REVIEW

Recent progress on the molecular pharmacology of propofol

[version 1; peer review: 4 approved]

Pei Tang¹, Roderic Eckenhoﬀ ²

¹Department of Anesthesiology, University of Pittsburgh, 3550 Terrace Street, Pittsburgh, PA, 15261, USA

²Department of Anesthesiology & Critical Care, University of Pennsylvania, 3400 Spruce St, Philadelphia, PA, 19104, USA

V1 First published: 29 Jan 2018, 7(F1000 Faculty Rev):123
<https://doi.org/10.12688/f1000research.12502.1>

Latest published: 29 Jan 2018, 7(F1000 Faculty Rev):123
<https://doi.org/10.12688/f1000research.12502.1>

Abstract

The precise mechanism by which propofol enhances GABAergic transmission remains unclear, but much progress has been made regarding the underlying structural and dynamic mechanisms. Furthermore, it is now clear that propofol has additional molecular targets, many of which are functionally influenced at concentrations achieved clinically. Focusing primarily on molecular targets, this brief review attempts to summarize some of this recent progress while pointing out knowledge gaps and controversies. It is not intended to be comprehensive but rather to stimulate further thought, discussion, and study on the mechanisms by which propofol produces its pleiotropic effects.

Keywords

propofol, ligand-gated ion channels, GABA, voltage-gated ion channels

Open Peer Review

Approval Status

	1	2	3	4
version 1 29 Jan 2018

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Gustav Akk**, Washington University School of Medicine, St Louis, USA
2. **Tim Hales**, University of Dundee, Dundee, UK
3. **Eintrei Christina**, Linköping University, Linköping, Sweden
4. **Stuart A. Forman**, Massachusetts General Hospital, Massachusetts, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Roderic Eckenhoff (roderic.eckenhoff@uphs.upenn.edu)

Author roles: Tang P: Conceptualization, Investigation, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing;

Eckenhoff R: Conceptualization, Investigation, Methodology, Resources, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The research was supported by funding from the NIH (Pei Tang, R01GM056257 and R01GM066358; Roderic G. Eckenhoff, P01GM55876). The funders had no role in the decision to prepare or publish this review article.

Copyright: © 2018 Tang P and Eckenhoff R. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Tang P and Eckenhoff R. **Recent progress on the molecular pharmacology of propofol [version 1; peer review: 4 approved]** F1000Research 2018, 7(F1000 Faculty Rev):123 <https://doi.org/10.12688/f1000research.12502.1>

First published: 29 Jan 2018, 7(F1000 Faculty Rev):123 <https://doi.org/10.12688/f1000research.12502.1>

Introduction

Propofol is now the most commonly used general anesthesia induction agent in the world and is being used for total intravenous general anesthesia and sedation with increasing frequency. It is well tolerated and may be associated with fewer post-anesthesia effects than many of our other general anesthetics, factors that have undoubtedly contributed to its entrenched position in various clinical applications. However, propofol has adverse effects, including pain on injection, hypotension, hypoventilation, bradycardia, and hyperlipidemia¹. Aside from clinical usage, propofol is being used extensively in basic neuroscience research to better understand consciousness, memory, and learning²⁻⁴. For example, a recent study reveals a previously unknown mechanism of unconscious memory under propofol anesthesia, suggesting that general anesthesia acts at stages beyond cellular coding to disrupt sensory integration for higher-order association².

The success of this drug is all the more remarkable given how little we know of its full spectrum of molecular targets and actions. Although it has long been considered to be dominantly γ -aminobutyric acid-ergic (GABAergic)^{5,6}, recent research has indicated that it is not exclusively so and in fact may rely on other molecular targets to produce even its principal desired effect: unconsciousness or hypnosis. This review will briefly cover recent research on how propofol functions on ligand-gated ion channels and then cover other recently revealed molecular targets.

Ligand-gated ion channels

Pentameric ligand-gated ion channels (pLGICs), particularly GABA type A receptors (GABA_ARs), have been extensively investigated as molecular targets for propofol in the past⁷⁻⁹. Propofol typically inhibits cation-selective pLGICs, including the nicotinic acetylcholine receptor (nAChR)¹⁰⁻¹³ and prokaryotic homologues from *Gloeobacter violaceus* (GLIC)^{14,15} and *Erwinia chrysanthemi* (ELIC)^{16,17}. In contrast, propofol at clinical concentrations potentiates agonist-evoked currents of the anion-selective GABA_ARs and glycine receptors (GlyRs) and increases the frequency of channel opening^{5,6,18,19}. Propofol can also directly activate GABA_ARs at intermediate concentrations, but then inhibit conductance at high, supra-clinical concentrations^{6,19}. Exploration of the structural basis of propofol action on pLGICs is still at an early stage. Only a few crystal structures or cryo-electron microscopy structures of eukaryotic pLGICs have been determined²⁰⁻²⁴, and none of these structures includes anesthetics. In contrast, propofol and other general anesthetics as well as alcohols have been successfully co-crystallized with the prokaryotic GLIC^{25,26} and ELIC^{17,27-29}.

The crystal structure of GLIC in a presumed open/desensitized state shows propofol localized to an intra-subunit pocket at the extracellular end of the transmembrane domain α -helices²⁵. Photoaffinity labeling of a propofol analogue to purified GLIC in solution leads to the same propofol location as observed in the crystal structure³⁰. This *intra-subunit* transmembrane pocket is probably a common anesthetic-binding site for *inhibition* of pLGICs. For example, desflurane binds close to this location in

GLIC²⁵, and propofol inhibits ELIC via binding to the equivalent site³¹. Similarly, propofol³², etomidate^{33,34}, and halothane³⁵ also bind to an intra-subunit site within the δ subunit helix bundle of the eukaryotic nAChR, another pLGIC that is inhibited by anesthetics.

