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NIH INSOMNIA ABSTRACT

Neurobiology of Insomnia

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Over the last 10 years, much of the brain circuitry that regulates sleep and wakefulness has become more clear. In particular, wakefulness appears to be a product of the concerted action of an ascending arousal system, including monoaminergic and cholinergic neurons in the brainstem, peptidergic neurons (containing orexin or melanin-concentrating hormone) in the lateral hypothalamus, and neurons containing acetylcholine or gamma-aminobutyric acid (GABA) in the basal forebrain.[1] The major components of the ascending arousal system are inhibited by the ventrolateral preoptic nucleus (VLPO), which is made up of sleep-active, inhibitory neurons that contain both GABA and galanin. The VLPO neurons are, in turn, inhibited by the arousal systems, and their mutual inhibition results in the switching between wakefulness and sleep.[1,2]

The brain circuitry for insomnia, however, has not received much study. Georgina Cano, Ph.D., and I developed a rat model for insomnia in which rats are left to sleep in the cage of another male rat. They are quite territorial, and this causes considerable anxiety. The rats have difficulty falling asleep but eventually do sleep under homeostatic pressure; however, as that pressure wears off 4–6 hours into the sleep cycle, they begin waking up and cannot fall back asleep. When the brains of these rats were examined during this interval insomnia, it was found that there is an excess expression of Fos (a protein that is found in neurons that have recently been active) in the medial prefrontal cortex and central nucleus of the amygdala and the histaminergic tuberomammillary nucleus and noradrenergic locus coeruleus, while Fos activity in the VLPO is curtailed. It was also discovered that lesions of the medial prefrontal cortex and the amygdala have differential effects on the recovery of nonrapid eye movement versus rapid eye movement sleep and that drugs that affect the histaminergic system, likewise, differentially affect the two states. It is believed that drugs that act to reinforce the activity of the VLPO may be a better choice for reinstating sleep in stress-induced insomnia rather than using drugs (like classical GABA agonists) that work downstream of the VLPO and, thus, do not restore either slow-wave or rapid eye movement sleep adequately.[3]

REFERENCES

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