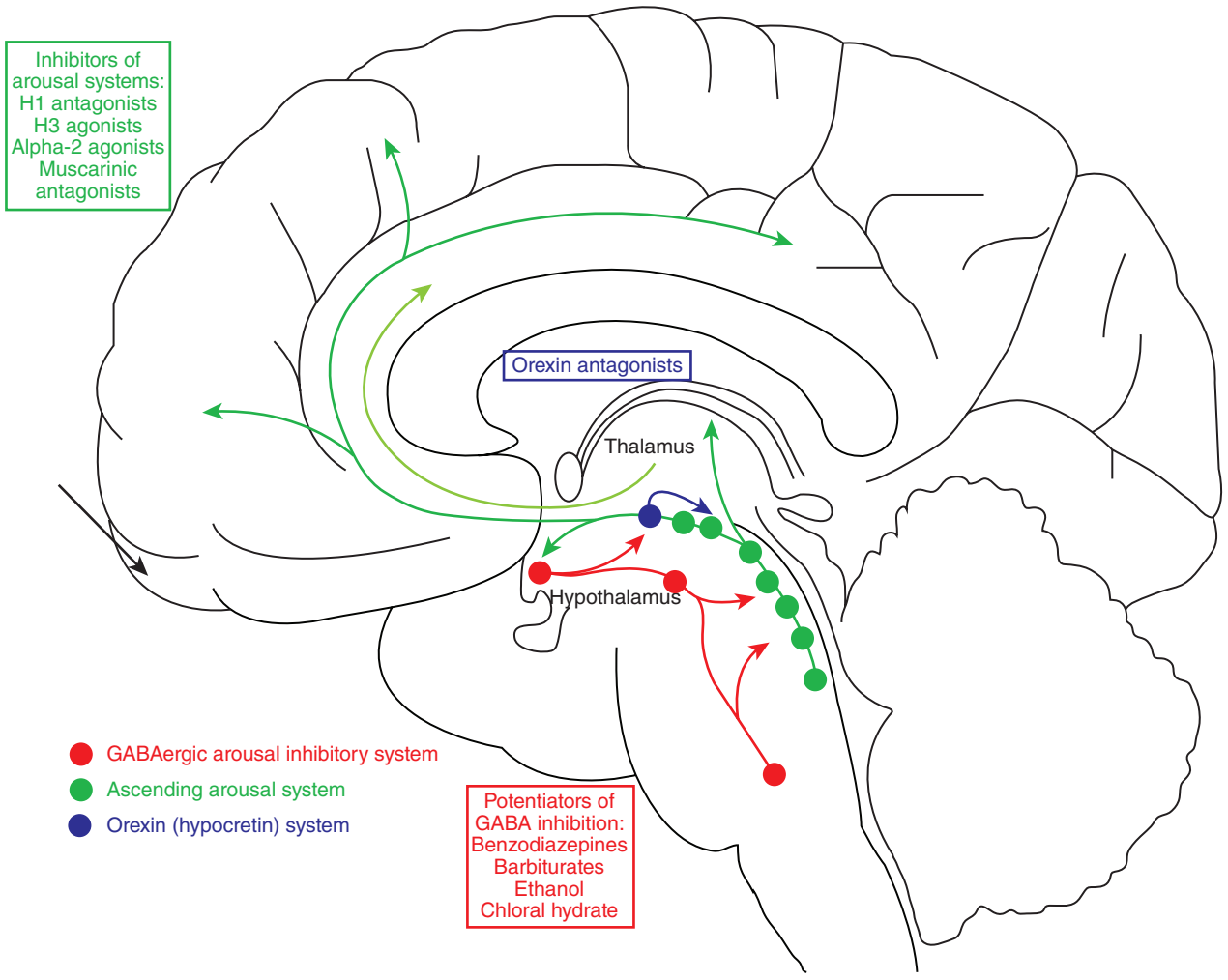

FIGURE 38-2 Relationship of drugs for insomnia with wake-sleep systems. The arousal system in the brain (*green*) includes monoaminergic, glutamatergic, and cholinergic neurons in the brainstem that activate neurons in the hypothalamus, thalamus, basal forebrain, and cerebral cortex. Orexin neurons (*blue*) in the hypothalamus, which are lost in narcolepsy, reinforce and stabilize arousal by activating other components of the arousal system. The sleep-promoting system (*red*) consists of GABAergic neurons in the preoptic area, lateral hypothalamus, and brainstem that inhibit the components of the arousal system, thus allowing sleep to occur. Drugs used to treat insomnia include those that block the effects of arousal system neurotransmitters (*green and blue*) and those that enhance the effects of γ-aminobutyric acid (GABA) produced by the sleep system (*red*).

increase monoamine tone (e.g., serotonin or norepinephrine reuptake inhibitors) tend to reduce the amount of REM sleep. Damage to the neurons that promote REM sleep atonia can produce REM sleep behavior disorder, a condition in which patients act out their dreams (see below).

SLEEP-WAKE CYCLES ARE DRIVEN BY HOMEOSTATIC, ALLOSTATIC, AND CIRCADIAN INPUTS

The gradual increase in sleep drive with prolonged wakefulness, followed by deeper slow-wave sleep and prolonged sleep episodes, demonstrates that there is a *homeostatic* mechanism that regulates sleep. The neurochemistry of sleep homeostasis is only partially understood, but with prolonged wakefulness, adenosine levels rise in parts of the brain. Adenosine may act through A1 receptors to directly inhibit many arousal-promoting brain regions. In addition, adenosine promotes sleep through A2a receptors; inhibition of these receptors by caffeine is one of the chief ways in which people fight sleepiness. Other humoral factors, such as prostaglandin D_2, have also been implicated in this process. Both adenosine and prostaglandin D_2 activate the sleep-promoting neurons in the ventrolateral preoptic nucleus.

Allostasis is the physiologic response to a threat that cannot be managed by homeostatic mechanisms (e.g., the presence of physical danger or psychological threat). These stress responses can severely impact the need for and ability to sleep. For example, insomnia is very common in patients with anxiety and other psychiatric disorders. Stress-induced insomnia is even more common, affecting most people at some time in their lives. Positron emission tomography (PET) studies in patients with chronic insomnia show hyperactivation of the components of the ascending arousal system, as well as their targets in the limbic system in the forebrain (e.g., cingulate cortex and amygdala). The limbic areas are not only targets for the arousal system, but they also send excitatory outputs back to the arousal system, which contributes to a vicious cycle of anxiety about wakefulness that makes it more difficult to sleep. Approaches to treating insomnia rely on drugs that either inhibit the output of the ascending arousal system (green and blue in Fig. 38-2) or potentiate the output of the sleep-promoting system (red in Fig. 38-2). However, behavioral approaches (cognitive behavioral therapy and sleep hygiene) that may reduce forebrain limbic activity at bedtime are often equally or more successful.

Sleep is also regulated by a strong *circadian* timing signal, driven by the suprachiasmatic nuclei (SCN) of the hypothalamus, as described below. The SCN sends outputs to key sites in the hypothalamus, which impose 24-h rhythms on a wide range of behaviors and body systems, including the wake-sleep cycle.

PHYSIOLOGY OF CIRCADIAN RHYTHMICITY

The wake-sleep cycle is the most evident of many 24-h rhythms in humans. Prominent daily variations also occur in endocrine,