A significant role of β 3GABA_AR in behavioral effects of propofol and etomidate has been demonstrated by the reduced sensitivity of β 3(N265M) mice³⁶, and considerable progress has been made in revealing the underlying mechanisms³⁶⁻⁴³. Two recent articles^{42,43} have described sites for propofol in expressed α β GABA_AR, albeit with somewhat different locations. In one case, *ortho*-propofol diazirine (*o*-PD) was found to adduct to a β 3 residue at the transmembrane/extracellular domain interface⁴³ while *azi*-propofol *meta* (*aziPm*) formed an adduct with residues deeper in the α 1 β 3 transmembrane domain interface⁴². Differences are likely due to different photochemistry of *o*-PD and *aziPm*. The less thermally stable *o*-PD is thought to undergo more complex chemistry on illumination and produce a longer-lived reactive intermediate than the carbene generated by illumination of *aziPm*. This more stable and likely more hydrophilic *o*-PD photoproduct then has more time to seek preferential photochemistry partners, such as the β 3 histidine267 residue that may line the pore. A means of distinguishing such photochemical artifacts from specific binding is an ability of the parent drug to inhibit or “protect” the candidate site from photoadduction. Thus, *aziPm* photoadduction was indeed inhibited by propofol, but it is not reported whether *o*-PD was. Another important difference is the milieu in which the receptor resides during photolabeling. For the *aziPm* studies, the expressed α β GABA_AR resides in a detergent/lipid mixture, but the *o*-PD studies were performed with the recombinant receptor in *Spodoptera frugiperda* (Sf9) cell lipid membranes. Neither milieu is perfectly matched to the native neuronal membranes in which GABA_AR normally resides. Thus, further studies will be required to give confidence that these sites are indeed physiologically relevant.

There are often multiple anesthetic-binding sites for a given anesthetic in a particular protein^{31,34,42,44-46}. The existence of multiple anesthetic sites has introduced a more challenging question: which specific site or sites among all those identified are responsible for the functional modulation? An effective way to answer this question is to use chimeras containing domains from different channels that have opposite responses to anesthetics. For example, photolabeling of ELIC with the light-activated derivative of propofol, *aziPm*⁴⁷, identified multiple *aziPm*-binding sites in the extracellular domain and one intra-subunit site in the transmembrane domain³¹. To determine the functionally relevant propofol-binding site(s), we constructed an ELIC–GABA_AR chimera^{16,28,31} that contains the ELIC extracellular domain and the transmembrane domain of α 1 β 3GABA_AR. In contrast to inhibiting ELIC, propofol potentiates the ELIC–GABA_AR chimera as it does on α 1 β 3GABA_AR. These results support a functionally dominant propofol-binding site in the transmembrane domain of ELIC^{16,31}. In heteromeric GABA_ARs, propofol binds to multiple allosteric sites at the transmembrane β – α and α – β interfaces^{37,42}. Both potentiation and direct activation of GABA_ARs are mediated by the same propofol-binding sites⁴⁸,

but it is not clear whether one site plays a more critical role than others. It is also important to realize that propofol binding affects, not only channel activity but also receptor assembly and trafficking^{49,50}.

A homomeric pLGIC, such as GLIC, has five identical subunits and five equivalent binding sites of each type; the crystal structure shows five propofol molecules bound symmetrically in the transmembrane domain²⁵. Is full occupancy of all five sites necessary for functional modulation? Molecular dynamic simulations suggest that asymmetric binding of propofol to only one, two, or three GLIC sites accelerated channel dehydration, increased conformational heterogeneity of the pore-lining helices, and shifted GLIC toward a closed-channel conformation⁵¹ as compared with symmetrical (five-site) occupancy. Similarly, in homo-pentameric pLGICs, occupancy of from one to three sites by anesthetics has been found to be sufficient to potentiate channel currents^{52–55}. Thus, it appears that maximum functional effects are produced by asymmetric occupancy of these channels.

The effect of propofol binding on channel function is largely determined by the intrinsic dynamics of the channel. The cation-conducting GLIC is inhibited by clinically relevant concentrations of general anesthetics^{14,15}. The introduction of three mutations at the selectivity filter and one at the hydrophobic gate converted wild-type (wt) GLIC into GLIC4, an anion channel¹⁵. None of the mutated residues is within the propofol-binding pocket, so propofol binding is probably the same in both GLIC4 and wtGLIC^{25,30,31}. Nevertheless, propofol is unable to inhibit GLIC4 as it does wtGLIC¹⁵. Molecular dynamic simulations revealed that, compared with wtGLIC's pore, GLIC4's pore was more resistant to perturbation from propofol binding¹⁵. These results underscore the importance of pore dynamics and conformation in ligand modulation of channel functions.

