Insomnia

Helen A. Baghdoyan, Ralph Lydic

Insomnia is the most prevalent sleep disorder, affecting approximately 10% of the general population (NIH Consensus Panel Report, 2005). A diagnosis of chronic insomnia is based on patient complaints of difficulty falling asleep, difficulty staying asleep, early morning awakenings, and/or nonrestorative sleep for more than one month. These disturbances in sleep occur despite adequate opportunity for sleep and are accompanied by distress and/or impaired daytime functioning (Roth et al., 2010). Insomnia is classified as primary if the sleep disturbance does not result from other illnesses (psychiatric or medical), other sleep disorders, or the effects of substance abuse (Hall-Porter et al., 2010). Primary insomnia increases the risk for developing depression (Yokoyama et al., 2010), can lead to impaired ability to perform complex attentional tasks (Hall-Porter et al., 2010), and is associated with decreased health-related quality of life (Kyle et al., 2010). Insomnia creates a substantial economic burden due to absenteeism from work and reduced productivity (Léger & Bayon, 2010). Comorbid insomnia is the term used to describe chronic sleep disturbances that result from other illnesses, side effects of medications used to treat those illnesses, or drug abuse (NIH Consensus Panel Report, 2005). Comorbid insomnia is by far the most prevalent type, and reciprocal interactions between insomnia and coexisting illnesses are now recognized (Glidewell et al., 2010).

Human sleep is a complex phenotype regulated by interactions between environmental factors and multiple genes (Drake et al., 2008). Studies of twins have provided clear evidence of a genetic contribution to insomnia (Dauvilliers et al., 2005). One striking example of genetically based insomnia is fatal familial insomnia, which is caused by a point mutation in the prion protein gene (Montagna et al., 2003) (see Ch. 50). This disease is always fatal and is

characterized by a loss of slow-wave sleep due to degeneration of the thalamus.

Neurochemical mechanisms of primary insomnia are poorly understood. Current models of insomnia are focused on hyperarousal caused by an interaction between biological, cognitive and emotional factors (Hall-Porter et al., 2010). Functional neuroimaging during sleep has provided support for the hypothesis that in patients with insomnia key brain regions regulating wakefulness (see text of this chapter) do not deactivate during sleep, nor are these brain regions adequately activated during wakefulness (Nofzinger, 2008). These data emphasize the importance of preclinical studies aiming to characterize sleep-dependent neurochemical changes in the multiple brain regions that regulate sleep and wakefulness.

Pharmacological treatment of insomnia involves a wide range of agents, and the efficacy of these agents fits with what is known about the underlying neurochemistry of sleep. Drugs approved for the treatment of insomnia by the United States Food and Drug Administration include nine benzodiazepine receptor agonists (BzRAs), the melatonin MT1 and MT2 receptor agonist ramelteon, and most recently the tricyclic antidepressant doxepin (Roth et al., 2010). BzRAs, which are recommended as first-line pharmacologic treatment, have a binding site on the $GABA_A$ receptor complex and act as allosteric modulators to enhance inhibition mediated by endogenous GABA. BzRAs are thought to increase sleep by inhibiting wakefulness-promoting monoaminergic and cholinergic neurons. Although some BzRAs have a benzodiazepine structure (flurazepam, triazolam, temazepam, estazolam, quazepam) and others are non-benzodiazepines (eszopiclone, zaliplon, zolpidem, zolpidem extended-release), all of these drugs bind to $GABA_A$ receptors composed of α1-3,5β2,3γ2,3 subunits (see Ch. 18). Whereas the benzodiazepines have similar affinity for all four α subunits, the non-benzodiazepine zolpidem has greater affinity for α1 than for the other α subtypes and the non-benzodiazepine eszopiclone is thought to have

relatively high affinity for the α1 and α3 subtypes (Hambrecht-Wiedbusch et al., 2010; Roth & Roehrs, 2010). How these binding affinities translate into differential responses in patients is not yet known.

A point mutation expressed as an altered β3 subunit of the $GABA_A$ receptor complex has been identified in humans (Buhr et al., 2002). Of relevance to insomnia is that functional analyses of human $GABA_A$ receptors containing the mutated β3 subunit showed that the mutation causes faster deactivation of the chloride ion channel (Buhr et al., 2002). Such a mutation could have the effect of decreasing GABAergic transmission. One patient with chronic insomnia was found to have this mutation, suggesting the intriguing possibility that reduced GABAergic inhibition may contribute to insomnia in humans (Buhr et al., 2002). Mice lacking the β3 subunit show altered sleep responses to the benzodiazepine midazolam (Wisor et al., 2002), and point mutations in the α1 subunit cause mice to be insensitive to the sleep-inducing effects of diazepam (Tobler et al., 2001). An exciting opportunity for sleep neurochemistry is identification of genetically modified neurotransmitter receptor systems that increase risk for insomnia.

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