Models of Insomnia

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Chapter 78

Up until the late 1990s there were only two models regarding the etiology and pathophysiology of insomnia. The relative lack of theoretical perspectives was due to at least three factors. First, the widespread conceptualization of insomnia as owing directly to hyperarousal may have made it appear that further explanation was not necessary. Second, the long-time characterization of insomnia as a symptom carried with it the clear implication that insomnia was not itself worth modeling as a disorder or disease state. Third, for those inclined toward theory, the acceptance of the behavioral models (i.e., the 3P behavioral model and the stimulus control model[1,2]), and the treatments that were derived from them, might have had the untoward effect of discouraging the development of alternative or elaborative models.

Since the 1990s there has been a proliferation of theoretical perspectives on the etiology and pathophysiology of insomnia that includes ten human models* and three animal models. In this chapter, six models (Box 78-1) are described and critiqued: the classic 3P behavioral model,[1] the stimulus control model,[2] and four models that are arguably the most influential of the modern perspectives†: the neurocognitive model,[3] the psychobiological inhibition model,[4] the *Drosophila* model,[5,6] and the rodent model.[7]

THE DEFINITION OF INSOMNIA

Currently, insomnia is conceptualized in terms of chronicity, type, and subtype. *Chronicity* refers to whether the insomnia is acute or chronic. *Type* refers to the forms of insomnia that have been identified as distinct nosologic entities including (for adults) idiopathic insomnia, psychophysiologic insomnia, paradoxical insomnia, insomnia due to inadequate sleep hygiene, and insomnia comorbid with medical or psychiatric illness. *Subtype* refers to the insomnia phenotype (initial, middle, late, or mixed insomnia). The formal definition of these entities, and discussion about their orthogonality and clinical utility, may be found elsewhere in this volume. What is relevant for the present chapter is that these diagnostic distinctions exist and thus must be taken into account by the various models; that is, each model must indicate which type of insomnia (and subtype, if pertinent) is being modeled.

THE STIMULUS CONTROL MODEL

Basic Description

Stimulus control, as originally described by Bootzin,[2] is based on the behavioral principle that one stimulus may elicit a variety of responses, depending on the conditioning history. A simple conditioning history, wherein a stimulus is always paired with a single behavior, yields a high probability that the stimulus will yield only one response. A complex conditioning history, wherein a stimulus is paired with a variety of behaviors, yields a low probability that the stimulus will yield only one response. In persons with insomnia, the normal cues associated with sleep (e.g., bed, bedroom, bedtime, etc.) are often paired with activities other than sleep. For instance, in an effort to cope with insomnia, the patient might spend a large amount of time in the bed and bedroom awake and engaging in activities other than sleep. The coping behavior appears to the patient to be both reasonable (e.g., staying in bed at least permits the patients to rest) and reasonably successful (engaging in alternative activities in the bedroom sometimes appears to result in cessation of the insomnia). These practices, however, set the stage for stimulus dyscontrol, the lowered probability that sleep-related stimuli will elicit the desired response of sleepiness and sleep. Figure 78-1 provides as schematic representation of stimulus control and stimulus dyscontrol.

Strengths and Weaknesses

The treatment that is derived from stimulus control theory is one of the most widely used behavioral treatments, and its efficacy has been well established.[8-12] The success of the therapy, however, is not sufficient evidence to say that stimulus dyscontrol is the factor, or one of the factors, responsible for predisposition to, the precipitation of, or the perpetuation of insomnia.* This is the case because the therapy includes active components that are not based solely on learning or behavioral theory. For instance, the treatment specifies that the patient should spend awake time somewhere other than the bed and that the sleep schedule should be fixed. These two interventions also influence the homeostatic and circadian regulation of sleep. Thus, the efficacy of stimulus control therapy does not necessarily provide evidence for the stimulus control model. In fact, one investigation found that the reverse of stimulus control instructions also improved sleep continuity.[13]

Another limitation of the stimulus control perspective is that it focuses solely on instrumental conditioning. That is, there are activities that can be engaged in that reduce or enhance the probability of the occurrence of sleep. The original model does not explicitly delineate how classical conditioning might also be an operational factor. That is, the regular pairing of the physiology of wake with sleep-related stimuli might lead to a scenario where sleep-related stimuli become conditioned stimuli for wakefulness. This latter possibility, although not part of the classical stimulus control perspective, is clearly consistent with it.

*A complete listing of theories and models, along with citations, is contained in Appendix 1 on the website.

†Although it is difficult to assess which models are the most influential, one approach would be based on a citation index metric. Using this index, it does indeed appear that the four contemporary models described in this chapter are the most influential.

*The conceptual time frame for causality in terms of "predisposition, precipitation, and perpetuation" was first articulated as part of the 3P model. It is used in this context to illustrate the complexity of modeling what "cause" insomnia.

Box 78-1 Potential Implications for Treatment of Insomnia

Stimulus Control Model
One unexplored implication for treatment is that physically altering the sleep environment may be helpful (e.g., paint the room a different color)

Spielman Model
The 3P model suggests that insomnia is perpetuated by sleep extension and thus should be managed with treatment protocols that restrict time in bed (i.e., compress the sleep period).

One implication for treatment is that sleep compression need not occur in a radical fashion, but could be accomplished over days or weeks.[19]

Neurocognitive Model
The neurocognitive model suggests that patients with insomnia suffer from an attenuation of the normal mesograde amnesia of sleep.

One unexplored implication for treatment is that potentiation of the normal mesograde amnesia of sleep via the use of more traditional hypnotics (e.g., benzodiazapines with effects on long-term memory) might serve to augment clinical gains, if not in general, then at least in patients with substantial sleep state misperception.

Psychobiological Inhibition Model
According to the psychobiological inhibition model, chronic insomnia is less a hyperarousal disorder and more a disorder characterized by the failure to inhibit wakefulness.

One implication for treatment is that persistent wakefulness may be the result of hypersecretion of orexin, and thus orexin antagonism might have a place in the management of insomnia.

***Drosophila* Model**
The *Drosophila* model suggests that there may be a strong genetic component to insomnia that may be related to reduced sleep ability.

One implication of the model is that it, like the 3P model, suggests that sleep opportunity should be a major focus for treatment.

Cano-Saper Model
The Cano-Saper model suggests that insomnia represents a hybrid state, one that is, from a neurobiological perspective, part wake and part sleep.

One implication for treatment, which has not yet been tested empirically, is that corticotropin releasing hormone antagonist represent an alternative way of alleviating disturbed sleep continuity.

Implications for Current and Future Research and Therapeutics

Given the efficacy of stimulus control therapy, as it is classically rendered, it would be useful to determine how much treatment outcome from cognitive behavior therapy (CBT) owes to the manipulation of this factor. One way to assess the relative importance of stimulus control would be as part of a dismantling study. To date no such study has been conducted as a single, large-scale, randomized trial.* Alternatively, experimental studies could be used to determine which, if any, specific stimuli are most associated with sleep continuity disturbance and whether alteration of these stimuli produces enhanced clinical gains.

