Implications for Mechanisms of Anesthesia

Anesthetic Properties of 4-Iodopropofol

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Background: Positive modulation of γ-aminobutyric acid type A (GABA_A) receptor function is recognized as an important component of the central nervous system depressant effects of many general anesthetics, including propofol. The role for GABA_A receptors as an essential site in the anesthetic actions of propofol was recently challenged by a report that the propofol analog 4-iodopropofol (4-iodo-2,6-diisopropylphenol) potentiated and directly activated GABA_A receptors, yet was devoid of sedative–anesthetic effects in rats after intraperitoneal injection. Given the important implications of these findings for theories of anesthesia, the authors compared the effects of 4-iodopropofol with those of propofol using established in vivo and in vitro assays of both GABA_A receptor–dependent and –independent anesthetic actions.

Methods: The effects of propofol and 4-iodopropofol were analyzed on heterologously expressed recombinant human GABA_A α1β2γ2 receptors, evoked population spike amplitudes in rat hippocampal slices, and glutamate release from rat cerebrocortical synaptosomes in vitro. Anesthetic potency was determined by loss of righting reflex in Xenopus laevis tadpoles, in mice after intraperitoneal injection, and in rats after intravenous injection.

Results: Like propofol, 4-iodopropofol enhanced GABA-induced currents in recombinant GABA_A receptors, inhibited synaptic transmission in rat hippocampal slices, and inhibited sodium channel–mediated glutamate release from synaptosomes, but with reduced potency. After intraperitoneal injection, 4-iodopropofol did not produce anesthesia in mice, but it was not detected in serum or brain. However, 4-iodopropofol did produce anesthesia in tadpoles (EC50 = 2.5 ± 0.5 μM) and in rats after intravenous injection (ED50 = 49 ± 6.2 mg/kg).

Conclusions: Propofol and 4-iodopropofol produced similar actions on several previously identified cellular and molecular targets of general anesthetic action, and both compounds induced anesthesia in tadpoles and rats. The failure of 4-iodopropofol to induce anesthesia in rodents after intraperitoneal injection is attributed to a pharmacokinetic difference from propofol rather than to major pharmacodynamic differences.

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bicuculline, dimethylsulfoxide, and trypsin were obtained from Sigma Chemical Co. (St. Louis, MO); Percoll was obtained from Pharmacia (Uppsala, Sweden); adenine triphosphate and HEPES were obtained from Calbiochem (San Diego, CA); Diprivan® was obtained from AstraZeneca Pharmaceuticals (Wilmington, DE); and Intralipid was obtained from Baxter Healthcare Corp. (Deerfield, IL). Pure propofol was obtained from Aldrich Chemical (St. Louis, MO) or was a gift from AstraZeneca Pharmaceuticals. 4-Iodopropofol was synthesized by aromatic halogenation of propofol with iodonium chloride. It was purified to apparent homogeneity by silica gel chromatography followed by high-performance liquid chromatography using isocratic elution from a 100 × 4.6-mm C18 column (5-µ particle size) in 67% (vol/vol) acetonitrile-0.04% acetic acid (vol/vol), pH 4.0. Structure was confirmed in CDCl3 by proton nuclear magnetic resonance at the Rockefeller University NMR Facility (New York, NY). All other chemicals were of analytical grade. Propofol and 4-iodopropofol were dissolved in dimethylsulfoxide and serially diluted into buffer to achieve the desired final concentrations for in vitro studies. Solutions were sonicated immediately before use.

**Electrophysiologic Recordings from Recombinant GABA<sub>₆</sub> Receptors**

**Transfection.** Human GABA<sub>₆</sub> receptor cDNAs were expressed using the vector pCIS2, which contains one copy of the strong promoter from cytomegalovirus and a polyadenylation sequence from simian virus 40. These constructs were used to transfect human embryonic kidney (HEK) 293 cells (American Type Culture Collection, Rockville, MD) as described previously. HEK 293 cells were maintained in culture on glass coverslips; cells were passaged weekly by trypsin treatment up to 15 times before being discarded and replaced with early passage cells. Each coverslip of cells was transfected using the Ca<sub>₉</sub>Po<sub>₄</sub> precipitation technique. One to five micrograms of each cDNA (α<sub>₃</sub>, β<sub>₂</sub>, and γ<sub>₂</sub>) were used per coverslip. Cells were exposed to the cDNA for 24 h in an atmosphere containing 3% CO<sub>₂</sub>, after which the cDNA solution was removed and replaced with fresh culture medium in an atmosphere of 95% O<sub>₂</sub>-5% CO<sub>₂</sub>.