Other molecular targets of propofol

The search for other molecular targets has occurred in three principal ways. The first approach examined the transcriptomic, proteomic, or metabolomic response to propofol exposure in cells or intact animals. Depending on the analysis of the data, this approach has led to hundreds of potential molecular substrates⁵⁶. Because it is rarely clear whether, or how many of, these substrates are actually direct molecular binding targets of propofol, additional studies are required; some have been reported. In the second approach, propofol was altered to allow it to covalently bind to its targets on exposure to ultraviolet light (photolabeling), thereby serving as a tag. Tagged proteins then are discovered by using a variety of other technologies. In some cases, the tag is a radiolabel on the altered anesthetic, and scintillation counting and mass spectrometry (MS) are used to detect and identify adducted proteins. More commonly today, the tag is simply the additional mass of the adduct, and tagged proteins can be identified with shotgun MS approaches. The Achilles heel of this approach is that the identified targets are heavily biased toward the most abundant proteins, such as mitochondrial complexes, tubulin, and voltage-dependent anion channels⁵⁷. In fact, known targets of propofol, such as GABA_AR (above), were not detected and this is presumably because of their low abundance. Thus, in the

third approach, photolabeling approaches were refined to include another functional group on the aziPm molecule, in this case an alkyne (in place of the remaining isopropyl), in order to attach subsequent groups after photolabeling by using “click” chemistry⁵⁸. Remarkably, this heavily modified clickable photoactive derivative of propofol was still a potent general anesthetic and was still GABAergic⁵⁹. Deploying this “aziPm-click” compound involved first photolabeling in the presence of synaptosomes and then using click chemistry to attach a biotin moiety to the propofol analogue now covalently bound to its direct binding targets. An avidin column captured all of these biotin-decorated proteins and then in-column proteolysis released peptides, which were identified by using MS. The results were startling. From a total of about 4,500 proteins identified by MS in crude synaptosomes, about 12% (540) were captured by using the click strategy, and, of these, about 200 were deemed to be “propofol specific” on the basis of propofol protection assays. Although many captured proteins may be simply associated with propofol targets and not themselves true propofol-binding targets, it is clear that propofol is a promiscuous drug, and dozens and perhaps hundreds of molecular targets are influenced at clinical concentrations. In contrast to the results of the simple “shotgun” approach, several of the captured proteins were low-abundance ion channels and, gratifyingly, several synaptic GABA_AR subunits. This is the first demonstration of direct propofol binding to GABA_AR when still in its native synaptic environment. Curiously, only α and β subunits were captured, despite the relative abundance of the γ subunit in synapses. Subsequent molecular dynamic simulations provided a plausible explanation. The γ - β and γ - α interfaces were overly hydrated as compared with the α - β ones, indicating that water was competing with binding of the propofol analogue. This aligns with results discussed above in that the resulting asymmetric binding pattern around the heteropentamer (Figure 1) should be more functionally provocative than a symmetric one where all interfaces are occupied⁵¹. Moreover, this implies the importance of H-bonding within the interfacial sites, a hypothesis directly tested with a propofol variant that replaced the hydroxyl with an isosteric fluorine. The resulting “fropofol” molecule has physicochemical properties very similar to those of propofol but no anesthetic or sedative properties whatsoever. This highlights the importance of the hydroxyl in functionally relevant targets⁶⁰ like the GABA_AR. Propofol should be distinguished from other non-immobilizers (for example, the cyclobutanes⁶¹), as those molecules had such pronounced physicochemical differences that a lack of activity was almost certainly due to very low water solubility. Propofol, however, still has significant effects on myocardial (but not skeletal) contractility, indicating that these targets lack an important H-bond in their sites⁶⁰. This is one of the first demonstrations that primary and side effects are separable through fairly minor changes to the alkylphenol molecule.

Voltage-gated ion channels

Monovalent voltage-gated ion channels (VGICs), which are necessary for setting membrane potential and the initiation and propagation of action potentials, are plausible targets of anesthetics. In general, potassium channels are relatively insensitive to propofol⁶², although most inhalational anesthetics and

Figure 1. Asymmetric occupancy of the $\alpha\beta\gamma$ GABA_A receptor by propofol. (A) Photolabeling has identified interfacial binding sites for propofol (colored blobs) in the transmembrane region (seen from the extracellular view here). Furthermore, several lines of evidence now suggest that asymmetric occupancy of these sites confers a larger change in activity than symmetric occupancy (all five subunits). Click-enabled propofol analogues have confirmed asymmetric occupancy of $\alpha\beta\gamma$ GABA_A receptor sites in their native, unperturbed state in that only α and β subunits were photoadducted. The mechanism in the case of this heteropentamer is differential affinity of the interfaces. (B) The relationship between H-bond probability (P_{hb}) and affinity (pK_D) from molecular dynamic simulations shows where each interfacial binding site lies. The two γ -containing interfaces have a much lower P_{hb} and therefore lower affinity.

alcohols inhibit them⁶³. Sodium channels, on the other hand, appear to be inhibited by clinically relevant propofol concentrations⁶⁴. The precise mechanisms are not yet clear, but evidence for anesthetic sites on these VGICs exists. Propofol and sevoflurane sites in the simpler Kv_x channels have been revealed by photolabeling studies^{62,65}, while evidence for propofol sites in the more complex Nav_x channels has been largely through molecular modeling and mutagenesis, although isoflurane sites have been revealed via nuclear magnetic resonance studies⁶⁶. The data suggest at least two general classes of anesthetic sites. First, binding to an important “hinge” site, located between the voltage sensor and the pore domain (S4–5 linker) at the intracellular membrane surface, can alter activity in either direction⁶³, and, second, the pore domain itself.

The pore is an amphiphilic environment fairly well suited to anesthetics, occupancy of which would be expected to produce inhibition. The direction of modulation in these many examples of Kv_x and Nav_x will then depend on relative affinity, and therefore occupancy, of each of these sites.