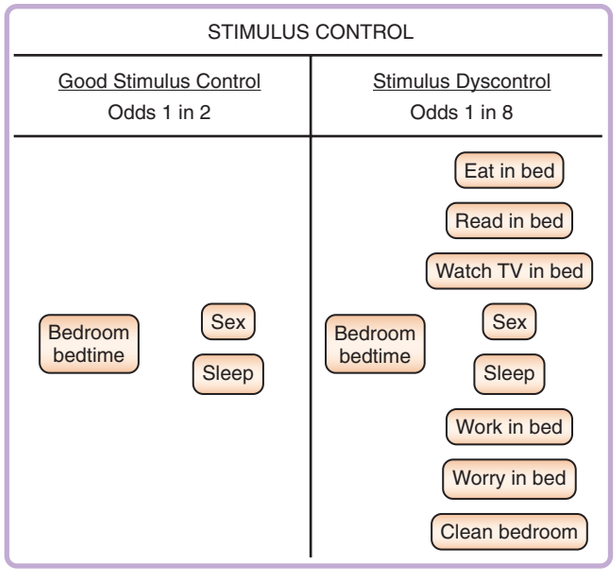

Figure 78-1 The instrumental conditioning perspective on stimulus control. *Left,* Good stimulus control: The bedroom is tightly coupled with sleep and sex where, given the orthogonality and equal probability of events, the probability of association of bedroom to sleep is 1 in 2. *Right,* Stimulus dyscontrol: The bedroom is no longer a strong associate of sleep and sex where, given the orthogonality and equal probability of events, the probability of association of bedroom to sleep is 1 in 8. The treatment implication of stimulus dyscontrol is the voluntary elimination of the nonsleep associations except for sex, which should result in instrumental conditioning.

THE 3P MODEL

The 3P behavioral model,[1] also known as the Spielman model, the three-factor model, or the behavioral model is the first fully articulated model of insomnia to gain widespread acceptance. The model delineates how insomnia occurs acutely and how acute insomnia becomes chronic and self-perpetuating. The model is based on the interaction of three factors. The first two factors (the predisposing and precipitating factors) represent a stress-diathesis conceptualization of how insomnia comes to be expressed. The third factor (the perpetuating factor) represents how behavioral considerations modulate chronicity. A schematic representation of this model is presented in Figure 78-2.

Basic Description

Predisposing factors extend across the entire biopsychosocial spectrum. Biological factors are likely to include increased basal metabolic rate, hyperreactivity, and or fundamental alterations to the neurotransmitter systems associated with sleep and wakefulness.* Psychological factors include

*The possibility of altered neurotransmission in insomnia (e.g., reduced GABAnergic tone) was recently explored by Winkelman and colleagues. See SLEEP 31(11)2008:1499-1506.

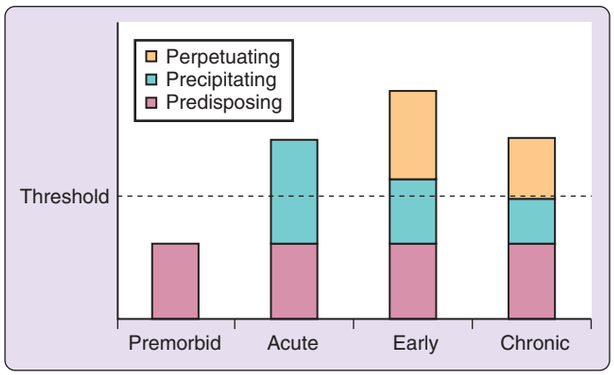

Figure 78-2 The classic 1987 rendition of the 3P model. There is a more recent representation of the model in Chapter 144. The reader is encouraged to compare the two versions of the model. The differences (e.g., allowing the predisposing factors to be represent as variable with time), while subtle, are theoretically important.

worry or the tendency to be excessively ruminative. Social factors, although rarely a focus at the theoretical level, include such things as the bed partner keeping an incompatible sleep schedule or social pressures to sleep according to a nonpreferred sleep schedule (e.g., child rearing).

Precipitating factors, as the name implies, are acute occurrences that trigger disturbance of sleep disturbance. The primary triggers are thought to be related to life stress events (including medical and psychiatric illness).

Perpetuating factors refer to the actions the insomniac person adopts that are intended to compensate for, or cope with, sleeplessness. Research and treatment have focused on three kinds of perpetuating factors: the practice of nonsleep activities in the bedroom, the tendency to stay in bed while awake, and the tendency to spend excessive amounts of time in bed. Stimulus control speaks to the first two of these considerations (as reviewed earlier).

The classic version of the 3P model focuses primarily on the last of these considerations. Excessive time in bed (or sleep extension) refers to the tendency of patients with insomnia to go to bed earlier or to get out of bed later or to engage in napping. The patient enacts such changes (compensatory activities) to increase the opportunity to get more sleep; these changes are likely highly self-reinforcing (in the short term) because they allow lost sleep to be "recovered" and the daytime effects of lost sleep to be ameliorated. The tendency toward sleep extension is, in the long term, problematic. Sleep extension leads to a mismatch between sleep opportunity and sleep ability.[1,14] The greater the mismatch, the more likely the person will spend prolonged periods wake during the given sleep period, and that this will occur regardless of what predisposed the individual to the insomnia and precipitated it.

Strengths and Weaknesses

The greatest strengths of the 3P model is that the therapy based on the theory (sleep restriction) is conceptually appealing to sleep medicine clinicians and scientists, the model is highly face valid for patients (especially when it is delivered as part of therapy), and the therapy itself (which is also compatible with, and a logical clinical application of, the two-process model of normal sleep[15]) *appears to be* very efficacious. The equivocation regarding efficacy represents one of the models weaknesses.

There have been very few studies evaluating sleep restriction therapy as a monotherapy,[8,9] and no studies evaluating the relative efficacy of sleep restriction therapy (using dismantling designs) as component of CBT. It is therefore difficult to assess the extent to which treatment efficacy supports the 3P model itself. Further, even if there were large-scale studies showing that sleep-restriction therapy produces large effects, the validation of the model would still require empirical studies (see later).

The model (while compatible with the two-process model of sleep–wake regulation) does not explicitly take into account the influences of the circadian system and sleep–wake homeostasis. Further, the model does not provide a detailed account of how one transitions from good sleep to acute insomnia (i.e., how does the precipitating factor precipitate disturbance of sleep continuity?).

In the original model it is implied that the predisposition to insomnia varies across patients but is a trait factor (static over time) within the individual patient. Presumably the postulated between-subject variability means that some patients are not prone to insomnia, some are marginally at risk, and still others are at high risk. Although it stands to reason that the vulnerability for insomnia exists on a continuum (i.e., is normally distributed), it is also plausible that everyone is at risk for acute insomnia and that this is so to the extent that insomnia represents an adaptive response to stress (i.e., real or perceived threat prevents the inhibition of wakefulness; this idea is addressed by the Cano-Saper rodent model and the psychobiological inhibition model). The postulate of within-subject variability (risk being static over time) also may be open to question. Some predispositions may be indeed be hardwired (addressed by the *Drosophila* model) but it also stands to reason that some predispositions vary over the lifespan (e.g., new sleep environments or partners, pregnancy or childrearing, altered hormonal status, effects of aging. The newer rendition of the 3P model (reviewed in Chapter 144) reconciles this issue by explicitly allowing predisposing factors to vary with time).[16]

As with stimulus control, the 3P model focuses on instrumental conditioning. It does not explicitly take into account the role of classical conditioning in chronic insomnia, i.e., the likely possibility that the regular co-occurrence of wakefulness with sleep-related stimuli might lead to a second-order, and perhaps more virulent, perpetuating factor: conditioned wakefulness or conditioned arousal.

The 3P model does provide a conceptual framework for understanding types or subtypes of insomnia. For example, it addresses why some subjects have psychophysiologic insomnia as opposed to paradoxical insomnia and why, in either case, the insomnia is expressed as one phenotype as opposed to another (initial versus middle versus late insomnia).

Implications for Current and Future Research and Therapeutics

Most of the tenets of the 3P model are untested and await empirical demonstrations. Several avenues for research are possible. Family studies or medical anthropology studies could be used to evaluate the predisposition toward

insomnia. Stress-induction studies in good sleepers, like those, for example, conducted by Hall and colleagues,[17,18] could be use to produce acute insomnia and to evaluate how a variety of biopsychosocial factors mediate the magnitude of the stress response. Longitudinal studies could be used to confirm whether the putative perpetuating factor of sleep extension does indeed mediate the transition from acute to chronic insomnia.

