CARLEY AND ASSOCIATES\textsuperscript{1} REPORT ON A CAREFULLY CONDUCTED STUDY IN SLEEPING RATS, PROVIDING FURTHER EVIDENCE OF THE COMPLEX ROLE OF SYSTEMIC SEROTONIN IN THE REGULATION OF BREATHING AND APNEA. The pharmacologic manipulation in the present study involved systemic administration of specific cannabinoid agents which are known to inhibit the excitatory effects of serotonin on peripheral ganglion cells. The data are very clear in showing that the high rate of apnea observed in sleeping rats in REM sleep is significantly reduced by these agents; furthermore, the exacerbation of sleep apnea normally induced by systemic serotonin administration was also blocked by cannabinoid agents. These authors defend the relevance of their findings to human sleep-disordered breathing and claim that their results provide a rationale for exploring the use of cannabimimetic drugs in explaining sleep-related breathing disorders.

These findings speak to the search for a pharmacological treatment of sleep apnea. This is important research because the problem of sleep apnea is so prevalent, and current treatments such as CPAP or mandibular advancement are not suitable and/or tolerated by many patients. At the same time, the problem of sorting out the effects of neurotransmitters, such as serotonin, on apnea is extremely complicated because these chemicals have multiple receptor subtypes with different and sometimes opposite effects on ventilatory control, and their effects will differ depending on systemic or central sites of action. Additionally, these drugs have diverse physiologic effects on sleep architecture, arousal responses, and the output of both phrenic and hypoglossal motorneurons.\textsuperscript{2,3} Furthermore, the sensory sites of action of serotonergic agents are widespread, including both mechano- and chemoreceptor neurons in the periphery.\textsuperscript{4} The current study advances our understanding by demonstrating an inhibitory coupling between cannabinoids and serotonin receptors in the peripheral nervous system, which has a significant influence on central apnea expression.

As these data accumulate in animal models, such as the sleeping rat or dog or anesthetized cat, questions arise concerning the fundamental causes of sleep apnea and their species dependence.

- The sleeping rat presumably experiences only purely central apneas (although the status of the upper airway in these animals is uncertain). How relevant are data in this model to obstructive or so-called mixed apneas as experienced in humans? The authors argue that all obstructive and central apneas have a similar “dysregulation of central motor neural output patterning.”\textsuperscript{1} Airway obstruction occurs when instability of neural control coincides with airways susceptible to narrowing and/or collapse—a susceptibility rarely found in experimental animals but common in humans. I agree that central neural control instability is a significant determinant of sleep-disordered breathing; but this does not mean that all airway obstructions in sleep require unstable, abnormal neural control or that they will all be eliminated by simply increasing or stabilizing respiratory motor output. Furthermore, sleep state—especially REM—and serotonin availability also have significant effects on reflex regulation of upper airway patency via hypoglossal motor neurons.\textsuperscript{5} Thus, to ensure relevance to the human condition we need to study and understand the effects of any pharmacological intervention on motor output to both pump and upper-airway muscles and their interactive effects on the different types of apnea.

- Do central apneas have similar causes in rats and humans? The great majority of apneas in sleeping rats occur following a sigh (or augmented inspiration) and therefore are likely to be mediated, at least in large part, via inhibitory vagal feedback from lung stretch. In humans on the other hand, while lung inflation, per se, can cause significant inhibition and destabilization of respiratory motor output, it is unlikely that the amount of lung stretch usually associated with normal spontaneous sighs will cause apnea.\textsuperscript{6,7} It follows, then, if the effects of systemic serotonin antagonists are primarily via their influence at the level of vagal receptors,\textsuperscript{4} species differences will be an important determinant of their effects on ventilatory control. Moreover, an additional complexity is that augmented inspirations commonly occur during state transitions to or toward wakefulness;\textsuperscript{8} thus their occurrence and/or magnitude may be susceptible to any pharmacologic effects on even subtle or transitory changes in sleep state.

- Central apneas in the rat occurred primarily in REM, whereas central apneas in humans with idiopathic central sleep apnea or with hypoxic-induced periodic breathing or with Cheyne-Stokes respiration in heart failure occur primarily in NREM sleep.\textsuperscript{9,10} Given the rodent’s high susceptibility to change its metabolic rate in various environments, perhaps a reduced metabolic rate renders this species more susceptible to central apnea during REM sleep.

- Both rats and humans reduce central apnea occurrence and/or periodic breathing via the administration of supple-
mental inspired \text{CO}_2^{9,10,11}$—a finding which might implicate hypocapnia as a cause of apnea when PaCO$_2$ is reduced below the sensitive apneic threshold in sleep. On the other hand, the apneic threshold is highly changeable, depending on the magnitude and specific type of stimulus to background ventilatory drive.$^{12,13}$ Equally important, the prevailing level of hyper- or hypoventilation will also dictate the amplification with which any ventilatory overshoot is translated into a reduction in PaCO$_2$, (i.e., so-called “plant gain”). Accordingly, we need to know the effect of any pharmacological intervention on the prevailing level of background ventilation and PaCO$_2$ and preferably also on the magnitude of the hypocapnic-induced or lung volume-induced apneic threshold.

In summary, the findings of Carley et al.$^1$ provide a significant advance toward furthering our understanding of how systemic serotonergic receptors influence breathing in sleep. This study builds on previous studies in sleeping rats and dogs which showed beneficial effects of specific serotonin receptor antagonists on central and/or obstructive sleep apnea and in limited trials in human patients in whom sleep-disordered breathing was reduced to varying extents via pharmacological inhibition of serotonin uptake in the brain.$^2, 14-17$ Much remains to be uncovered in this worthwhile venture, including how the agonists and antagonists of serotonin and its receptor subtypes affect each of the mechanisms currently known to contribute to the various types of sleep-disordered breathing in animal and human models. As implied from the above discussion, we also need to challenge current concepts concerning the constellation of risk factors and underlying mechanisms which precipitate control system instabilities at the levels of both the phrenic and hypoglossal motor outputs resulting in sleep apnea and periodicity. Clearly, neither the causes nor the solutions to this complex problem have a magic bullet!

REFERENCES