HCN-1

The importance of the hyperpolarization-activated cyclic nucleotide-regulated (HCN) channels to propofol actions was demonstrated by a diminished sensitivity to propofol in HCN1-knockout mice⁶⁷. Moreover, HCN channels are thought to, in part, underlie the afferent hyperexcitability resulting in neuropathic pain. Propofol and related alkylphenols inhibit the HCN-1 channel at subhypnotic concentrations, making the alkylphenol a reasonable chemotype for further medicinal chemistry to create an analgesic drug with less hypnotic potency^{68–71}. This recent work suggests that increasing the bulk and hydrophobicity of the alkylphenol side chains (for example, 2,6-Di-tert-butylphenol) accomplishes this to some degree, lending confidence that an entirely novel class of analgesic, useful for neuropathic pain, may emerge from the alkylphenol chemotype⁷². Binding sites and mechanisms by which the alkylphenols inhibit this channel are not yet clear, but the recent publication of a cryo-electron microscopy structure⁷³ should facilitate work in the area.

Kinesin

Building on work over the previous two decades which implicated actin, tubulin, and other cellular or synaptic cytoskeleton and transport machinery in general anesthetic action^{74–76}, investigators recently examined the effects of propofol on the anterograde motor kinesin. Kinesin is like a locomotive that runs along microtubule “tracks” by using its dimeric motor heads to step from β to β tubulin subunit⁷⁷. Should these tracks be decorated with bound anesthetic molecules, it is plausible that motor function and ultimately transport would be altered. In single-molecule experiments, where, instead of its usual cargo, kinesin is attached to a fluorescent bead and microtubules are immobilized on a substrate, it was noticed that clinically relevant concentrations of propofol reduced run length by half and had no effect on velocity⁷⁸. In other words, the train goes just as fast but derails. This might indicate extensive tubulin binding of propofol, but could also be due to effects within kinesin itself. If the latter, the single-molecule results suggest that the propofol site is allosteric to the nucleotide-binding site and that it is not influencing ATPase activity. Most likely, an allosteric site in kinesin is formed when the motor head binds to β tubulin. In either case, though, the result is the same, and cargo is transported by these anterograde kinesins reaching their destinations more slowly or not at all. Depending on redundancy, this may have important consequences in terms of the critical timing of cellular/neuronal activity. Applying the anesthetic-null variant propofol (see above) had no effect, lending some credence to the possibility that kinesin modulation underlies propofol-induced unconsciousness. It is also plausible that an interaction between kinesin and propofol underlies a number of propofol’s less desirable actions, such as neurotoxicity at the extremes of age⁷⁹.

TRPx receptors

It is well known that propofol both causes pain on injection and sensitizes nociception. The candidate molecular targets for transducing these effects are the widely distributed TRPA and TRPV receptors^{80,81}. TRPA-1, in particular, is known to be

modulated by propofol in a biphasic manner: activated at low, clinically relevant concentrations and inhibited at higher concentrations. The mechanism or mechanisms by which propofol produces these actions are suggested by recent mutagenesis⁸² and photolabeling results with aziPm⁸³. For example, the canonical “hinge” region of these channels, connecting sensor to pore domains and typically located in and around the cytoplasmic face of the transmembrane region, forms a binding site whereby, when occupied, the open state is stabilized, enhancing current flow (Figure 2). However, when the channel is in the open state, a lower-affinity pore site is created which becomes progressively occupied as the propofol concentration is raised, reducing current flow. This sequential occupancy of two sites of differing affinity and effect is presumably responsible for the bimodal modulation of the TRPA-1 receptor and may be a general model for actions on other channels. Since activation of a nociceptor is not a desirable attribute of a general anesthetic, it would be important

to determine characteristics of the binding site in order to use medicinal chemistry approaches to weaken binding to this activating site. This may not only reduce pain of injection but also increase anesthetic potency, depending on the central nervous system (CNS) distribution of the TRPA-1 receptor.

SIRT-2 deacetylase

On evaluation of the propofol-binding proteome of various CNS tissues, it was found that myelin contained a highly specific protein target of propofol that was ultimately determined to be the SIRT-2 deacetylase⁸⁴. The acetylase and deacetylase enzymes are key intracellular regulators of a wide variety of events⁸⁵; thus, an effect of anesthetics would be expected to have far-reaching consequences. Since a binding target does not necessarily indicate a functional target, a number of experiments were conducted to determine whether propofol had an effect on SIRT-2 deacetylase activity and at a clinically relevant concentration. Indeed,

Figure 2. Recent examples of propofol-binding proteins. In both the TRPA1 (A, B) and SIRT2 (C, D), note that the propofol-enhanced active or open state (B, D) suggests that the alkylphenol-binding pocket is actually enlarged somewhat as compared with the closed or inactive state (A, C). We believe that this is an example of enhanced affinity as a result of reduction in the entropic penalties of binding and may be a common feature in conformationally sensitive binding, a form of “induced fit”. The yellow stippled shapes in (A) and (B) represent multiple poses of both propofol and aziPm when docked in the vicinity of the photolabeled residues. In (C) and (D), the red shapes are photolabeled residues and the black shape is the surface rendering of the cavity occupied by propofol.

when isolated SIRT-2 was exposed to low-micromolar concentrations of propofol, its activity was significantly inhibited, and the structural mechanism was characterized (Figure 2)⁸⁴. Though unlikely to underlie the primary, desired action of propofol, this interaction may underlie one or more of the many side effects of propofol. Since acetylation and methylation systems are responsible for epigenetic regulation, this interaction could even be responsible for delayed or persistent effects of propofol, such as developmental neuromodulation⁷⁹.