As for therapeutics, the 3P model has served as the conceptual basis for one treatment modality in particular: sleep restriction. This therapy, while believed by many to be the single most potent component of CBT, was developed to target one particular factor (of the three) and only as it is expressed in one particular form (i.e., sleep extension). This may explain the overall value of multicomponent CBT in that the other treatment components, it can be argued, address other perpetuating factors (e.g., stimulus control addresses engaging in nonsleep activities in the bedroom, cognitive therapy addresses the problem of catastrophic or dysfunctional thinking about insomnia, sleep hygiene addresses the misuse of counter fatigue measures). Thus, the question at hand is: In what ways might the 3P model lend itself to identifying alternative treatment targets with standard or alternative methods?[19] One possibility is to develop therapies or adapt existing therapies to target predisposing factors. Such treatments could be used to increase treatment response, decrease the risk for reoccurrence (as an adjuvant to traditional CBT), or prevent first episodes of insomnia.

In the case of treatment response, depotentiation of predisposing factors might serve to augment outcomes to the extent that they are more, as opposed to less, operational. Treatment response may be boosted if the patient is hypermetabolic by nature by providing relaxation training, if the patient is anxious by nature by providing anxiolytic treatments (medical or psychotherapeutic), or if the patient is (for social reasons) sleeping in a nonpreferred sleep phase by providing some form of chronotherapy (e.g., progressive shifts in sleep scheduling, bright light treatment, or adjuvant treatment with melatonin).

In the case of preventing relapse, one could address the factors discussed earlier or could develop interventions to prevent perpetuating factors from becoming operational during recurrence (new episodes of acute insomnia). In this instance the tendency toward sleep extension could be considered a predisposing factor. This being the case, a brief behavioral intervention could be designed that specifically targets sleep extension as a means for coping with acute insomnia. Alternatively (or in addition), rational approaches to fatigue management could be developed, such as giving instructions on how to compensate for short-term sleeplessness in a way that allows normal sleep homeostasis. In the case of prophylaxis, it might well be possible to prevent many cases of chronic insomnia by replacing sleep hygiene with an empirically validated set of rules.

THE NEUROCOGNITIVE MODEL

Basic Description

The neurocognitive model[3] is based on, and is an extension of, the 3P behavioral model as described by Spielman and colleagues.[1] The central tenets of the model include:

- a pluralistic perspective of hyperarousal (cortical, cognitive and somatic arousal);
- the specification that cortical arousal (as opposed to cognitive or somatic arousal) is central to the etiology and pathophysiology of insomnia;
- the proposition that cortical arousal, in the context of chronic insomnia, occurs as a result of classical conditioning and permits cognitive processes that do not occur with normal sleep;
- the proposition that sleep initiation and maintenance problems do not occur because of hyperarousal per se but because of increased sensory and information processing at sleep onset and during non–rapid eye movement (NREM) sleep;
- the suggestion that sleep state misperception derives from increased sensory and information processing at during NREM sleep or the attenuation of the normal mesograde amnesia of sleep.

As with the "3P" behavioral model of insomnia, it is posited that acute insomnia occurs in association with predisposing and precipitating factors and that chronic insomnia occurs in association with perpetuating factors.[1] The primary perpetuating factor is a form of instrumental conditioning that occurs with sleep extension. The neurocognitive model posits that classical conditioning can also serve as perpetuating factor for chronic insomnia and stipulates that hyperarousal needs to be construed and assessed in terms of its component domains: cognitive, somatic, and cortical arousal. With these considerations in mind, it is suggested that repeated pairing of sleep-related stimuli with insomnia-related wakefulness (arousal) ultimately causes sleep-related stimuli to elicit (or maintain) higher than usual levels of cortical arousal at around sleep onset or during the sleep period. This form of arousal is not thought to be paralleled by somatic arousal (which is posited to be more characteristic of acute insomnia) and is thought to precede, and act as the biological substrate for and precipitant of, cognitive arousal in the context of chronic insomnia.

Conditioned cortical arousal is, in turn, hypothesized to contribute to disturbance of sleep continuity or to sleep state misperception via enhanced sensory processing, enhanced information processing, and long-term memory formation. Enhanced sensory processing (detection of endogenous or exogenous stimuli and, potentially, the emission of startle or orienting responses) around sleep onset and during NREM sleep is thought to directly interfere with sleep initiation or maintenance. Enhanced information processing (detection of, and discrimination between, stimuli and the formation of a short term memory of the stimulating events) during NREM sleep is thought to blur the phenomenologic distinction between sleep and wakefulness and thus contributes to sleep state misperception. Enhanced long-term memory (detection of, and discrimination between, stimuli and recollection of the stimulating event hours after its occurrence) around sleep onset and during NREM sleep is thought to interfere with the subjective experience of sleep initiation and duration and thus contributes to the discrepancies between subjectively and objectively assessed sleep continuity.

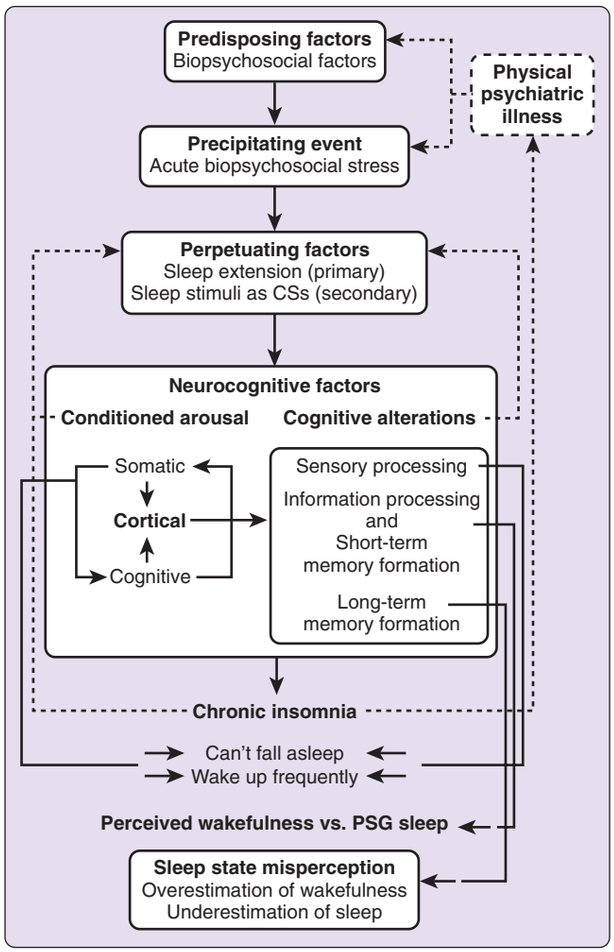

Figure 78-3 The neurocognitive model shown here differs from prior versions in several ways: *Dotted lines* are provided to highlight feedback loops; *solid lines* represent feedforward loops. The examples provided for perpetuating factors have been changed. The primary factor is designated as sleep extension (previously denoted as increased time in bed and staying awake in bed). The secondary factor is designated as sleep stimuli as conditioned stimuli. This is meant to represent when sleep stimuli become conditioned stimuli for wakefulness (arousal). CSs, ▪▪▪; PSG, polysomnographic.

Conditioned cortical arousal is hypothesized to be self-reinforcing, and for essentially two reasons. First, because sleep-related stimuli (X) act as conditioned stimuli for cortical arousal (Y), the pairing is self-reinforcing. That is, if X elicits Y, and the occurrence of Y reinforces the association of X and Y, then pairing is self-reinforcing. Second, because cortical arousal permits processes associated with wakefulness, it is likely that the elicited arousal will, on each occasion, be amplified because of ongoing sensory processing, enhanced information processing, and long-term memory formation. Taken together, these considerations virtually guarantee that the insomnia will, in the absence of its original precipitants, continue unabated and will not be subject to extinction, as usually occurs with classical conditioning. See Figure 78-3 for a schematic representation of the model.

