

## Gaps That Wake You Up

A commentary on Beck et al. Modafinil Increases Arousal Determined by P13 Potential Amplitude: An Effect Blocked by Gap Junction Antagonists. *SLEEP* 2008;31(12):1647-1654.

Jerome M. Siegel, PhD

*Department of Psychiatry, University of California, Los Angeles, CA*

ALTHOUGH MODAFINIL HAS BECOME ONE OF THE MOST WIDELY PRESCRIBED STIMULANTS AND IS AN APPROVED TREATMENT FOR NARCOLEPSY, SHIFT work disorder, and the residual sleepiness in treated sleep apnea, its mode of action is poorly understood. It has been suggested that it acts by binding to the dopamine transporter thus inhibiting dopamine reuptake, thereby activating dopamine receptors.<sup>1</sup> Modafinil is effective in hypocretin (orexin) knockout animals, demonstrating that, contrary to a prior claim, hypocretin is not needed to mediate its effects.<sup>2</sup> One study showed that modafinil selectively activates a localized cell group in the anterior hypothalamus,<sup>3</sup> however another showed that it produces a widespread activation of many brain regions.<sup>4</sup>

Now Beck et al.<sup>5</sup> present new data suggesting that modafinil acts by opening "gap junctions" between neurons. The classical view of neuronal communication is that neurons interact by transmitter release acting through receptors which either open ion channels or activate proteins within the neuronal soma of postsynaptic cells to produce membrane polarization changes. However, it is now known that some groups of neurons are electrically coupled, such that changes in membrane potential are rapidly communicated through pores linking adjacent cells, allowing bidirectional ion currents. Gap junctions are thought to exist between GABAergic cells of the pedunculopontine nucleus, a nucleus also containing cholinergic cells.<sup>6</sup> These cholinergic cells are involved in regulating REM sleep through brainstem connections as well as the cortical EEG through thalamic projections.<sup>7</sup> Gap junctions are also present in the coeruleus and subcoeruleus nuclei, cortical cells, and nucleus reticularis of the thalamus, which has a critical role in generating the EEG. It has been demonstrated that the number or size of gap junctions can be increased by neurotransmitter action.<sup>8,9</sup>

One way of assessing arousal is to measure the amplitude of an auditory evoked positive response peaking approximately 13 msec after the initiation of the stimulus, the P13 wave. Prior work by this group<sup>5</sup> and others has suggested that this wave is generated by the pedunculopontine nucleus, a brainstem nucleus containing cholinergic cells. Beck et al.<sup>5</sup> showed that microinjection of modafinil into this nucleus in rats increased

the amplitude of this wave. They also showed that this effect was blocked by gap junction antagonists (carbenoxolone or mefloquine). An earlier study had shown that modafinil also increased the electrical coupling of cortical interneurons.<sup>10</sup>

Gap junctions allow more rapid spread of membrane polarization changes between neurons. This synchronizes the membrane potential of such neurons but also makes it more difficult to trigger action potentials, since by lowering the electrical resistance of the network relative to that of a single cell, a larger current is needed to reach a voltage sufficient to trigger action potentials, according to Ohm's law. It is this effect that is now hypothesized to be responsible for the arousing effect of modafinil. Because of the increased coupling of GABA cells in the pedunculopontine nucleus caused by modafinil, these cells become less active, releasing adjacent cholinergic cells from GABAergic inhibition. However, once an action potential is triggered in cells connected by gap junctions it will tend to occur in all cells in the network because of the rapid flow of sodium currents between cells. This will produce an explosive and synchronous output of the network. This effect is seen in fish, which use gap junctions to generate synchronized action potentials in cells mediating the tail flip and in snails, which use synchronized action potentials to release a protective cloud of ink.

Beck et al.'s finding does not exclude the possibility that some of modafinil's action is mediated by chemical synapses including those affecting monoaminergic transport or receptor systems, amino acid or cholinergic mechanisms. Indeed Beck et al.'s study suggests the need for further work to determine the extent to which systemic administration of modafinil acts through gap junction mechanisms as opposed to more conventional chemical synaptic mechanisms. It also raises the possibility that the effects of other alertness controlling drugs may be mediated by their effects on gap junctions rather than by acting exclusively through chemical synapses.

### DISCLOSURE STATEMENT

Dr. Siegel has indicated no financial conflicts of interest.

### REFERENCES

1. Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y. Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil. *J Neurosci* 2008; 28:8462-9.
2. Willie JT, Renthal W, Chemelli RM, et al. Modafinil more effectively induces wakefulness in orexin-null mice than in wild-type littermates. *Neuroscience* 2005;30:983-95.

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Address correspondence to: Jerome M. Siegel, PhD, VA GLAHS Sepulveda 151A3, UCLA Dept. of Psychiatry, 16111 Plummer St., North Hills CA 91343; Tel: (818) 891-7711, Ext: 7581; Fax: (818) 895-9575; E-mail: JSiegel@ucla.edu

3. Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. *Proc Natl Acad Sci U S A* 1996;93:14128-33.
4. Scammell TE, Estabrooke IV, McCarthy MT, et al. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci* 2000;20:8620-8.
5. Beck P, Odle A, Wallace-Hunt T, Skinner RD, Garcia-Rill E. Modafinil increases arousal determined by P13 potential amplitude: an effect blocked by gap junction antagonists. *Sleep* 2008;31:1647-1654.
6. Garcia-Rill E, Heister DS, Ye M, Charlesworth A, Hayar A. Electrical coupling: novel mechanism for sleep-wake control. *Sleep* 2007;30:1405-14.
7. Siegel JM. REM sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*. 4 ed. Philadelphia: Elsevier Saunders, 2005:120-35.
8. Hestrin S, Galarreta M. Electrical synapses define networks of neocortical GABAergic neurons. *Trends Neurosci* 2005;28:304-9.
9. Beierlein M, Gibson JR, Connors BW. A network of electrically coupled interneurons drives synchronized inhibition in neocortex. *Nat Neurosci* 2000;3:904-10.
10. Urbano FJ, Leznik E, Llinas RR. Modafinil enhances thalamocortical activity by increasing neuronal electrotonic coupling. *Proc Natl Acad Sci U S A* 2007;104:2554-9.