Summary

Much progress has been made in understanding the mechanisms of propofol's actions on its canonical molecular target, the GABA_AR, but a role for other molecular targets is gaining momentum. Propofol is undeniably a promiscuous anesthetic ligand, and its diverse molecular targets are integrated in a manner

that is still poorly characterized. Finally, evidence suggests that further medicinal chemistry of the alkylphenol chemotype may allow enhancement of selected actions.

Competing interests

The authors declare that they have no competing interests.

Grant information

The research was supported by funding from the NIH (Pei Tang, R01GM056257 and R01GM066358; Roderic G. Eckenhoff, P01GM55876).

The funders had no role in the decision to prepare or publish this review article.

References

- Vuyk J, Sitsen E, Reekers M: **Chapter 30 Intravenous Anesthetics**. *Miller's Anesthesia*, 8th edition. Edited by Miller RD, Cohen, N.H., Eriksson, L.I., Fleisher, L.A., Weiner-Kronish, J.P., Young, W.L. Philadelphia, Elsevier, 2015; 821–863.
[Reference Source](#)
- Jia L, Tang P, Brandon NR, *et al.*: **Effects of Propofol General Anesthesia on Olfactory Relearning**. *Sci Rep*. 2016; 6: 33538.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Purdon PL, Pierce ET, Mukamel EA, *et al.*: **Electroencephalogram signatures of loss and recovery of consciousness from propofol**. *Proc Natl Acad Sci USA*. 2013; 110(12): E1142–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Schrouff J, Perlberg V, Boly M, *et al.*: **Brain functional integration decreases during propofol-induced loss of consciousness**. *Neuroimage*. 2011; 57(1): 198–205.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hales TG, Lambert JJ: **The actions of propofol on inhibitory amino acid receptors of bovine adrenomedullary chromaffin cells and rodent central neurones**. *Br J Pharmacol*. 1991; 104(3): 619–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Orser BA, Wang LY, Pennefather PS, *et al.*: **Propofol modulates activation and desensitization of GABAA receptors in cultured murine hippocampal neurons**. *J Neurosci*. 1994; 14(12): 7747–60.
[PubMed Abstract](#)
- Franks NP, Lieb WR: **Molecular and cellular mechanisms of general anaesthesia**. *Nature*. 1994; 367(6464): 607–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hemmings HC Jr, Akabas MH, Goldstein PA, *et al.*: **Emerging molecular mechanisms of general anesthetic action**. *Trends Pharmacol Sci*. 2005; 26(10): 503–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Forman SA, Miller KW: **Anesthetic sites and allosteric mechanisms of action on Cys-loop ligand-gated ion channels**. *Can J Anaesth*. 2011; 58(2): 191–205.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Forman SA, Chiara DC, Miller KW: **Anesthetics target interfacial transmembrane sites in nicotinic acetylcholine receptors**. *Neuropharmacology*. 2015; 96(Pt B): 169–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Flood P, Ramirez-Latorre J, Role L: **Alpha 4 beta 2 neuronal nicotinic acetylcholine receptors in the central nervous system are inhibited by isoflurane and propofol, but alpha 7-type nicotinic acetylcholine receptors are unaffected**. *Anesthesiology*. 1997; 86(4): 859–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Violet JM, Downie DL, Nakisa RC, *et al.*: **Differential sensitivities of mammalian neuronal and muscle nicotinic acetylcholine receptors to general anesthetics**. *Anesthesiology*. 1997; 86(4): 866–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Dilger JP, Vidal AM, Mody HI, *et al.*: **Evidence for direct actions of general anesthetics on an ion channel protein. A new look at a unified mechanism of action**. *Anesthesiology*. 1994; 81(2): 431–42.
[PubMed Abstract](#)
- Weng Y, Yang L, Corring PJ, *et al.*: **Anesthetic sensitivity of the *Gloeobacter violaceus* proton-gated ion channel**. *Anesth Analg*. 2010; 110(1): 59–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Tillman T, Cheng MH, Chen Q, *et al.*: **Reversal of ion-charge selectivity renders the pentameric ligand-gated ion channel GLIC insensitive to anaesthetics**. *Biochem J*. 2013; 449(1): 61–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Tillman TS, Seyoum E, Mowrey DD, *et al.*: **ELIC-α7 Nicotinic acetylcholine receptor (α7nAChR) chimeras reveal a prominent role of the extracellular-transmembrane domain interface in allosteric modulation**. *J Biol Chem*. 2014; 289(20): 13851–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chen Q, Kinde MN, Arjunan P, *et al.*: **Direct Pore Binding as a Mechanism for Isoflurane Inhibition of the Pentameric Ligand-gated Ion Channel ELIC**. *Sci Rep*. 2015; 5: 13833.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sanna E, Garau F, Harris RA: **Novel properties of homomeric beta 1 gamma-aminobutyric acid type A receptors: actions of the anesthetics propofol and pentobarbital**. *Mol Pharmacol*. 1995; 47(2): 213–7.
[PubMed Abstract](#)
- Adodra S, Hales TG: **Potentiation, activation and blockade of GABA_A receptors of clonal murine hypothalamic GT1-7 neurones by propofol**. *Br J Pharmacol*. 1995; 115(6): 953–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Morales-Perez CL, Noviello CM, Hibbs RE: **X-ray structure of the human α4β2 nicotinic receptor**. *Nature*. 2016; 538(7625): 411–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Hassaine G, Deluz C, Grasso L, *et al.*: **X-ray structure of the mouse serotonin 5-HT₃ receptor**. *Nature*. 2014; 512(7514): 276–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Miller PS, Aricescu AR: **Crystal structure of a human GABA_A receptor**. *Nature*. 2014; 512(7514): 270–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Huang X, Chen H, Michelsen K, *et al.*: **Crystal structure of human glycine receptor-α3 bound to antagonist strychnine**. *Nature*. 2015; 526(7572): 277–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Du J, Lü W, Wu S, *et al.*: **Glycine receptor mechanism elucidated by electron cryo-microscopy**. *Nature*. 2015; 526(7572): 224–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Nury H, Van Renterghem C, Weng Y, *et al.*: **X-ray structures of general**