Strengths and Weaknesses

Strengths

In general, the major strengths of the neurocognitive model are that it allows a pluralistic perspective on the concept of arousal; it does not require that hyperarousal be so intense as to directly interfere with sleep initiation and maintenance but instead posits that arousal only be sufficiently intense as to permit processes that are characteristic of wakefulness and can perpetuate wakefulness (stimulus detection, startle, orienting, stimulus identification, intention or action, and long-term recall); it delineates a mechanism beyond that of instrumental conditioning (i.e., classical conditioning as a perpetuating factor); it specifies how chronic insomnia takes on a life of its own (i.e., is self-reinforcing), and its hypotheses are falsifiable. Two lines of research (indirect and direct) provide support for the model.

The indirect evidence derives from observations about the effects of sleep on long-term memory in good sleepers and perceived wakefulness during sleep recorded on a polysomnograph (PSG) in patients with insomnia. With respect to the former, there is good evidence that normal sleepers cannot recall information from periods immediately prior to sleep,[20-23] during sleep,[24-28] or during brief arousals from sleep.[29,30] Thus, normal sleep is indeed characterized by a dense amnesia for events occurring at around sleep onset and during sleep.

With respect to the latter, there is substantial evidence that when awakened from PSG-defined sleep, patients with insomnia (as opposed to good sleepers) tend to perceive themselves to be awake rather than asleep.[31-38] This tendency, better known as *sleep state misperception*, is consistent with the neurocognitive model's perspective regarding sensory and information processing during sleep. That is, if one cue for "knowing" that one is asleep is the lack of awareness for events occurring during sleep, and if it is the case that patients with insomnia exhibit increased levels of sensory and information processing during sleep, then it would be expected that the greater level of awareness for events occurring during PSG-defined sleep serves to blur the phenomenologic distinction between sleep and wakefulness so that patients with insomnia would have difficulty indentifying PSG sleep as sleep. In this instance, what remains open to question is whether sleep state misperception can be correlated with objective measures of cortical arousal—such as by quantitative electroencephalography (qEEG), analyses of cyclic alternating pattern (CAP), or brain metabolic functional imaging—or with objective measures of increased sensory and information processing during sleep (i.e., via evoked-response potentials [ERPs]).

The direct evidence pertains to whether patients with insomnia exhibit increased cortical or central nervous system (CNS) arousal as measured by qEEG and positron emission tomography (PET), increased sensory or information processing as measured by ERPs, an attenuation in the normal mesograde amnesia of sleep, or association between sleep state misperception and objective measures of cortical arousal or ERP abnormalities. Patients with primary insomnia have been found to exhibit higher levels of cortical arousal (in terms of increased NREM high-frequency EEG) as compared to good sleepers[39-43] or patients with insomnia comorbid with major depression.[43a]

Cortical arousal (as well as increased activity involving subcortical areas and circuits) has also been observed in patients with insomnia using PET techniques.[44,45] Altered sensory and information processing have been observed with ERPs.[46-47] Correlational analyses provide evidence that that beta and gamma activity is negatively associated with the perception of sleep quality[17,48] and is positively associated with the degree of subjective-objective discrepancy.[43] There is some evidence that patients with sleep state misperception disorder (paradoxical insomnia) have been found to exhibit more beta and gamma EEG activity than good sleepers or patients with primary insomnia.[49] One study shows that patients with insomnia are better able to recognize word stimuli played during sleep-onset intervals and during early NREM sleep. This latter finding provides support for the hypothesis that there is an attenuation in the normal mesograde amnesia that accompanies sleep in patients with chronic insomnia.

Weaknesses

The primary limitations of the neurocognitive model are its failure to adequately account for the transition from good sleep to acute insomnia (like the 3P behavioral model, it primarily describes chronic insomnia), the importance of circadian and homeostatic influences on sleep, and the possibility that cortical arousal constitutes a permissive factor for worry, rumination, and monitoring behavior. The original model does not clearly address whether conditioned cortical arousal represents hyperarousal or the newer concept of the failure to inhibit wakefulness. With respect to this last point, the summary endeavors to clarify this issue by suggesting that chronic insomnia (versus acute insomnia) is perpetuated by a form of conditioned arousal that is more akin to alert wakefulness than to hyperarousal (physiologic and neurobiological states that occur with flight-or-fight–type stress responses). Finally, whereas the neurocognitive model does provide a conceptual framework for two types of insomnia (psychophysiologic and paradoxical insomnia) and how insomnia becomes self perpetuating (via classical conditioning), the model does not explicitly address how it is relevant for the other insomnia types or subtypes.

Implications for Current and Future Research and Therapeutics

There is evidence supporting the viability of the neurocognitive model, but many of the model's central tenets require further empirical validation. Apart from the research required to support the behavioral base of the model, further work is needed showing that cognitive processes (sensory and information processing and long-term memory) are reliably altered during the sleep period in patients with chronic insomnia and that altered cognitive processing has clear neurobiological concomitants (e.g., altered metabolic activity in specific brain regions) and functional consequences (sleep continuity disturbance and sleep state misperception).

Novel experimental paradigms need to be developed to test the model's core hypotheses. For example, if classical conditioning is an operative factor, experimental paradigms could also be used to evaluate whether sleep-related stimuli may be conditioned to elicit wakefulness. Experiments of this type will most likely need to be conducted in animals because they run the risk of experimental effects persisting beyond the conduct of the experiment itself. If mesograde amnesia is a primary determinant of perceived sleep quantity and quality, it should also be possible to assess the relative importance of this factor using compounds that promote amnesia (with or without sedative properties) in combination with the manipulation of situation cues. Experiments of this type will need to be conducted in humans given the centrality of self-reported sleep continuity.

The neurocognitive model may provide some insight into the potential mechanisms of action of existing therapeutics and also some guidance regarding potential targets for new treatments. In the case of existing therapeutics, pharmacotherapy might effective to the extent that the various compounds block sensory and information processing or promote amnesia within the sleep period. This idea, first espoused by Mendelson,[50-55] seems probable given the effects of benzodiazepines and benzodiazepine receptor agonists on arousal thresholds and memory formation. Sleep restriction therapy might also work via these mechanisms to the extent that this treatment modality serves to deepen sleep (augment the endogenous form of sleep-related mesograde amnesia).

Potential avenues for new medical treatments include the assessment of compounds that have greater-than-normal amnestic potential for their efficacy as hypnotics, provided that such effects can be limited to the desired sleep period and the use of diurnal stimulant therapy to promote wake extension and thereby their potential to diminish nocturnal cortical arousal via increased sleep pressure. Potential avenues for behavioral treatment include inpatient protocols that use more-intensive forms of sleep restriction therapy to promote counterconditioning, such as what is now being done with intensive sleep retraining therapy.[56]

THE PSYCHOBIOLOGICAL INHIBITION MODEL

Basic Description

The psychobiological inhibition model[15] states that stressful life events precipitate both physiologic and psychological arousal, and the consequences of this are the occurrence of selective attending to the life stressor and the occurrence of insomnia symptoms. In the case of acute insomnia, it is thought that physiologic or psychological arousal is sufficient to interfere with the normal homeostatic and circadian regulation of sleep (i.e., is sufficient to prevent the normal inhibition of wakefulness). The acute insomnia might resolve or be perpetuated based on the extent to which the stress state resolves and the patient does not attend to the acute insomnia. The shift of attention from the life stressor, implicitly or explicitly, to the insomnia symptoms is posited to be the critical event that transitions acute insomnia to a form of sleep disturbance that is self-perpetuating. A schematic representation of the model is presented in Figure 78-4.