**Electrophysiology.** Between 24 and 72 h after removal of the cDNA, coverslips were transferred to a large chamber (60 ml) and perfused continuously (20 ml/min) with extracellular medium. Recordings from HEK 293 cells were made using the whole-cell patch clamp technique as described previously. Patch pipettes contained 145 mM N-methyl-D-glucamine hydrochloride, 5 mM dipotassium adenophosphate, 1.1 mM EGTA, 2 mM MgCl<sub>₂</sub>, 5 mM HEPES-KOH (pH 7.2), and 0.1 mM CaCl<sub>₂</sub>. Pipette resistance was 4-5 MΩ. The extracellular medium contained 145 mM NaCl, 5 mM KCl, 1.5 mM CaCl<sub>₂</sub>, 1 mM MgCl<sub>₂</sub>, 6 mM D-glucose, and 10 mM HEPES-NaOH (pH 7.4). HEK 293 cells were voltage clamped at −60 mV. In addition to continuous slow bath perfusion, drugs and solutions were applied rapidly by local perfusion using a motor-driven solution exchange device. Laminar flow was achieved by driving all solutions at identical flow rates via a multichannel pump. The solution changer was driven by protocols in an acquisition program as previously described. Responses were digitized using the acquisition program; data are presented as mean ± SEM.

**Hippocampal Slice Recordings**

**Preparation.** Adult male Sprague-Dawley rats (80–100g) were anesthetized with diethyl ether (3.4 vol%), and the brain was rapidly removed and placed in ice-cold (5°C) and pregassed (95% O<sub>₂</sub>-5% CO<sub>₂</sub>) artificial cerebrospinal fluid (ACSF; composition: 134 mM NaCl, 3.5 mM KCl, 2.0 mM CaCl<sub>₂</sub>, 1.25 mM KH<sub>₂</sub>PO<sub>₄</sub>, 2 mM MgSO<sub>₄</sub>, 16 mM NaHCO<sub>₃</sub>, and 10 mM D-glucose). The hippocampal formation was dissected, and transverse slices (450–500 µm) were cut using a Vibratome (Campden Instruments, Oxford, United Kingdom) tissue slicer. Hippocampal slices were equilibrated for at least 1 h at room temperature (20–22°C) in an incubation chamber filled with ACSF and continually bubbled with 95% O<sub>₂</sub>-5% CO<sub>₂</sub>.

**Electrophysiology.** Individual slices were transferred to a recording chamber and equilibrated for an additional 5–10 min before recording. Oxygenated ACSF solution was continuously perfused through the chamber at a flow rate of 2.0 ml/min. Bipolar tungsten microelectrodes were placed in stratum radiatum to electrically stimulate Schaffer-collateral fiber inputs to CA1 pyramidal neurons. Glass recording electrodes filled with ACSF (2–5 MΩ) were placed in stratum pyramidale-oriens to record stimulus-evoked population spike field potentials. Paired stimulus pulses (0.01–0.03-ms duration; 10–80 µA at 1.0–5.0 V; 60-ms interpulse interval) were delivered via constant current isolation units from a two-channel stimulator at stimulus rates of 0.05–0.1 Hz. Field potential signals were amplified (∝1,000), filtered (1 Hz to 10 KHz bandwidth), conditioned (DC offset or AC coupled), and digitally stored for later analysis (A/D with 20.0-µs resolution on a 486 50 MHz microcomputer using software from DataWave Technologies, Longmont, CO). Population spike amplitudes were measured from threshold to peak negativity. After preequilibration, a control period (30 min) of electrical stimulation and recording was performed to establish the stability of each preparation. All preparations used for the study met minimum criteria for population spike amplitudes of at least 6 mV and amplitude variability of less than 5% during the initial control recording period. Test solutions were perfused into the recording chamber until steady state drug effects were observed (usually 20–30 min). Washout of drug effects was performed with drug-free ACSF after each administration of

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test solution. Only a single concentration of anesthetic was tested on each brain slice to avoid tachyphylaxis, desensitization, or cross-agent contamination. Field potential measures are expressed as mean ± SD from five individual determinations. Statistical comparisons were made using analysis of variance with post hoc Tukey tests on time-matched control versus drug data. In control experiments, 0.1–2.0% (vol/vol) dimethylsulfoxide did not alter cellular responses.