- anaesthetics bound to a pentameric ligand-gated ion channel. *Nature*. 2011; 469(7330): 428–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
26. **F** Sauguet L, Howard RJ, Malherbe L, *et al.*: Structural basis for potentiation by alcohols and anaesthetics in a ligand-gated ion channel. *Nat Commun*. 2013; 4: 1697.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 27. Pan J, Chen Q, Willenbring D, *et al.*: Structure of the pentameric ligand-gated ion channel GLIC bound with anesthetic ketamine. *Structure*. 2012; 20(9): 1463–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 28. Chen Q, Wells MM, Tillman TS, *et al.*: Structural Basis of Alcohol Inhibition of the Pentameric Ligand-Gated Ion Channel ELIC. *Structure*. 2017; 25(1): 180–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 29. Spurny R, Billen B, Howard RJ, *et al.*: Multisite binding of a general anesthetic to the prokaryotic pentameric Erwinia chrysanthemi ligand-gated ion channel (ELIC). *J Biol Chem*. 2013; 288(12): 8355–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 30. Chiara DC, Gill JF, Chen Q, *et al.*: Photoaffinity labeling the propofol binding site in GLIC. *Biochemistry*. 2014; 53(1): 135–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 31. Kinde MN, Bu W, Chen Q, *et al.*: Common Anesthetic-binding Site for Inhibition of Pentameric Ligand-gated Ion Channels. *Anesthesiology*. 2016; 124(3): 664–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 32. Jayakar SS, Dailey WP, Eckenhoff RG, *et al.*: Identification of propofol binding sites in a nicotinic acetylcholine receptor with a photoreactive propofol analog. *J Biol Chem*. 2013; 288(9): 6178–89.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 33. Chiara DC, Hong FH, Arevalo E, *et al.*: Time-resolved photolabeling of the nicotinic acetylcholine receptor by [³H]azetomidate, an open-state inhibitor. *Mol Pharmacol*. 2009; 75(5): 1084–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 34. **F** Hamouda AK, Stewart DS, Husain SS, *et al.*: Multiple transmembrane binding sites for *p*-trifluoromethylidiaziriny-*l*-etomidate, a photoreactive *Torpedo* nicotinic acetylcholine receptor allosteric inhibitor. *J Biol Chem*. 2011; 286(23): 20466–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 35. Chiara DC, Dangott LJ, Eckenhoff RG, *et al.*: Identification of nicotinic acetylcholine receptor amino acids photolabeled by the volatile anesthetic halothane. *Biochemistry*. 2003; 42(46): 13457–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Jurd R, Arras M, Lambert S, *et al.*: General anesthetic actions *in vivo* strongly attenuated by a point mutation in the GABA_A receptor beta3 subunit. *FASEB J*. 2003; 17(2): 250–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. **F** Eaton MM, Germann AL, Arora R, *et al.*: Multiple Non-Equivalent Interfaces Mediate Direct Activation of GABA_A Receptors by Propofol. *Curr Neuropharmacol*. 2016; 14(7): 772–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 38. **F** Forman SA, Miller KW: Mapping General Anesthetic Sites in Heteromeric γ -Aminobutyric Acid Type A Receptors Reveals a Potential For Targeting Receptor Subtypes. *Anesth Analg*. 2016; 123(5): 1263–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 39. **F** Nourmahad A, Stern AT, Hotta M, *et al.*: Tryptophan and Cysteine Mutations in M1 Helices of α 1 β 3 γ 2L γ -Aminobutyric Acid Type A Receptors Indicate Distinct Intersubunit Sites for Four Intravenous Anesthetics and One Orphan Site. *Anesthesiology*. 2016; 125(6): 1144–58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 40. **F** Chiara DC, Jounaidi Y, Zhou X, *et al.*: General Anesthetic Binding Sites in Human α 4 β 3 δ γ -Aminobutyric Acid Type A Receptors (GABA_ARs). *J Biol Chem*. 2016; 291(51): 26529–39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 41. **F** Eaton MM, Cao LQ, Chen Z, *et al.*: Mutational Analysis of the Putative High-Affinity Propofol Binding Site in Human β 3 Homomeric GABA_A Receptors. *Mol Pharmacol*. 2015; 88(4): 736–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 42. Jayakar SS, Zhou X, Chiara DC, *et al.*: Multiple propofol-binding sites in a γ -aminobutyric acid type A receptor (GABA_AR) identified using a photoreactive propofol analog. *J Biol Chem*. 2014; 289(40): 27456–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. **F** Yip GM, Chen ZW, Edge CJ, *et al.*: A propofol binding site on mammalian GABA_A receptors identified by photolabeling. *Nat Chem Biol*. 2013; 9(11): 715–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 44. Bondarenko V, Mowrey D, Liu LT, *et al.*: NMR resolved multiple anesthetic binding sites in the TM domains of the α 4 β 2 nAChR. *Biochim Biophys Acta*. 2013; 1828(2): 398–404.