This model substantially distinguishes itself from earlier perspectives in three fundamental and related ways. First, the point of departure for the model is the

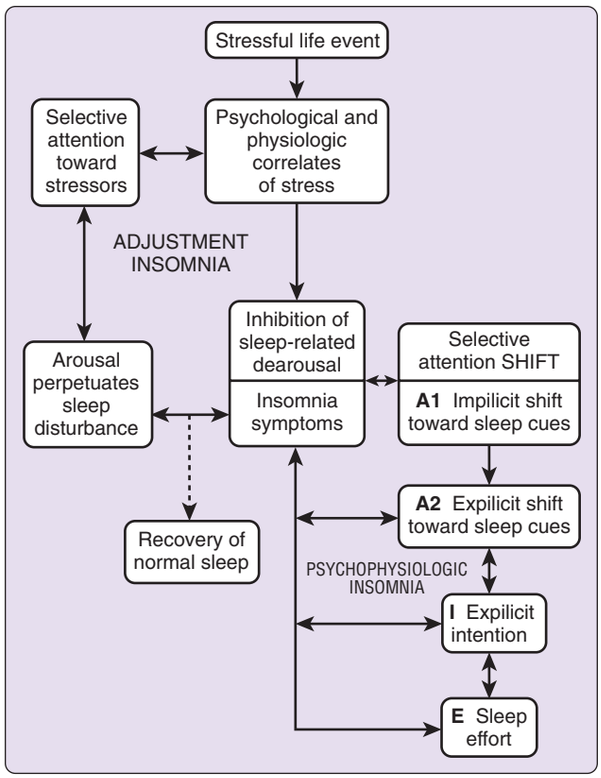

Figure 78-4 Proposed evolution of psychophysiologic insomnia from adjustment insomnia following the attention-intention-effort (A-I-E) pathway.

psychobiological framework for normal sleep that is inherent in the stimulus control perspective[4] and formally delineated in the two-process model of sleep–wake regulation.[57] Second, it is proposed (and was the first etiologic model to do so) that persistent sleep continuity disturbance occurs in relation to a failure to inhibit wakefulness (as opposed to conditioned hyperarousal). Third, the model is focused on how cognitive factors (as opposed to behavioral or physiologic factors) serve to perpetuate insomnia.

Psychobiological Framework for Normal Sleep

Espie[4,58] suggests that for normal sleepers, homeostatic and circadian processes default to good sleep, not to insomnia, and that like other neurobehavioral systems, this is ensured by plasticity and automaticity. *Plasticity* refers to the ability of the sleep system to adjust to, and/or accommodate, situational factors that disrupt normal sleep-wake functioning (e.g., circumstances that require that sleep be temporarily foreshortened or extended). In transient or acute insomnia, the norm would be the recovery of good sleep, reflecting the system's plasticity in function. *Automaticity* refers to the involuntary nature of sleep initiation and sleep maintenance. That is, that sleep is initiated and maintained automatically by the well-established conditioned associations between sleep-related stimuli and sleep and by the two-process system that governs the timing and duration of sleep and wake. Thus, under normal circumstances, sleep occurs passively (without attention, intention, or effort).

Insomnia as the Failure to Inhibit Wakefulness

The majority of insomnia models conceptualize insomnia as a disorder of hyperarousal. That is, the inability to initiate or maintain sleep derives from the occurrence of a level of arousal that is simply incompatible with sleep, where such arousal occurs acutely in relation to stress and chronically in relation to behavioral factors[58] or classical conditioning. Espie, however, has proposed an important alternative point of view, suggesting that insomnia occurs in association with a failure to inhibit wakefulness. That is, the psychobiological inhibition model suggests that in the early stages of chronic insomnia, problems with sleep initiation or sleep maintenance can occur because of fundamental alteration in the functioning of the neurobiological mechanisms that normally inhibit wakefulness and permit sleep to occur. Such an alteration is likely to be systemic; it occurs with real or perceived threat and is part of the larger flight-or-fight response. This alteration, which should dissipate along with the resolution of the acute stressor, may be potentiated by cognitive processes.

Cognitive Factors Trigger the Failure to Inhibit Wakefulness

The failure to inhibit wakefulness (in the context of chronic insomnia) is hypothesized to result from three related cognitive phenomena collectively referred to as the attention-intention-effort (A-I-E) pathway.[4] Each of the three phenomena are thought to act in concert, and in a hierarchical fashion, to transition acute stress-induced insomnia into a form of insomnia that is self-perpetuating. This is thought to occur as follows. First, when the person is unable to sleep, his or her attention is drawn to an otherwise automatic process. The very process of attending, in turn, prevents perceptual and behavioral disengagement. Second, because a primary function of attention is to promote action in response to perceived need or threat, an intentional (purposive) process is initiated that acts to further inhibit the normal downregulation of arousal. Third, when the person is unable to sleep, active effort is expended trying to fall asleep, and this effort, like enhanced attention and intention, serves only to further prevent the inhibition of wakefulness.

In sum, the psychobiological inhibition model provides a generic common pathway to chronic insomnia. Insomnia occurs in a persistent fashion when there is a sufficient level of attention, intention, or effort to outweigh good stimulus control or the intrinsic drives of the two-process system.

Strengths and Weaknesses

Strengths

There is substantial support, in general, for the concept that attention bias or selective attention plays a role in mental illness.[59] It has been found to be operational for a wide range of psychiatric disorders including panic disorder, hypochondriasis, eating disorders, obsessional disorders, generalized anxiety disorder, and posttraumatic stress disorder.[60-64] In fact, the data within these domains are sufficiently compelling that it has been argued that attention bias may have a causal role in most, if not all, anxiety disorders.[63] The concept is that the anxious person is preoccupied with danger and threat and thus

selectively attends to threat-related stimuli as he or she perceives that the danger is imminent but also potentially avoidable.

Attention bias has also been implicated in habit and dependence disorders. In this case, however, attention is not focused on threat-related stimuli per se but instead on the object of the addiction.[64] For example, in alcoholism, patients are thought to selectively attend to alcohol-related cues and that this form of attention bias can moderate or mediate addiction by producing craving. In the case of insomnia, attention bias is likely to operate in a manner akin to anxiety and dependence disorders (attention to threat or object of craving), and this might account for the nosologic requirement that insomnia (psychophysiologic insomnia) include "excessive focus on, and heightened anxiety about, sleep".[64, p. 7]

Apart from the general perspective that attention bias is relevant for mental disorders, there is also a significant amount of experimental evidence supporting the psychobiological inhibition model, and especially with respect to sleep-related attention bias and sleep-related effort. To date eight studies have been conducted whose findings reliably indicate:

- sleep-related mental preoccupation may be associated with the transition from acute to persistent insomnia in cancer patients[65];
- subjects with psychophysiologic insomnia exhibit heightened levels of attention bias as compared to good sleepers and subjects with delayed sleep phase syndrome[66,67];
- attention bias to sleep-related stimuli detected in patients with psychophysiologic insomnia may be driven by threat[57,67-69];
- there are positive linear relationships between sleep-related attentional bias and self-reported sleep quality and sleepiness;
- subjects with psychophysiologic insomnia exhibit "effortful preoccupation with sleep."[70]

Another strength of the psychobiological inhibition model is that it allows an objective means of indexing cognitive processes in insomnia. In practice, insomnia patients complain primarily of mental events interfering with sleep, including intrusive thoughts, racing thoughts, increased worry, and the inability to disengage attending to environmental noise or bodily sensations. Although such mental events appear central to the experience of insomnia, their assessment has relied primarily on self-report measures. Thus, a major strength of the psychobiological inhibition model is it concepts may be operationally defined and tested with objective measures like the computerized emotional Stroop task, the induced-change blindness task, and the dot probe task.

