ACS Chemical Neuroscience

In This Issue

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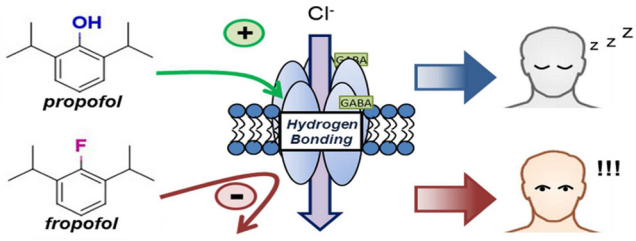
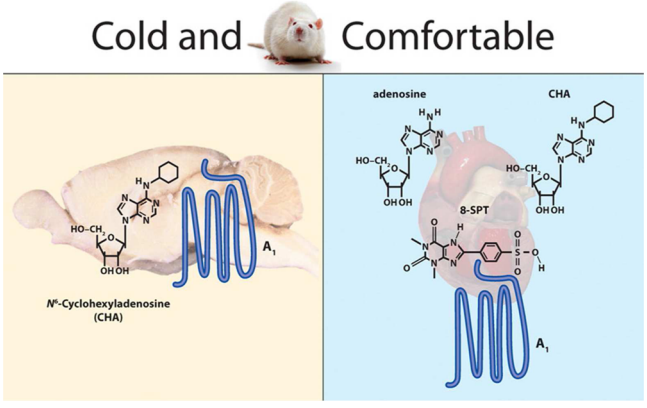
UNDERSTANDING THE EFFECTS OF A GENERAL ANESTHETIC



General anesthetics are among the most widely used therapeutics in health care today; however, these drugs are also known to have potentially serious side effects. The chemical properties of these drugs that lend toward these diverse effects remain elusive. In the current issue, Woll et al. (DOI: 10.1021/acschemneuro.5b00078) investigate a key chemical property of the anesthetic propofol—its ability to form hydrogen bonds—by creating a hydrogen bond-null analogue called "fropofol". These findings are significant because previous work has been unable to definitively determine if the propofol hydroxyl is important for target recognition or for solvation.

The authors demonstrate that the desired and adverse biological effects of an important general anesthetic can be separated through alteration of a single key chemical feature. They first synthesize "fropofol" which substitutes fluorine for propofol's 1-hydroxyl, thereby diminishing the capability of the molecule to hydrogen bond. The comparison of the protein binding properties for the two ligands within two protein models allowed for distinction of the two principle pharmacophoric features, hydrophobicity and hydrogen bond propensity. Within two animal models (tadpole and mouse), the authors demonstrate that the hydroxyl is absolutely necessary for hypnotic activity. This effect is likely explained by differential activity on the $GABA_A$ receptor. Differential activity is shown to be due to differential binding, indicating that a hydrogen bond in the $GABA_A$ allosteric site is a critical molecular recognition feature. The adverse effect of propofol, depression of myocardial contractility, is also shared by fropofol. This is the first evidence that the desired and adverse effects of a general anesthetic might be separable through rational drug design.

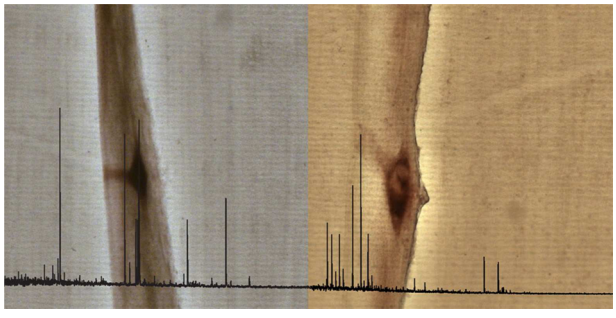
INDUCING THERAPEUTIC HYPOTHERMIA IN A RAT MODEL



Shivering is one of the most problematic issues in targeted temperature management and is controlled with pharmacological adjuncts, such as paralytics, narcotics, sedatives, meperidine, and buspirone with little regard to mechanism of action. Hibernating species enter hibernation via activation of adenosine A_1 receptors (A_1AR) within the CNS. In the current issue, Jinka et al. (DOI: 10.1021/acschemneuro.5b00056) aim to mimic this mechanism to induce therapeutic hypothermia in rats.

To achieve a clinically feasible means of drug administration, the authors targeted the CNS by combining an A1AR agonist that readily penetrates the blood-brain barrier with an adenosine receptor antagonist that does not pass the blood-brain barrier. The A_1AR agonist, ^6N-cyclohexyladenosine, produces prolonged periods of mild hypothermia, and bradycardia, the primary peripheral side effect of A_1AR agonists, can be managed with the adenosine receptor antagonist, 8-(*p*-sulfophenyl)theophylline while sparing effects of ^6N-cyclohexyladenosine on body temperature. The authors further show that cooling rats in this manner increases survival after cardiac arrest.

DISCOVERY OF NOVEL NEUROPEPTIDES



Neuropeptides are known to have dramatic effects on neurons and synapses. To explore the potential role of neuropeptides in the motor nervous system, Konop et al. (DOI: 10.1021/cn5003623) characterized the peptides present in single excitatory motorneurons in the parasitic nematode *Ascaris suum* and sequenced them by tandem mass spectrometry.

The authors use mass spectrometry to detect and sequence 14 neuropeptides from single dissected identified motorneurons; six of them being novel. This was followed by further confirmation of the cellular expression of the genes that encode these peptides by in situ hybridization. The preliminary characterization of biological activity is also discussed.

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