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 45. Bondarenko V, Mowrey DD, Tillman TS, *et al.*: NMR structures of the human α 7 nAChR transmembrane domain and associated anesthetic binding sites. *Biochim Biophys Acta*. 2014; 1838(5): 1389–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 46. Chen Q, Cheng MH, Xu Y, *et al.*: Anesthetic binding in a pentameric ligand-gated ion channel: GLIC. *Biophys J*. 2010; 99(6): 1801–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 47. **F** Hall MA, Xi J, Lor C, *et al.*: *m*-Azipropofol (AziPm) a photoactive analogue of the intravenous general anesthetic propofol. *J Med Chem*. 2010; 53(15): 5667–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 48. Ruesch D, Neumann E, Wulf H, *et al.*: An allosteric coagonist model for propofol effects on α 1 β 2 γ 2L γ -aminobutyric acid type A receptors. *Anesthesiology*. 2012; 116(1): 47–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 49. **F** Li Y, Wu Y, Li R, *et al.*: Propofol Regulates the Surface Expression of GABAA Receptors: Implications in Synaptic Inhibition. *Anesth Analg*. 2015; 121(5): 1176–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 50. **F** Speigel I, Bichler EK, Garcia PS: The Influence of Regional Distribution and Pharmacologic Specificity of GABA_A Subtype Expression on Anesthesia and Emergence. *Front Syst Neurosci*. 2017; 11: 58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 51. **F** Mowrey D, Cheng MH, Liu LT, *et al.*: Asymmetric ligand binding facilitates conformational transitions in pentameric ligand-gated ion channels. *J Am Chem Soc*. 2013; 135(6): 2172–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 52. Roberts MT, Phelan R, Erlichman BS, *et al.*: Occupancy of a single anesthetic binding pocket is sufficient to enhance glycine receptor function. *J Biol Chem*. 2006; 281(6): 3305–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
 53. Rayes D, De Rosa MJ, Sine SM, *et al.*: Number and locations of agonist binding sites required to activate homomeric Cys-loop receptors. *J Neurosci*. 2009; 29(18): 6022–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 54. Beato M, Groot-Kormelink PJ, Colquhoun D, *et al.*: The activation mechanism of α 1 β 1 homomeric glycine receptors. *J Neurosci*. 2004; 24(4): 895–906.
[PubMed Abstract](#) | [Publisher Full Text](#)
 55. Amin J, Weiss DS: Insights into the activation mechanism of rho1 GABA receptors obtained by coexpression of wild type and activation-impaired subunits. *Proc Biol Sci*. 1996; 263(1368): 273–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
 56. **F** Tang J, Xue Q, Ding H, *et al.*: Proteomic profiling of the phosphoproteins in the rat thalamus, hippocampus and frontal lobe after propofol anesthesia. *BMC Anesthesiol*. 2014; 14: 3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 57. **F** Weiser BP, Kelz MB, Eckenhoff RG: *In vivo* activation of azipropofol prolongs anesthesia and reveals synaptic targets. *J Biol Chem*. 2013; 288(2): 1279–85.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 58. **F** Meghani NM, Amin HH, Lee BJ: Mechanistic applications of click chemistry for pharmaceutical drug discovery and drug delivery. *Drug Discov Today*. 2017; 22(11): 1604–1619.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 59. Woll KA, Murlidaran S, Pinch BJ, *et al.*: A Novel Bifunctional Alkylphenol Anesthetic Allows Characterization of γ -Aminobutyric Acid, Type A (GABA_A)₁ Receptor Subunit Binding Selectivity in Synaptosomes. *J Biol Chem*. 2016; 291(39): 20473–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 60. Woll KA, Weiser BP, Liang Q, *et al.*: Role for the propofol hydroxyl in anesthetic protein target molecular recognition. *ACS Chem Neurosci*. 2015; 6(6): 927–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 61. Burkat PM, Lor C, Perouansky M, *et al.*: Enhancement of α 5-containing γ -aminobutyric acid type A receptors by the nonimmobilizer 1,2-dichlorohexafluorocyclobutane (F6) is abolished by the β 3(N265M) mutation. *Anesth Analg*. 2014; 119(6): 1277–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 62. Bu W, Liang Q, Zhi L, *et al.*: Sites and Functional Consequence of Alkylphenol Anesthetic Binding to Kv1.2 Channels. *Mol Neurobiol*. 2017; 1–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
 63. Covarrubias M, Barber AF, Carnevale V, *et al.*: Mechanistic Insights into the Modulation of Voltage-Gated Ion Channels by Inhalational Anesthetics. *Biophys J*. 2015; 109(10): 2003–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 64. Ouyang W, Wang G, Hemmings HC Jr: Isoflurane and propofol inhibit voltage-gated sodium channels in isolated rat neurohypophyseal nerve terminals. *Mol Pharmacol*. 2003; 64(2): 373–81.
[PubMed Abstract](#) | [Publisher Full Text](#)