Finally, and perhaps most important, a major strength of the psychobiological inhibition model is the extent to which one of its central tenets (inhibition of wakefulness) is supported by both animal and human data. In the case of the former, Cano-Saper's rodent model[7] serves to highlight that there is indeed a neurobiological substrate for the concept of the failure to inhibit wakefulness and it appears to be dysregulated in rodents exposed to the cage-exchange paradigm. In humans, studies using evoked response potential methodology[46,47] suggest that patients with insomnia exhibit a diminished capacity to inhibit exterioception.

Limitations

Much of psychobiological inhibition model and the A-I-E pathway that remains to be validated (particularly the intention and effort components). Moreover, studies conducted in Glasgow now need to be replicated and extended by other research groups. An important consideration for subsequent studies will be the extent to which the psychobiological inhibition model and the A-I-E pathway apply across the range of primary insomnia types (e.g., psychophysiologic insomnia versus idiopathic and paradoxical insomnias) and the insomnia subtypes (initial, middle and late insomnias). Finally, and perhaps most difficult, is the need to create conceptualizations and measures that allow a clear distinction between, and an assessment of, the relative importance of the two primary concepts now thought to undergird the incidence and severity of insomnia: arousal or hyperarousal and the failure to inhibit wakefulness (or function typical of wakefulness).

Implications for Current and Future Research and Therapeutics

As previously suggested, the psychobiological inhibition model offers a generic common pathway to insomnia. Consequently, the model can accommodate a common pathway explanation for the effectiveness of many existing elements of cognitive behavioral therapy for insomnia (CBT-I). The model's potential explanatory power, however, is not limited to elements of CBT-I but also likely extends to potential mechanisms of action for existing medical therapeutics.

With respect to CBT-I, any behavioral or cognitive intervention that augments the inhibition of wakefulness should permit the reinstatement of normal sleep. Sleep restriction might exert its therapeutic effects via the reinstatement of sleep automaticity. That is, sleep restriction serves to increase homeostatic pressure for sleep to a point where sleep will occur inevitably and without attention, intention, or effort. Stimulus control may strengthen adaptive and automatic dearousal associations of bed and sleep and thereby diminish the conditioning effects that inhibit downregulation. Finally, relaxation, distraction, and imagery methods might reduce worry about sleep, and paradoxical intention methods might entirely refocus the A-I-E pathway away from sleep preoccupation.

With respect to the medical management of insomnia, the psychobiological inhibition model suggests that the mechanisms for existing therapies reside in their capacity to promote relaxation, inhibit exterioception, and derail sleep-related attention, intention, and effort. Clearly these are features of traditional sedatives (e.g., barbiturates, benzodiazepines, and benzodiazepine receptor agonists) but also might apply to the off-label use of antipsychotics (e.g., quetiapine, olanzapine).

Finally, the model also offers a perspective that might allow the development of new approaches. From the CBT or psychotherapeutic point of view, the psychobiological inhibition model clearly carries with it the suggestion that sensory gating training or (alternatively) mindfulness therapies may be successfully used to treat insomnia. From the

pharmacologic point of view, the psychobiological inhibition model clearly carries with it the suggestion that it may be productive to antagonize wake-promoting or wake-consolidating systems and that one such approach would be via orexin antagonism.

THE *DROSOPHILA* MODEL

Basic Description

The conceptual basis for the *Drosophila* model (as an analogue of human insomnia) is that insomnia occurs, in part, in relation to predisposing factors. This fundamental tenet of the behavioral model suggests that chronic insomnia may have a genetic component and that a portion of the variance in the incidence of insomnia[71,72] should be related to factors that are heritable, for example, the strength and plasticity of the sleep system, the trigger threshold for and intensity of the flight-or-fight response, or the strength and plasticity of sleep homeostasis and circadian processes. Consistent with this point of view is that insomnia tends to run in families and that persons with a family history of insomnia are more anxious and prone to stress-related sleep disturbances.[73,74] Thus, if insomnia results, in part, from predisposing trait characteristics, the identification of the underlying mechanisms should be feasible using genetic strategies.

Given the complexity and number of traits observed for insomnia, it seems unlikely that single gene mutations will result in an animal model that adequately captures the human condition. An alternative approach is to identify natural variants in a population that simultaneously exhibit several behavioral characteristics of insomnia. The phenotypic variation in these individuals is likely to be the result of minor changes in many genes and as a consequence is more likely to reflect the diversity of the human disorder.[75] The natural polygenic variation can be amplified over successive generations using laboratory selection and can be identified using whole-genome arrays.[76] This is the approach that undergirds the *Drosophila* model.

Evaluation of a normative dataset of wild-type *Canton-S* (*Cs*) *Drosophila* indicated that they display a sufficient range of sleep times and activity levels to make them suitable for laboratory selection (Figure 78-5A, *green bars*). *Drosophila* that demonstrated reduced sleep time in combination with increased sleep latency, reduced sleep bout duration, and elevated levels of waking activity (*insomnia-like*, referred to as *ins-l flies*) were selected and bred over successive generations. As seen in Figure 78-5B, total sleep time was progressively reduced during selection and stabilized after 60 generations. At generation 65, more than 50% of *ins-l* flies obtained less than 60 minutes of sleep in a day, and the distribution of sleep times was shifted dramatically to the left (see Fig. 78-5A, *pink bars*). Not surprisingly, the decrease in sleep time (or increase in total wake time) in selected *Drosophila* came primarily at the expense of nighttime sleep (see Fig. 78-5C). As with human insomnia, *ins-l* flies showed increased latency from lights off to the first sleep bout of the night (see Fig. 78-5D), suggesting that they have difficulty initiating sleep.[77] The *ins-l* flies also exhibited difficulties maintaining sleep as evidenced by an inability to consolidate sleep into long bouts (average sleep bout duration; see Fig. 78-5E).[7] The maximum episode of consolidated sleep that can be generated by an *ins-l* fly is only 36 ± 9 minutes versus 257 ± 22 minutes in *Cs* flies. In addition to disrupted sleep, the *ins-l* flies exhibit increased locomotor activity during waking (1.86 ± 0.03 crossings) compared to *Cs* flies (1.42 ± 0.05 crossings).

To assess the extent to which the sleep patterns of the selectively bred *Drosophila* represent a reasonable analogue of human insomnia (chronic insomnia), the sleep of the *ins-l Drosophila* was evaluated for chronicity (i.e., stability of the abnormal sleep pattern over the life span) and wake state of the *ins-l Drosophila* was evaluated for evidence that the altered form of sleep was associated with daytime consequences (i.e., fatigue, sleepiness, impaired concentration or memory) or health outcomes (increased mortality). With respect to chronicity, it was found that the sleep profile remained stable in *ins-l Drosophila* over time. Total sleep for three representative *ins-l* flies and one *Cs* fly are shown in Figure 78-5F. These three *ins-l* flies obtained a total of 358 ± 128 minutes of sleep during their first 20 days of life (and this appears stable with time) versus 17,567 ± 655 minutes of sleep over the same time period in the *Cs* flies (and this appears to trend downward with aging). Thus, the observed stability of the sleep profile of the *ins-l* flies may be viewed as chronic (i.e., the sleep disturbance does not spontaneously remit with time).