Glutamate Release from Synaptosomes

Preparation. Synaptosomes were prepared from cerebral cortices of adult male Sprague-Dawley rats by the method of Dunkley et al. with minor modifications as previously described. Purified synaptosomes were suspended in HEPES buffered medium (composition: 140 mM NaCl, 5 mM KCl, 1 mM MgCl2, 1.2 mM Na2HPO4, 5 mM NaHCO3, 10 mM D-glucose, and 20 mM HEPES-NaOH, pH 7.4), pelleted by centrifugation at 8,000 × g for 5 min (equilibrium was complete at 10–20 min), after which the synaptosomes were returned to fresh tap water, where recovery was monitored. In all cases, normal swimming activity was restored within 30 min. Tadpole concentration–response data were fitted according to the method of Waud to a logistic equation (P = 100 × [D]n (D)n + EC50n)), where P is the percentage of the population anesthetized, [D] is the drug concentration, n is the slope, and EC50 is the drug concentration for a half-maximum effect.

Behavioral Effects in Tadpoles and Rodents

Loss of Righting Reflex in Tadpoles. General anesthetic potency was determined as previously described. Briefly, Xenopus laevis tadpoles (Xenopus 1, Ann Arbor, MI) in the preblot bud stage of development (stages 43–50) were maintained in an aerated aquarium at 20–22°C. For randomized blind anesthetic potency experiments, approximately 10 tadpoles were placed in each of 10 glass beakers containing 300 ml tap water (20–22°C) with or without propofol or 4-iodopropofol (0.1–30 μM). Except for the tap water control, all beakers contained 0.1% dimethylsulfoxide, a concentration that was not associated with morbidity or anesthesia. The anesthetic end point was defined as the lack of a purposeful and sustained swimming response after a gentle inversion with a smooth glass rod. The number of anesthetized tadpoles was recorded every 10 min for 120 min (equilibrium was complete at 10–20 min), after which the tadpoles were returned to fresh tap water, where recovery was monitored. In all cases, normal swimming activity was restored within 30 min. Tadpole concentration–response data were fitted according to the method of Waud to a logistic equation (P = 100 × [D]n (D)n + EC50n)), where P is the percentage of the population anesthetized, [D] is the drug concentration, n is the slope, and EC50 is the drug concentration for a half-maximum effect.

Sedative–Hypnotic Effects in Mice and Rats. Effects of propofol and 4-iodopropofol were evaluated in mice after intraperitoneal injection and in rats after intravenous injection using the behavioral index of Lowson et al. Anesthesia was defined as loss of the righting reflex and a reduced response to tail pinch.

Adult male C57BL/6 mice (20–25 g) were monitored for 2 h after intraperitoneal injection of drug dissolved in 0.02 ml of dimethylsulfoxide. Control mice injected with dimethylsulfoxide alone showed no behavioral effects. Serum and brain concentrations of propofol and 4-iodopropofol were determined at the time of the peak propofol effect by decapitation and collection of venous and arterial blood and rapid dissection of the forebrain.

Adult male Sprague-Dawley rats (150–250 g) were monitored for 2 h after intravenous injection through a 24-gauge 19-mm catheter. To avoid the toxicity of intravenous dimethylsulfoxide used as a vehicle, stock solutions of 0.45 m propofol or 0.9 m 4-iodopropofol in dimethylsulfoxide were diluted into Intralipid 20% intravenous fat emulsion to yield 56 mM (10 mg/ml) propofol or 112 mM (34 mg/ml) 4-iodopropofol for injection. Injections (volumes of 0.15–0.43 ml) were made over 20 s and were followed by a flush of 0.5 ml of 0.9% (wt/vol) NaCl. Injection of the dimethylsulfoxide–Intralipid vehicle alone produced no behavioral effects. Control experiments demonstrated that the propofol emulsion was equipotent with Diprivan® 1% (wt/vol) propofol injectable propofol emulsion.
Drug Concentrations

Free concentrations of propofol and 4-iodopropofol in synaptosome assays were analyzed in the buffer phase after equilibrium dialysis to take into account high tissue binding. For in vivo experiments, serum and brain specimens were collected 10 min after intraperitoneal injection of propofol and 4-iodopropofol immediately after animals were killed by decapitation. After extraction into acetonitrile, samples were analyzed by high-performance liquid chromatography using isocratic elution in 67% (vol/vol) acetonitrile–0.04% acetic acid (vol/vol), pH 4.0, on a 100 × 4.6-mm C18 column (5-μ particle size) with dibutylphthalate as internal standard. Drug concentrations were quantified using peak area determinations compared with external standards.