65. Woll KA, Peng W, Liang Q, *et al.*: **Photoaffinity Ligand for the Inhalational Anesthetic Sevoflurane Allows Mechanistic Insight into Potassium Channel Modulation.** *ACS Chem Biol.* 2017; **12**(5): 1353–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. Kinde MN, Bondarenko V, Granata D, *et al.*: **Fluorine-19 NMR and computational quantification of isoflurane binding to the voltage-gated sodium channel NaChBac.** *Proc Natl Acad Sci U S A.* 2016; **113**(48): 13762–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
67. Chen X, Shu S, Bayliss DA: **HCN1 channel subunits are a molecular substrate for hypnotic actions of ketamine.** *J Neurosci.* 2009; **29**(3): 600–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
68. Funahashi M, Mitoh Y, Matsuo R: **The sensitivity of hyperpolarization-activated cation current (I_h) to propofol in rat area postrema neurons.** *Brain Res.* 2004; **1015**(1–2): 198–201.
[PubMed Abstract](#) | [Publisher Full Text](#)
69. Cacheaux LP, Topf N, Tibbs GR, *et al.*: **Impairment of hyperpolarization-activated, cyclic nucleotide-gated channel function by the intravenous general anesthetic propofol.** *J Pharmacol Exp Ther.* 2005; **315**(2): 517–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
70. Ying SW, Abbas SY, Harrison NL, *et al.*: **Propofol block of I_h contributes to the suppression of neuronal excitability and rhythmic burst firing in thalamocortical neurons.** *Eur J Neurosci.* 2006; **23**(2): 465–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
71. Tibbs GR, Rowley TJ, Sanford RL, *et al.*: **HCN1 channels as targets for anesthetic and nonanesthetic propofol analogs in the amelioration of mechanical and thermal hyperalgesia in a mouse model of neuropathic pain.** *J Pharmacol Exp Ther.* 2013; **345**(3): 363–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
72. Tibbs GR, Posson DJ, Goldstein PA: **Voltage-Gated Ion Channels in the PNS: Novel Therapies for Neuropathic Pain?** *Trends Pharmacol Sci.* 2016; **37**(7): 522–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
73. Lee CH, Mackinnon R: **Structures of the Human HCN1 Hyperpolarization-Activated Channel.** *Cell.* 2017; **168**(1–2): 111–120.e11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
74. Emerson DJ, Weiser BP, Psonis J, *et al.*: **Direct modulation of microtubule stability contributes to anthracene general anesthesia.** *J Am Chem Soc.* 2013; **135**(14): 5389–98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
75. Craddock TJ, St George M, Freedman H, *et al.*: **Computational predictions of volatile anesthetic interactions with the microtubule cytoskeleton: implications for side effects of general anesthesia.** *PLoS One.* 2012; **7**(6): e37251.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. Turina D, Gerhardsson H, Bjornstrom K: **Orexin A reverses propofol and thiopental induced cytoskeletal rearrangement in rat neurons.** *J Physiol Pharmacol.* 2014; **65**(4): 531–41.
[PubMed Abstract](#) | [F1000 Recommendation](#)
77. Verhey KJ, Kaul N, Soppina V: **Kinesin assembly and movement in cells.** *Annu Rev Biophys.* 2011; **40**: 267–88.
[PubMed Abstract](#) | [Publisher Full Text](#)
78. Benseal BM, Guzik-Lendrum S, Masucci EM, *et al.*: **Common general anesthetic propofol impairs kinesin processivity.** *Proc Natl Acad Sci U S A.* 2017; **114**(21): E4281–E4287.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. Eckenhoff RG, Jevtovic-Todorovic V: **Chapter 15 Perioperative and Anesthesia Neurotoxicity.** *Miller's Anesthesia.* Edited by Miller RD, Cohen, N.H., Eriksson, L.I., Fleisher, L.A., Weiner-Kronish, J.P., Young, W.L. Philadelphia, Elsevier, 2015; 329–346.
[Reference Source](#)
80. Fischer MJ, Leffler A, Niedermirtl F, *et al.*: **The general anesthetic propofol excites nociceptors by activating TRPV1 and TRPA1 rather than GABA_A receptors.** *J Biol Chem.* 2010; **285**(45): 34781–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
81. Matta JA, Cornett PM, Miyares RL, *et al.*: **General anesthetics activate a nociceptive ion channel to enhance pain and inflammation.** *Proc Natl Acad Sci U S A.* 2008; **105**(25): 8784–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
82. Ton HT, Phan TX, Abramyan AM, *et al.*: **Identification of a putative binding site critical for general anesthetic activation of TRPA1.** *Proc Natl Acad Sci U S A.* 2017; **114**(14): 3762–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
83. Woll KA, Skinner KA, Gianti E, *et al.*: **Sites Contributing to TRPA1 Activation by the Anesthetic Propofol Identified by Photoaffinity Labeling.** *Biophys J.* 2017; **113**(10): 2168–2172.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
84. Weiser BP, Eckenhoff RG: **Propofol inhibits SIRT2 deacetylase through a conformation-specific, allosteric site.** *J Biol Chem.* 2015; **290**(13): 8559–68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. Li L, Yang XJ: **Tubulin acetylation: responsible enzymes, biological functions and human diseases.** *Cell Mol Life Sci.* 2015; **72**(22): 4237–55.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

- 1. Stuart A. Forman**
Dept. of Anesthesia Critical Care & Pain Medicine, Massachusetts General Hospital, Massachusetts, USA
Competing Interests: No competing interests were disclosed.
- 2. Eintrei Christina**
Linköping University, Linköping, Sweden
Competing Interests: No competing interests were disclosed.
- 3. Tim Hales**
University of Dundee, Dundee, UK
Competing Interests: No competing interests were disclosed.
- 4. Gustav Akk**
Department of Anesthesiology, Washington University School of Medicine, St Louis, MO, USA
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research