With respect to daytime consequences, the two types of *Drosophila* were evaluated for sleepiness, learning impairment, and motor or coordination difficulties. *Sleepiness* was assessed using a biomarker for sleepiness (amylase).[6] As seen in Figure 78-5G, *ins-l* flies show elevated levels of amylase relative to *Cs* flies, suggesting that they experience sleepiness (or increased sleep drive) during their primary wake period. Learning was assessed using aversive phototaxic suppression (APS).[78] In this task, flies learn to avoid a light that is paired with an aversive stimulus (quinine or humidity). In this paradigm it was shown that APS is sensitive to both sleep loss and sleep fragmentation.[79] For example, as seen in Figure 78-5H, learning is significantly impaired in the shortest sleeping *ins-l*$_{short}$ flies compared to *Cs* controls. To determine whether the selection protocol generated poor-learning *Drosophila* as a phenotype independent from the observed sleep deficit, learning in long-sleeping *ins-l* flies was also evaluated. Longer sleeping siblings maintained their ability to learn, indicating that the selection procedure did not inadvertently, and independent of sleep, contribute to poor learning. Motor and coordination difficulties were assessed by quantifying the number of spontaneous falls in young age-matched *Cs* and *ins-l* flies walking for 30 minutes in an obstacle-free environment. *Cs* flies rarely fall under these conditions. In contrast, *ins-l* flies often lose their balance (see Fig 78-5I).

Finally, health consequences were assessed in terms of mortality via a measure of lifespan duration. This approach derives from the epidemiologic studies in humans that suggest that sleep duration and insomnia are associated with an increased risk of all-cause mortality and reduced lifespan.[80] Accordingly, one would predict that if the selected lines have insomnia or are getting less sleep than they need, they would have a shortened lifespan. As seen in Figure 78-5J, this is indeed the case. It should be noted that the reduced lifespan observed in the *ins-l* flies is not a result of decreased fitness.

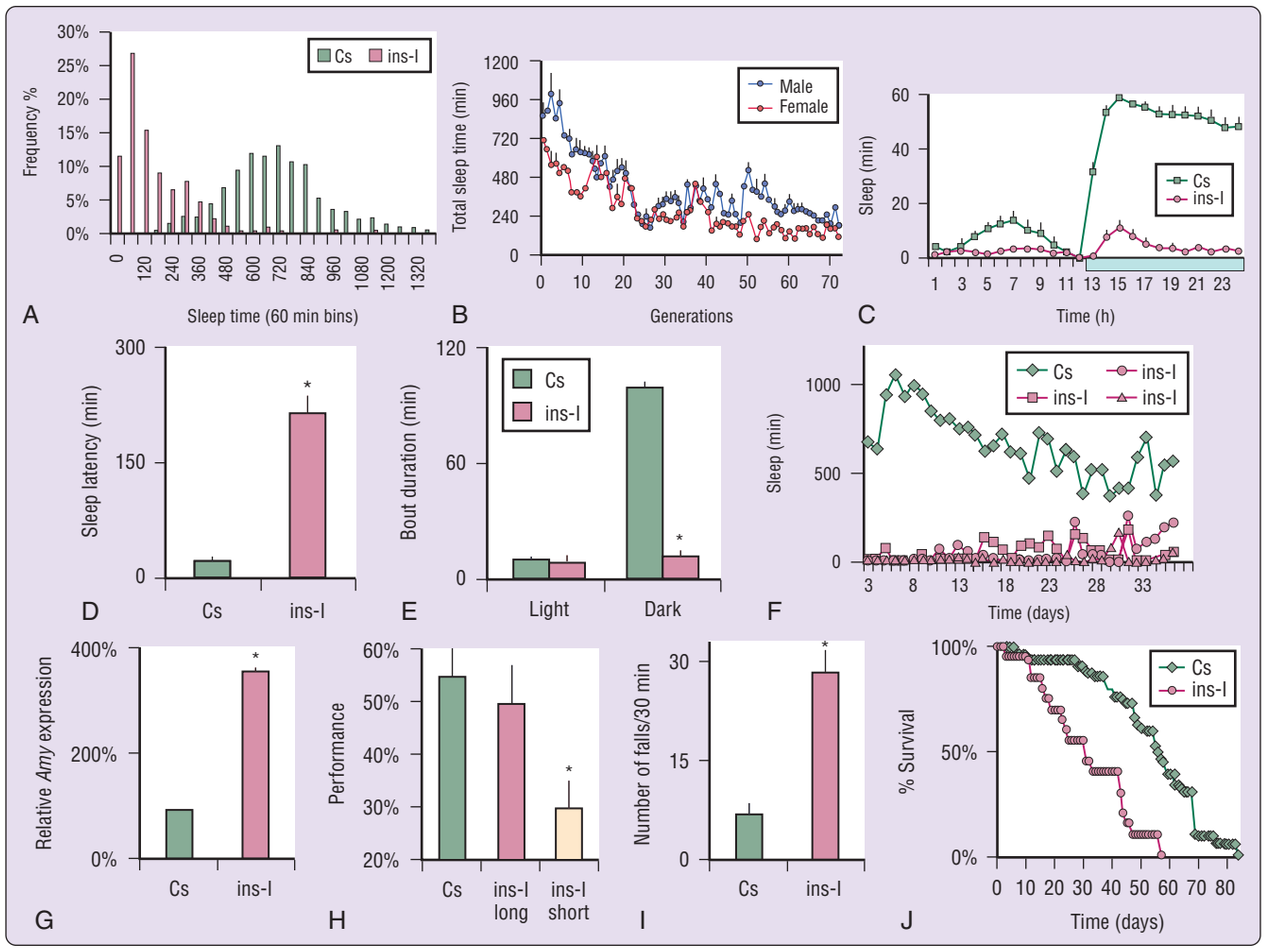

Figure 78-5 **A**, Frequency distribution of total sleep time in 60 min bins in wild type *Cs* flies ($n = 1000$) and in *ins-l* flies at generation 65 ($n = 364$). **B**, Total sleep time in males ($n = 40$) and females ($n = 40$) for successive generations of *ins-l* flies. **C,** Daily total sleep time is shown for 37 days in one *Cs* and three *ins-l* flies. **D**, Sleep in min/hr for 24 hr in *Cs* flies ($n = 32$) and *ins-l* flies ($n = 32$). The *gray rectangle* represents lights off. **E**, Sleep latency is increased in *ins-l* flies ($n = 28$) versus *Cs* flies ($n = 33$). **F,** Average sleep bout duration is reduced during the dark period in *ins-l* flies ($n = 32$) versus *Cs* flies ($n = 32$). **G,** Amylase mRNA levels are elevated in *ins-l* flies (% of Cs expression) at ZT0-1. **H,** Learning in *Cs* flies, longer-sleeping *ins-l* flies (average daily sleep time, 347 ± 55 min), and short-sleeping *ins-l* flies (average daily sleep time, 26 ± 7min) ($n = 10$ for each group) **I,** Number of falls during 30 minutes in *Cs* flies ($n = 20$) and *ins-l* flies ($n = 18$). **J,** Representative survival curve of aging *ins-l* compared to *Cs* flies (30 flies/group). *$P < .05$; error bars represent standard error of the mean.

In sum, the selection procedure was effective in producing animals with reduced total sleep time, increased sleep latency, and shortened sleeping bout duration. These sleep effects were found to be persistent and were associated with a variety of sequelae including diurnal sleepiness, impaired learning, motor or coordination difficulties, and increased mortality. Taken together, these findings suggest that the *Drosophila* model is a reasonable analogue of human insomnia (chronic insomnia).

Strengths and Weaknesses

A major strength of the *Drosophila* model is its approach: a naturally occurring set of sleep parameters (parameters that are commonly found in human insomnia) were operationally defined for use in the fly and amplified over successive generations using laboratory selection. Not only is the selection procedure an ideal one for a genetic study of insomnia, but also the use of multiple parameters ensures that the analogue condition more closely resembles the human expression of the disorder. Another strength of the model is the effort to demonstrate that the aggregate phenotype also exhibited daytime deficits with respect to sleepiness, learning impairment, coordination difficulties, and reduced lifespan.

