State of the (research) chimp

Because they are our closest animal relatives, the use of chimpanzees in research has brought about both valuable advances for human health and intense ethical controversy. The US is one of very few countries that currently allow research on chimpanzees. Both the European Union and the UK already prohibit invasive research on chimpanzees. In 2010, the US National Institutes of Health (NIH), a key source of federal funds for all types of biomedical research, commissioned a study by the Institute of Medicine (IOM) to assess the necessity of using chimpanzees in research. The IOM report, issued in December 2011, found that "while the chimpanzee has been a valuable animal model in past research, most current use of chimpanzees for biomedical research is unnecessary."

The report recommended that the use of chimpanzees in research be guided by three main principles: the knowledge to be gained must be necessary to advance human health; that knowledge must not be obtainable using other animal models or human subjects; and the chimpanzees' housing environments must very closely match their natural habitat. Francis Collins, NIH director, accepted the recommendations of the IOM report and is developing a plan to implement them. Furthermore, Collins stated in a press release, "We will not issue any new awards for research involving chimpanzees until processes for implementing the recommendations are in place."

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The IOM report identified several research areas in which the use of chimpanzees may be justified, but a consensus was not reached on one particular research topic: the development of a vaccine against hepatitis C virus (HCV). As many as 170 million people worldwide have chronic HCV infections, which can lead to liver failure. HCV infects only humans and chimpanzees, and the IOM committee could not agree on which species should be used in the final tests of a prophylactic HCV vaccine.

Some researchers are concerned that the indecision may delay vaccine development. Christopher Walker (Nationwide Children's Hospital, Columbus, OH), who studies HCV immunity in chimpanzees, told *Nature News*, "If you have an idea for an entirely new approach to vaccination, but can't get proof of that principle in animals, my fear is that it will never move ahead into human trials." And Thomas Rowell, director of New Iberia Research Center (LA), a large chimpanzee research center, told the *New York Times*, "Much of the work we do is done because the FDA won't allow the drug or vaccine to move into human trials without seeing data in relevant species."

Monica Harrington

SPECIFIC MELATONIN RECEPTOR PROMOTES A DEEPER SLEEP

Insomnia or insufficient sleep is a common malady, affecting millions of people worldwide. Mammalian sleep normally progresses from wakefulness to non-rapid eye movement sleep (NREMS) before transitioning to rapid eye movement sleep (REMS). NREMS is also called slow-wave, deep or restorative sleep because important functions such as memory consolidation and metabolic regulation occur during this phase. Existing pharmacologic treatments for insomnia, such as benzodiazepines, disrupt natural sleep progression and may result in cognitive dysfunction as well as dependence and abuse. Therefore, the development of new therapies that selectively increase NREMS without disrupting sleep progression has remained a clinical goal.

Melatonin, nicknamed the 'sleep hormone', is produced by the pineal gland in the absence of light stimulation and is involved in regulating sleep and circadian rhythms, as well as in depression and anxiety. Its effects on sleep in humans and in animals have been studied, but results have been inconclusive.

Melatonin acts via two receptors in the brain, MT_1 and MT_2, whose individual effects on sleep have yet to be defined. Newly published work from Gabriella Gobbi and colleagues (McGill University and McGill University Health Center, Montreal, Quebec, Canada) in collaboration with chemists from Carlo Bo University of Urbino and University of Parma in Italy now shows that the two receptors have opposing effects on sleep in rodents. Gobbi told the *Montreal Gazette*, "It was tough because we went against conventional wisdom on melatonin. We thought both receptors would promote sleep and it's not true—the receptors have opposite roles." MT_1 and MT_2 have conflicting roles in other systems as well: in the hippocampus, the two receptors differentially modulate GABA receptor function, and in the vascular system, MT_1 acts as a constrictor whereas MT_2 acts as a dilator.

The researchers used a new drug called UCM765 to selectively activate MT_2 receptors. Administration of 40 mg UCM765 per kg body weight in rats decreased latency to sleep by ~60%, decreased the amount of time spent awake by almost 40% and increased the duration of NREMS sleep by almost 50%, without affecting REMS (*J. Neurosci.* **31**, 18439–18452; 2011). These effects of UCM765 on NREMS were absent when MT_2 receptors were genetically or pharmacologically inactivated.

Gobbi's results showed that in rodents, activation of the MT_2 receptor specifically promoted NREMS without altering sleep progression. "Specifying the role of MT_2 receptors... represent[s] a major scientific breakthrough that may designate them as a promising novel target for future treatments of insomnia," Gobbi stated in a press release.

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