Results

Electrophysiologic Effects on Recombinant GABA<sub>4</sub> Receptors

The modulatory effects of propofol and 4-iodopropofol on responses elicited by an EC<sub>20</sub> concentration of GABA were determined for human GABA<sub>4</sub> α<sub>1</sub>β<sub>2</sub>γ<sub>2</sub> receptors (fig. 1). Propofol enhanced the GABA-induced current in a reversible and dose-dependent manner (EC<sub>50</sub> = 1.9 ± 0.4 μM; E<sub>max</sub> = 240% control; n = 1.6), as reported previously. Similarly, 4-iodopropofol enhanced the current activated by an EC<sub>20</sub> concentration of GABA, but with lower potency and efficacy (EC<sub>50</sub> = 11 ± 2.0 μM; E<sub>max</sub> = 94% control; n = 2.9). Both propofol (EC<sub>50</sub> = 10 ± 1.0 μM; E<sub>max</sub> = 67% maximal GABA response; n = 1.3) and
Propofol and 4-iodopropofol markedly depressed evoked population spike amplitudes from the CA1 neuron output after Schaffer collateral stimulation. The second response to a pair of stimuli was depressed to a greater degree than the first pulse responses, indicating that both agents increased paired pulse inhibition (fig. 2). Paired pulse inhibition is thought to be mediated by GABAergic interneurons that provide feedback inhibition onto CA1 pyramidal neurons.26 These inhibitory interneurons are activated by the discharge produced in response to the first pulse and compete with excitatory postsynaptic potential facilitation to modulate responses to the second pulse. For both drugs, concentrations of 30 μM completely blocked both the first and second pulse responses; however, concentrations of 5 μM (propofol) and 10 μM (4-iodopropofol) were sufficient to block second pulse responses. To determine whether enhanced GABAergic inhibition contributed to this depression, the GABAA receptor antagonist bicuculline (10 μM) was applied in the continued presence of test agents. Bicuculline reversed the effects of both propofol and 4-iodopropofol, and population spike amplitudes recovered to approximately 80% of control levels.

Presynaptic Effects on Neurotransmitter Release

The effects of propofol and 4-iodopropofol on endogenous glutamate release from rat cerebrocortical synaptosomes were compared as a neurochemical assay of their presynaptic actions. Propofol inhibited tetrodotoxin-sensitive (Na+ channel-dependent) veratridine-evoked glutamate release (fig. 3; 30% inhibition at 7 μM; P < 0.05; n = 3) more potently than tetrodotoxin-insensitive (Na+ channel-independent) KCl (30 ms)-evoked release (no significant effect at 28 μM), as shown previously.8 Propofol had no significant effect on basal release (0.81 ± 0.42 nmol · min⁻¹ · mg⁻¹; n = 10) compared with control (0.50 ± 0.07 nmol · min⁻¹ · mg⁻¹; n = 5; P > 0.05) at the highest concentration (28 μM) tested. 4-Iodopropofol also inhibited veratridine-evoked glutamate release (15% inhibition at 6 μM; P < 0.05; n = 3) more potently than KCl-evoked release (no significant effect at 27 μM). Inhibition of veratridine-evoked glutamate release by 4-iodopropofol (EC50 = 19 ± 1.1 μM) was of comparable potency to that by propofol (EC50 = 17 ± 1.2 μM). In addition, 4-iodopropofol caused a large increase in basal release of glutamate that was only partially (30%) Ca²⁺-dependent (1.1 ± 0.53 nmol · min⁻¹ · mg⁻¹ at 12 μM; P < 0.05; 1.8 ± 0.89 nmol · min⁻¹ · mg⁻¹ at 27 μM; P < 0.001; n = 3).

Behavioral Effects in Tadpoles and Rodents

Loss of Righting Reflex in Tadpoles. Concentrations of propofol or 4-iodopropofol greater than 1 μM induced reversible loss of righting reflex in X. laevis tadpoles (fig. 4). The concentration-response curves
could be fitted by a logistic equation with EC50 values of 1.9 ± 0.2 μM for propofol (n = 3.4) and 2.5 ± 0.5 μM for 4-iodopropofol (n = 1.5).

