Researchers pin down the genetics of going under

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(Medical Xpress)—Falling asleep in your bed at night and being "put to sleep" under general anesthesia – as well as waking up in the morning or coming out of anesthesia – aren't quite the same thing, yet they share some important similarities. Max Kelz, MD, PhD, assistant professor of Anesthesiology and Critical Care at the Perelman School of Medicine at the University of Pennsylvania, along with colleagues from Penn, UCSD, Howard Hughes Medical Institute, and Thomas Jefferson University, explored the distinctions between anesthetic unconsciousness and sleep by manipulating the genetic pathways known to be involved in natural sleep and studying the resulting effects on anesthetic states. Their work is published in PLOS Genetics.

Previous research by Kelz's team pointed to a neurological barrier, called neural inertia, that separates awareness from anesthetic unconsciousness and resists the transition from one state to the other. They also found that the processes by which the brain enters anesthesia and then later reemerges into consciousness are actually quite different—one isn't simply the reverse of the other. With this knowledge in hand, Kelz and his colleagues used a Drosophila model system to focus on the genetic pathways controlling neural inertia. "In this new study we sought to understand whether anesthetics were working on some of the natural systems that regulate normal sleep and wakefulness," says Kelz.

They found that four genes involved in natural sleep, Sh (Shaker), sss (sleepless), na, and unc79, also control neural inertia and thus the effects of induction and emergence of anesthetic unconsciousness. Various

mutations in these four genes profoundly affect neural inertia and can even collapse it completely. For example, says Kelz, "Mutations in the sleepless gene can cause some resistance to entering an anesthetic state, and an even larger impact on the exit from the anesthetic state. Flies with the sleepless mutation pop out of the anesthetic state at doses at which their normal siblings are still entering. When we moved sleepless around to different parts of the fly brain to figure out the circuits in which the gene works to alter wakefulness or the propensity to enter an anesthetic state, we found that we could completely dissociate the forward process of entering an anesthetic state from the reverse process of exiting."

This latest work confirms the existence of neural inertia as a state that naturally resists a change in the brain's consciousness, similar to a phenomenon studied by sleep scientists. "Sleep inertia is a phenomenon in which it can take minutes to hours before full cognitive power returns to us when we are abruptly awakened from natural sleep," Kelz explains. "We modeled the idea [neural inertia] off the natural process of sleep inertia. Not much is known mechanistically about sleep inertia or why that happens, but here we see the anesthetics as a model potentially for helping to understand sleep inertia."

Aside from distinct differences between induction of and emergence from anesthesia, the work shows that the neural pathways involved can vary with different anesthetic drugs. The present study was largely conducted using isofluorane, a common general anesthetic, but there seem to be many neurological roads to anesthetically-induced unconsciousness, not all of which involve the same genes. The experimenters found that with a different drug, halothane, their Drosophila subjects reacted quite differently.

"While I'd like to say that there's one general set of neurons upon which anesthetic drugs work, it's very clear that it's not that simple," Kelz says.

"Individual anesthetic agents probably have distinct molecular targets and have differential effects on some of the underlying circuits that help maintain wakefulness. When we looked at halothane, we found is that the story of these four genes [Sh, sss, na, and unc79] doesn't explain halothane's action. So we're really just scratching the surface in understanding a single anesthetic, isofluorane. There's undoubtedly much more going on before we can start to speak about any anesthetic or a generic anesthetic."

Trying to identify just how well the analogy of sleep as a metaphor for anesthesia holds is important not just from a scientific standpoint, but also from a therapeutic one. "There are some downsides to using existing anesthetic drugs," Kelz points out. "If we understood the good features of the anesthetics, the ways in which they cause a loss of consciousness, and if we could replicate the desirable effects by specifically tuning the brain's natural systems that regulate arousal, we might be able to avoid some of the undesirable actions of the anesthetic."

Such understanding could also benefit coma patients and those suffering from sleep disorders. "We might be able to come up with strategies for helping to extract patients from vegetative states, or come up with some novel therapies or ideas to treat many of the issues that plague sleep medicine," Kelz says.

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