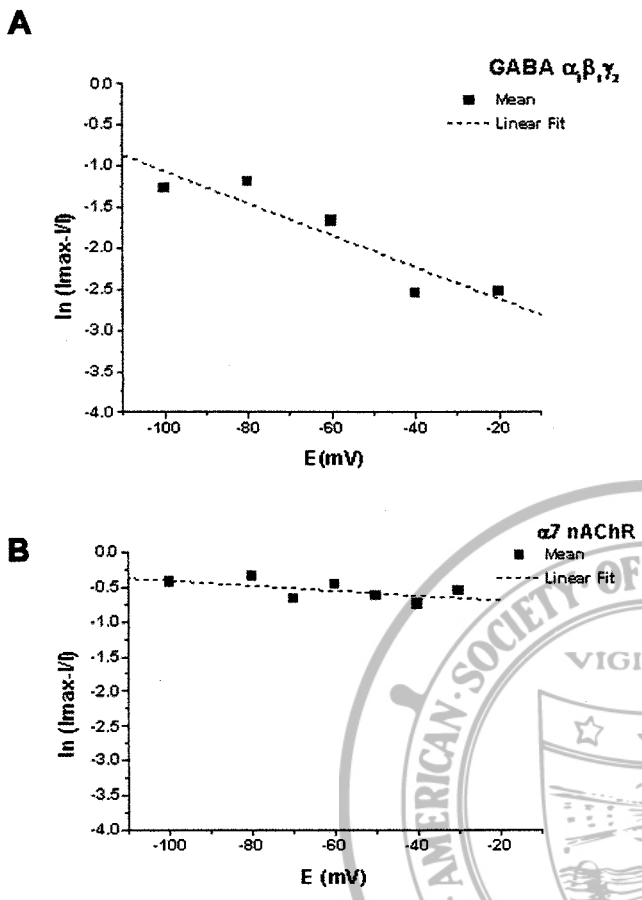

Fig. 5. Woodhull analysis of voltage dependence of peak current inhibition by droperidol. (*A*) The mean peak current activated by 500 nM γ-aminobutyric acid (GABA) that was inhibited by 100 nM droperidol was plotted semilogarithmically against holding potentials (n = 5–7) (E). The dotted line represents the results of linear regression with a slope of 0.019. (*B*) The mean peak current activated by 1 mM acetylcholine (ACh) that was inhibited by 6 μM droperidol was plotted semilogarithmically against holding potentials (E). The dotted line represents the results of linear regression. The slope was not significantly different from 0 (n = 3–7; $P > 0.05$, analysis of variance).

reduce binding or increase the unbinding rates of GABA. Our experiments are not equipped to measure the kinetics. However, another dopamine antagonist, chlorpromanzine, inhibits GABA currents by causing both a reduction in binding and an increase in unbinding rates for GABA in the $GABA_A$ receptor.[21]

Volatile anesthetics, barbiturates, propofol, and neurosteroids potentiate the GABA response, whereas ketamine, nitrous oxide, and xenon have little effect.[11,16,22–26] Droperidol is the only anesthetic drug that has been shown to inhibit the GABA response. Submaximal GABA inhibition may be responsible for a key side effect that limits the utility of droperidol in neuroleptanesthesia. At high antiemetic concentrations and concentrations that are present on emergence from neuroleptanesthesia, droperidol causes anxiety and dysphoria. Because GABA agonists are anxiolytic, this side effect might be caused by inhibition of inhibitory transmission by droperidol.

Fully efficacious GABA antagonists such as bicuculine and picrotoxin cause seizures. One might predict that antagonism of $GABA_A$ receptor activation by droperidol would cause it to be epileptogenic in clinical use, but it is not. Unlike many other anesthetics, however, droperidol does not reduce seizure activity.[27] Neuroleptanesthesia can be used for anesthesia in humans and animals when epileptic activity is desirable, as in seizure mapping and electroconvulsive therapy.[28] It is possible that either a 25% maximal inhibition of GABA activity is not sufficient to cause seizures in most situations or the combination with inhibition of excitatory nicotinic activity is protective.

The activation of the α_7 nAChR was inhibited by droperidol (fig. 3). The IC_{50} for this inhibition is 5.8 ± 0.53 μM. The inhibition is noncompetitive and minimally voltage-dependent. In consideration of whether the inhibitory concentration is clinically relevant, the shoulder of the concentration–response relation is perhaps more important than the concentration that results in a 50% maximal effect. If at clinically relevant concentrations there is no significant effect on a putative target, it is unlikely that the target is mediating the clinical drug action. In the case of the α_7 nAChR, clinically relevant droperidol concentrations are within the shoulder of the concentration–response relation for inhibition. Droperidol has prolonged central nervous system actions (hours) despite a relatively short terminal half-life (approximately 10 min), and it is thought that this is a result of preferential central nervous system uptake.[3] Therefore, central nervous system concentrations may be higher than measured plasma concentrations. It is therefore possible that inhibition of the activation of the α_7 nAChR mediates the anesthetic actions of droperidol. In contrast, there was no significant effect of clinically relevant concentrations of droperidol on the $\alpha_4\beta_2$ nAChR. Droperidol is unique among anesthetics that have nicotinic effects in that it preferentially acts on α_7 nAChRs. Volatile anesthetics inhibit heteromeric nAChRs more potently than α_7 nAChRs, whereas thiopental and ketamine inhibit both with approximately equal potency.[7–11]

Droperidol is also known to inhibit currents from human neuronal potassium channels in a similar concentration range to its effects on α_7 nAChRs, whereas human neuronal sodium channels are modulated by droperidol at more than 10 times droperidol concentrations.[29,30] However, inhibition of voltage-gated potassium currents by droperidol would be predicted to be excitatory in nature.

In conclusion, the α_7 nAChR can be considered as a putative target for mediating neuroleptanesthesia. Droperidol is unusual among anesthetics in that it causes submaximal inhibition of a GABA response. Inhibition of GABA activation may be responsible for anxiety and dysphoria, a common side effect of droperidol when used at anesthetic concentrations.

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