**Sedative–Hypnotic Effects in Mice.** Propofol (40–225 mg/kg body weight by intraperitoneal injection) produced dose-dependent sedative–hypnotic effects in mice (fig. 5). A dose of 200 mg/kg produced anesthesia 7–9 min after injection; recovery time varied from 45–120 min. 4-Iodopropofol (200–600 mg/kg body weight) had no hypnotic effects even at the highest dose tested. A maximum of level two effects (decreased coordination; Lowson et al.21) were observed after 15 min in 2 of 11 mice at 4-iodopropofol doses up to threefold higher than the highest propofol dose tested.

**Sedative–Hypnotic Effects in Rats.** Propofol (10 mg/kg body weight by intravenous injection) produced anesthesia in rats within 10 s, with a duration of loss of righting reflex of 7.2 ± 1.7 min (n = 9). Similar effects were observed with Diprivan®, a commercial preparation of propofol (10 mg/kg body weight by intravenous injection), which produced anesthesia within 10 s, with a duration of 7.0 ± 1.9 (n = 3). An equivalent molar dose of 4-iodopropofol (17 mg/kg) was devoid of behavioral effects, but higher doses produced ataxia followed by anesthesia within 10–30 s. Data from 14 animals are shown in figure 5; fitting to a logistic concentration–response function yielded an ED50 value of 49 ± 6.3 mg/kg. The duration of anesthesia was dose-dependent and ranged from 5 min at a dose of 51 mg/kg to 41 min at a dose of 85 mg/kg. Rats emerging from 4-iodopropofol sedation–anesthesia showed transient salivation, increased licking, dystonic limb movements, paraplegia,
and apparent intention tremor, effects that were not observed on emergence from propofol.

**Drug Concentrations in Mice**

At the peak of the propofol effect (10 min after intraperitoneal injection), the concentrations of propofol and 4-iodopropofol were measured in mouse serum and brain. The mean serum and brain propofol concentrations were 31 μg/ml and 20 μg/ml, respectively (n = 2) at a dose of 200 mg/kg. 4-Iodopropofol was not detected in serum or brain at doses of 200 mg/kg (n = 2) or 400 mg/kg (n = 3), with a lower limit of sensitivity 1 μg/ml. 4-Iodopropofol was easily detected when added directly to serum or brain as an external standard.

**Discussion**

Both propofol and 4-iodopropofol potentiate and directly activate isolated recombinant GABA<sub>A</sub> receptors, whereas propofol, but not 4-iodopropofol, produces anesthesia when administered by intraperitoneal injection in rats<sup>10</sup> or mice. In addition, both agents facilitate inhibitory GABAergic synaptic transmission in rat hippocampal slices and inhibit Na<sup>+</sup> channel-dependent glutamate release from isolated rat cortical nerve terminals. Furthermore, we found that 4-iodopropofol produces anesthesia in tadpoles and in rats after intravenous administration in contrast to its inactivity after intraperitoneal administration. We interpret the absence of behavioral effects produced by 4-iodopropofol after intraperitoneal injection as a pharmacokinetic difference from propofol since 4-iodopropofol was not detected in mouse serum or brain after intraperitoneal administration by this route.

Ligand-gated ion channels are among the most sensitive molecular targets for general anesthetic actions in vitro.<sup>27</sup> GABA<sub>A</sub> receptors figure prominently in the neuronal depression produced by most anesthetic agents,<sup>2,28</sup> and by propofol in particular.<sup>7,29</sup> The recent findings that the propofol analog 4-iodopropofol resembled propofol in its actions on heterologously expressed GABA<sub>A</sub> receptors (α<sub>1</sub>β<sub>2</sub>γ<sub>2s</sub>) but failed to produce sedation, ataxia, or loss of righting reflex in rats<sup>9,10</sup> cast doubt on the necessity of positive GABA<sub>A</sub> receptor modulation as a mechanism involved in the production of anesthesia. Sanna et al.<sup>10</sup> ascribed the inability of 4-iodopropofol to produce anesthesia despite positive GABA<sub>A</sub> receptor modulation to its reduced efficacy in direct receptor activation. Direct GABA<sub>A</sub> receptor activation has been observed for propofol,<sup>3,30</sup> etomidate,<sup>31</sup> pentobarbital,<sup>32</sup> and alphaxalone,<sup>33</sup> and has been proposed as an important aspect of anesthetic action.<sup>34</sup> We observed both potentiation of GABA-induced currents and direct activation of heterologously expressed α<sub>1</sub>β<sub>2</sub>γ<sub>2</sub> GABA<sub>A</sub> receptors by 4-iodopropofol, both with reduced efficacy and potency relative to propofol. This correlated with the reduced potency of 4-iodopropofol as a general anesthetic in vivo.

