An antidote for hypersomnia

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Researchers at Emory University School of Medicine have discovered that dozens of adults with an elevated need for sleep have a substance in their cerebrospinal fluid that acts like a sleeping pill.

The results are scheduled for publication online Wednesday by the journal *Science Translational Medicine*.

Some members of this patient population appear to have a distinct, disabling sleep disorder called "primary hypersomnia," which is separate from better-known conditions such as sleep apnea or narcolepsy. They regularly sleep more than 70 hours per week and have difficulties awakening. When awake, they still have reaction times comparable to someone who has been awake all night. Their sleepiness often interferes with work or school attendance, and conventional treatments such as stimulants bring little relief.

"These individuals report feeling as if they're walking around in a fog – physically, but not mentally awake," says lead author David Rye, MD, PhD, professor of neurology at Emory University School of Medicine and director of research for Emory Healthcare's Program in Sleep. "When encountering excessive sleepiness in a patient, we typically think it's caused by an impairment in the brain's wake systems and treat it with stimulant medications. However, in these patients, the situation is more akin to attempting to drive a car with the parking brake engaged. Our thinking needs to shift from pushing the accelerator harder, to releasing the brake."

In a clinical study with seven patients who remained sleepy despite above-ordinary sleep amounts and treatment with stimulants, Emory researchers showed that treatment with the drug flumazenil can restore alertness, although flumazenil's effectiveness was not uniform for all seven. Alertness was gauged through the psychomotor vigilance test, a measurement of reaction time.

Flumazenil is usually used in cases of overdose of benzodiazepines, a widely used class of anesthetics and sedatives such as diazepam (Valium) and zolpidem (Ambien). Evidence in the paper suggests that the sleep-inducing substance in patients' cerebrospinal fluid is not a benzodiazepine drug, even though flumazenil counteracts it. Identifying the mysterious "somnogen," which appears to be produced by the body, could give scientists greater insight into how our brains regulate states of consciousness such as alertness and sleep.

"Primary hypersomnias are disabling and poorly understood. This study represents a breakthrough in determining a cause for these disorders and devising a rational approach to therapy," says Merrill Mitler, PhD, a program director at the National Institute of Neurological Disorders and Stroke, part of the National Institutes of Health." Further research is required to determine whether or not the results apply to the majority of patients."

The team of researchers involved in this effort includes Rye; Andrew Jenkins, PhD, Emory assistant professor of anesthesiology; and Kathy Parker, PhD, RN, FAAN, previously at Emory and now at University of Rochester Medical Center.

The paper describes how samples of patients' cerebrospinal fluid (CSF) contain a substance that enhances the effects of the brain chemical GABA (gamma-amino butyric acid). GABA is one of the main inhibitory chemicals of the nervous system – alcohol, barbituates and

benzodiazepines all enhance the effects of GABA. In the laboratory, the size of the effect on GABA receptor function is more than twice as large in the hyper-sleepy patients, on average, than in control samples.

"In some of the more severely affected patients, we estimated the magnitude of the GABA-enhancing effect as nearly equivalent to that expected for someone receiving sedation for outpatient colonoscopy," Rye says. "This is a level of impaired consciousness that many subjects had to combat on almost a daily basis in order to live their usual lives."

The ICSD-2 (International Classification of Sleep Disorders) terms this disorder "primary hypersomnia" and the proposed DSM-V describes it as "major hypersomnolence disorder." Its prevalence is unclear. The Emory team's findings could potentially provide a biological definition and a treatment for an under-recognized sleep disorder.

The patients in the group examined in the paper have received a variety of diagnoses, including idiopathic hypersomnia and narcolepsy without cataplexy. Cataplexy is a sudden loss of muscle tone, sometimes triggered by surprise or strong emotion, characteristic to narcolepsy. Other members of the group are simply considered "long sleepers" (more than 10 hours per day).

In addition, the identity of the GABA-enhancing substance is not yet known, although Rye and Jenkins are devising strategies to pin it down. Based on its size and sensitivity to certain enzymes, it could be a peptide, similar to but not the same as the hormones oxytocin or hypocretin. Jenkins and his colleagues have shown that the sleep-inducing substance can act on GABA receptors that are not sensitive to benzodiazepines.

"Previous studies with flumazenil indicate that it does not have a wake-promoting effect on most people, so its ability to normalize vigilance in this subpopulation of extremely sleepy patients appears genuinely novel,"

Rye says.

More information: D.B. Rye, D.L. Bliwise, L.M. Trotti, P. Saini, J. Fairley, A. Freeman, P.S. Garcia, M.J. Owens, J.C. Ritchie and A. Jenkins. Modulation of vigilance in the primary hypersomnias by endogenous enhancement of GABA(A) receptors. *Science Trans. Med* 4, 161ra151 (2012).

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