Psychopharmacology of Wakefulness: Pathways and Neurotransmitters

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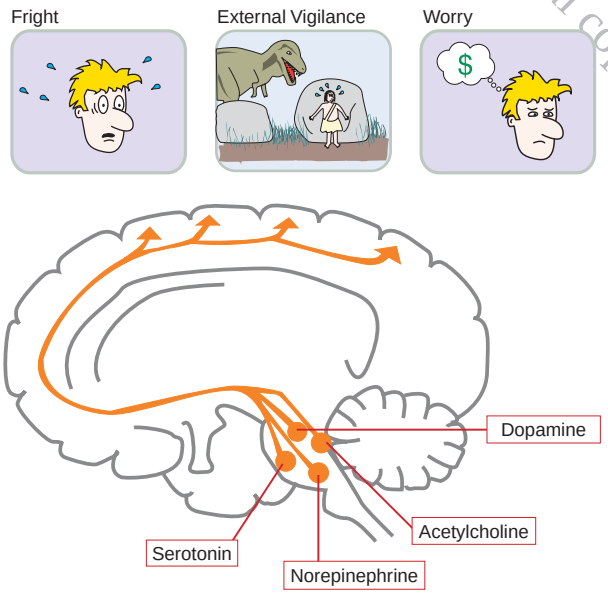
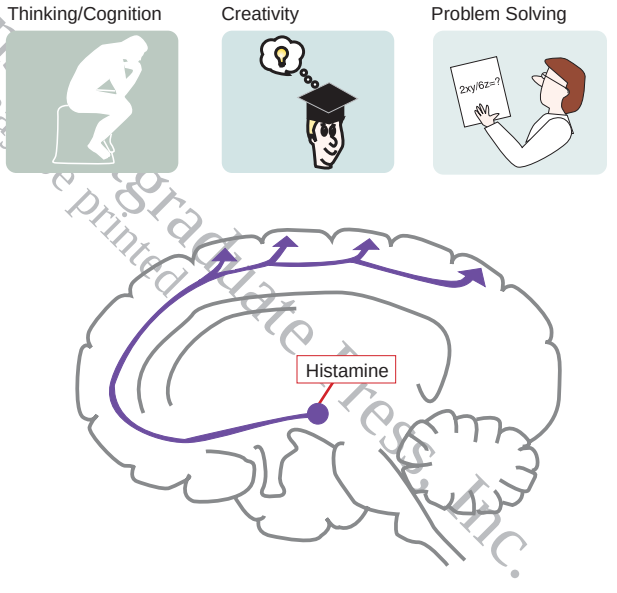
Issue: *The neuroanatomical substrate of wakefulness involves 2 parallel pathways that activate the cortex, one arising from neurons in the brainstem and another arising from neurons that make up a hypothalamic sleep-wake switch. Multiple neurotransmitters regulate wakefulness as do several drugs, including the novel wake-promoting agent modafinil.*

Figure 1. Stimulated Vigilance[a]



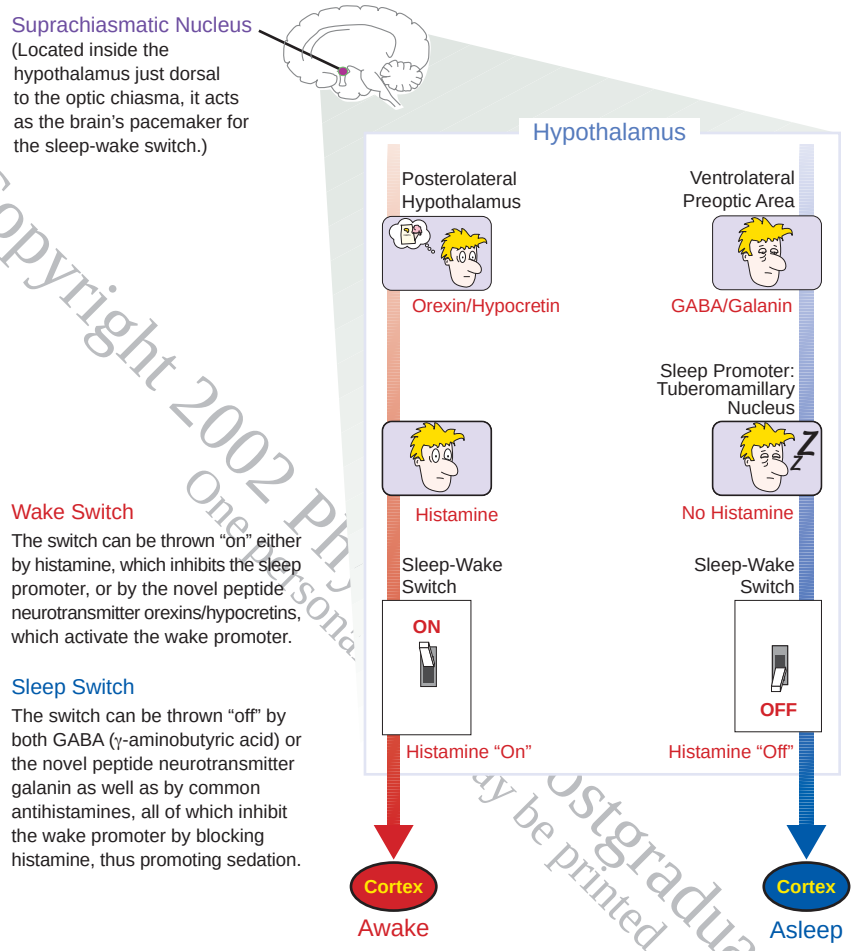
[a]Monoaminergic projections from brainstem to cortex via the ascending reticular activating system are illustrated here. Perhaps one form of arousal is a stimulated type of external vigilance, with tense hyperarousal, putting the individual on the lookout for threats from the environment. This type of arousal may be mediated by the monoamines dopamine, norepinephrine, serotonin, and acetylcholine via their ascending projections from the brainstem as part of the classical reticular activating system. The ability to activate this system enhances the survival of an individual in a hostile environment. Stimulants such as amphetamine and caffeine activate this system.

Figure 2. Calm Wakefulness[a]



[a]Another form of arousal may be a more reflective type of calm wakefulness, in which there is internal vigilance to executive functions as the individual focuses on cognitive tasks. Such wakefulness may be mediated by the ascending histaminergic neurons arising from the hypothalamus. The ability to activate this system would lead to problem solving, learning, and creativity. Not only can stimulants and caffeine activate this system when they also activate stimulated vigilance, but the novel wake-promoting agent modafinil can activate normal wakefulness selectively without turning on stimulated vigilance.

Figure 3. Flip-Flopping the Hypothalamic Sleep-Wake Switch[a]



[a]Normal wakefulness may be an all-or-nothing phenomenon, with the hypothalamus providing a reciprocal switching circuit so that the brain can be either "on" (calm wakefulness) or "off" (asleep). Such an arrangement would largely avoid intermediate states and allow relatively brief times to be spent in transitions between the waking or sleeping states. One model of the normal sleep-wake cycle proposes that wake-promoter and sleep-promoter neurons inhibit each other, thus causing oscillation between wakefulness and sleep.

New developments in the psychopharmacology of sleep and wakefulness were discussed last month.[1] Here we illustrate the pathways and neurotransmitters involved in the psychopharmacology of wakefulness.

REFERENCE

1. Stahl SM. Awakening to the psychopharmacology of sleep and arousal: novel neurotransmitters and wake promoting drugs. J Clin Psychiatry 2002;63:467–468

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