We also observed modulation by 4-iodopropofol of native GABA<sub>A</sub> receptors in rat hippocampal slices. Bicuculline-sensitive depression of CA1 pyramidal neuron output indicated that at least 80% of the depression produced by both agents was caused by an increase in GABA<sub>A</sub> receptor-mediated inhibition of first and second pulse responses. The increase in paired pulse inhibition resembles the GABAergic actions previously reported for barbiturates.<sup>35,36</sup> It is likely that most of the bicuculline-resistant effects result from depression of excitatory synaptic transmission, perhaps by presynaptic inhibition of glutamate release. Both agents similarly inhibited veratridine-evoked glutamate release, an in vitro model for presynaptic depression of excitatory synaptic transmission by general anesthetics, which may be mediated by Na<sup>+</sup> channel blockade.<sup>8,57</sup> Taken together, our results indicate that 4-iodopropofol closely resembles propofol in several in vitro assays of anesthetic action on both postsynaptic and presynaptic targets: potentiation and direct activation of GABA<sub>A</sub> receptors, GABAergic and non-GABAergic depression of hippocampal CA1 output, and inhibition of glutamate release from isolated nerve terminals.

Our results suggest a pharmacokinetic mechanism for the inability of intraperitoneal 4-iodopropofol to produce anesthesia in rodents. Although 4-iodopropofol was unable to produce anesthesia after intraperitoneal administration in rats<sup>10</sup> or mice (this study), it produced anesthesia in tadpoles and in rats after intravenous administration. The molar potency of intravenous 4-iodopropofol in producing anesthesia in rats (ED<sub>50</sub> = 49 mg/kg) is approximately sixfold less than that of propofol (ED<sub>50</sub> 5.0 mg/kg<sup>38</sup>), which should result in higher serum and brain concentrations at equipotent doses, barring pharmacokinetic differences. The lack of behavioral effects of intraperitoneal 4-iodopropofol was apparently caused by rapid metabolism or poor absorption after intraperitoneal injection since it was not detected in serum or brain when administered to mice at doses higher than those of propofol that did allow detection. Poor absorption is unlikely given the greater predicted lipophilicity of 4-iodopropofol compared with propofol.<sup>9</sup> Failure of oral doses of propofol up to 300 mg/kg to produce anesthesia in mice was likely caused by extensive hepatic metabolism after uptake into the portal circulation.<sup>39</sup> Greater first-pass hepatic metabolism compared with propofol as a result of enhanced susceptibility to nuclophilic attack at the α position could explain the inability of 4-iodopropofol to enter the systemic circulation and the brain after intraperitoneal injection and uptake into the portal system. This effect would be bypassed by direct transcutaneous absorption in the tadpole assay or by intravenous injection. Al-
though they did not measure it directly, Sanna et al. inferred passage of 4-iodopropofol across the blood-brain barrier based on its predicted lipophilicity, central anticonvulsant and anticonflict effects, and inhibition of hippocampal acetylcholine release measured by microdialysis in rats in vivo. It is possible that these effects are extremely sensitive to low (subanesthetic) concentrations of 4-iodopropofol or a metabolite (e.g., propofol) not detected in our analysis.

In conclusion, our results indicate that 4-iodopropofol possesses anesthetic properties in tadpoles and in rats when administered intravenously. Both 4-iodopropofol and propofol have similar effects on isolated recombinant GABA_A receptors, on synaptic transmission in rat hippocampal slices, and on glutamate release from isolated nerve terminals. Thus, 4-iodopropofol is a general anesthetic and does not represent a propofol analog with similar actions at GABA_A receptors but without sedative-hypnotic properties, as previously suggested. The similar actions and relative potencies of propofol and 4-iodopropofol on isolated GABA_A receptors, hippocampal synaptic transmission, and glutamate release is consistent with a role for any of these putative targets as relevant sites in the production of general anesthesia.

References

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