One weakness of the model is the inability to establish (as with any animal model) the subjective complaint of insomnia. Another weakness is a level of insomnia severity that is not analogous to that seen in humans: Total sleep times are a fraction of the total sleep time seen in non–*ins-l* flies. This might suggest to some that the selection process produced a new class of sleep mutant as opposed to an idiopathic form of insomnia. The demonstration of sleepiness the *ins-l* flies are controversial. The consensus view (based on the use of the multiple sleep latentcy test [MSLT]) is that patients with chronic insomnia do not exhibit pathologic sleepiness. Finally, the method of

assessment of sleepiness is also somewhat controversial to the extent that amylase is also used as a biomarker for stress.[81-84]

Implications for Current and Future Research and Therapeutics

There are a variety of possible directions for future research. Given the complexity of insomnia, it is likely that independent selections would potentially yield alternative outcomes. That is, the genes identified in the *ins-1* flies might only represent one potential pathway to insomnia. Thus, a greater understanding of insomnia may be advanced with additional selected lines. Further, the use of molecular-genetic and genomic strategies such as Affymetrix arrays, suppressor screens, and genetic mapping may be useful for the identification of the genes that are associated with the various aggregate phenotypes. Given this latter strategy, it is important to acknowledge that gene profiling in *Drosophila* obtained by laboratory selection is likely to reveal two classes of genes: those that are causative for a given behavior and those that are a consequence of the behavioral change.[85] Most studies have focused on identifying genes that are causative for a given behavior.[76,86,87] However, given that extended waking results in substantial physiologic impairment,[88,89] including death,[90,91] the latter set of genes may also be particularly important in the context of insomnia.

THE RODENT MODEL OF ACUTE INSOMNIA

Basic Description

A rat model of acute stress–induced insomnia has been developed using a species-specific psychological stressor, cage exchange. The aim of this model was to identify the brain circuitry activated in rats experiencing stress-induced insomnia to better understand the neurobiological basis of acute insomnia.

In the cage-exchange paradigm, stress is induced by manipulating the social context rather than by applying a continual physical stressor (e.g., tone, shock).[7,44] This is accomplished by transferring a male rat from his home cage, at the peak of the sleep period, to a soiled cage previously occupied by another male rat. Because rats are very territorial, exposure to the olfactory and visual cues of a competitor, even in its absence, induces a stress fight-or-flight response including activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis and sustained wakefulness. Several hours later, when the physiologic indicators of acute stress are attenuated, this manipulation induces a late period of disturbed sleep.

The brain circuitry activated during this late period of disturbed sleep was assessed by examining the expression of Fos, a transcription factor widely used as a marker of neuronal activity. Increased activation was observed in the cerebral cortex, limbic system, some arousal groups (locus coeruleus and tuberomamillary nucleus), and part of the autonomic system. Surprisingly, there was also simultaneous activation of the sleep-promoting areas: the ventrolateral preoptic area (VLPO) and the median preoptic nucleus. This coactivation results in a unique pattern of brain activity that differs from those observed during wake or normal sleep, because the sleep circuitry appears to be like that in a sleeping rat, whereas the arousal system and the cortex show a level of activation similar to those of wakefulness. The high level of cortical activation (as measured by Fos) was also associated with high-frequency EEG activity (distinctive of wakefulness) during NREM sleep. The co-occurrence of high-frequency EEG activity and traditional sleep frequencies also appears to represent a novel intermediate state that differs from both normal EEG sleep and wakefulness.

Subsequent experiments revealed that inactivation of discrete limbic or arousal regions, via cell-specific lesions or pharmacologic inhibition, allowed the recovery of specific sleep parameters and changed the pattern of brain activity in the cage-exchange paradigm.[7] This suggests that stress-induced insomnia requires the occurrence of a cascade of neuronal events along with the normal propensity for sleep. This cascade likely includes sensory inputs (olfactory and visual cues of a competitor) that activate limbic areas, which in turn activate part of the arousal system that subsequently activates the cerebral cortex. This latter event (cortical activation) may be measured as high-frequency EEG activity during NREM sleep, and it is eliminated after inactivating parts of the arousal system, which supports the proposed pattern of brain activation represented in Figure 78-6.

The proposition that this particular stress paradigm can induce a *novel intermediate state* needs to be considered within the context of normal sleep–wake control,[92,93] as the

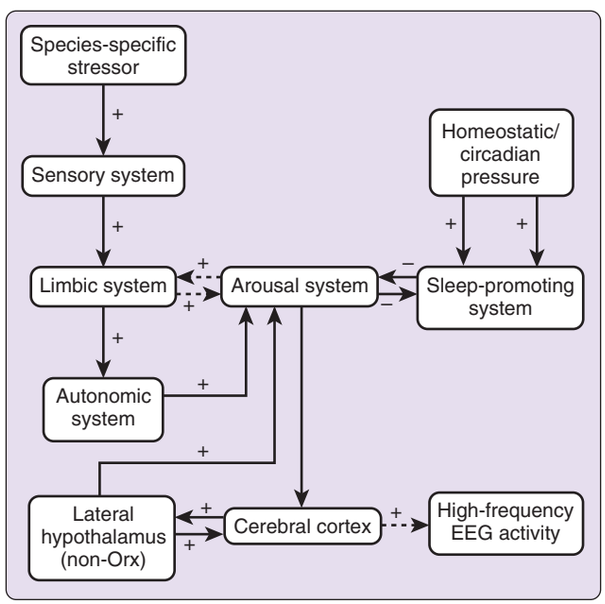

Figure 78-6 Putative circuitry involved in stress-induced insomnia: The olfactory signals are conveyed to the limbic system, which in turn activates the arousal and autonomic systems, as well as nonorexin neurons in the lateral hypothalamus. The cerebral cortex becomes highly activated by inputs from the arousal system and the lateral hypothalamus, which generates the high-frequency activity observed during NREM sleep. The reciprocal inhibition between the sleep and arousal systems would ordinarily prevent co-activation, but the homeostatic and circadian pressure keep the sleep system activated, whereas stress activates the arousal system, resulting in a unique pattern of brain activity.

existence of such a state represents an aberration of what is considered normal sleep and wake. As proposed by Saper and colleagues,[93] in normal animals there is a reciprocal inhibitory innervation between the main sleep-promoting neuronal group (VLPO), whose neurons are active during sleep, and the neuronal groups that compose the arousal system—the histaminergic tuberomammillary nucleus, the serotoninergic dorsal raphe, and the noradrenergic locus coeruleus—whose neurons are active during wakefulness. The authors have proposed that this reciprocal inhibition provides a control system that is analogous to an electrical flip-flop switch. In this case, when one side is strongly activated, it inhibits and deactivates the other side, which decreases the inhibitory input to itself (disinhibition) and reinforces its own activity. In the absence of other factors, this configuration renders a bistable circuit (stable in one or the other state), with rapid and complete transitions between states and no occurrence of intermediate states (co-activation). The circuit is switched from one state to the other due to the strong inputs generated by the gradual buildup of the circadian and homeostatic pressures. As summarized by Saper:

> *When this pressure to change becomes great enough, the same feedback properties that allow the flip-flop circuit to resist change will suddenly give way and rapidly produce a reversal of firing patterns. The flip-flop switch therefore changes behavioral state infrequently but rapidly, in contrast to the homeostatic and circadian inputs, which change continuously and slowly.*[93, p. 729]

In this context, the simultaneous activation of the VLPO and the arousal system in the cage-exchange paradigm is surprising. A possible explanation is that during stress-induced insomnia, the VLPO is fully activated because of both the homeostatic and circadian drives, but it is unable to turn off the arousal system because this is being excited intensely by inputs from the cortical and limbic systems. At the same time, the arousal system cannot turn off the VLPO because it is highly active owing to the stronger homeostatic pressure caused by the fact that the stressed rats are partially sleep deprived. This results in the simultaneous activation of opposing systems that normally are not activated in tandem, and the bistable circuit becomes inherently unstable: The switch is forced into an intermediate position. This scenario is represented in Figure 78-7.

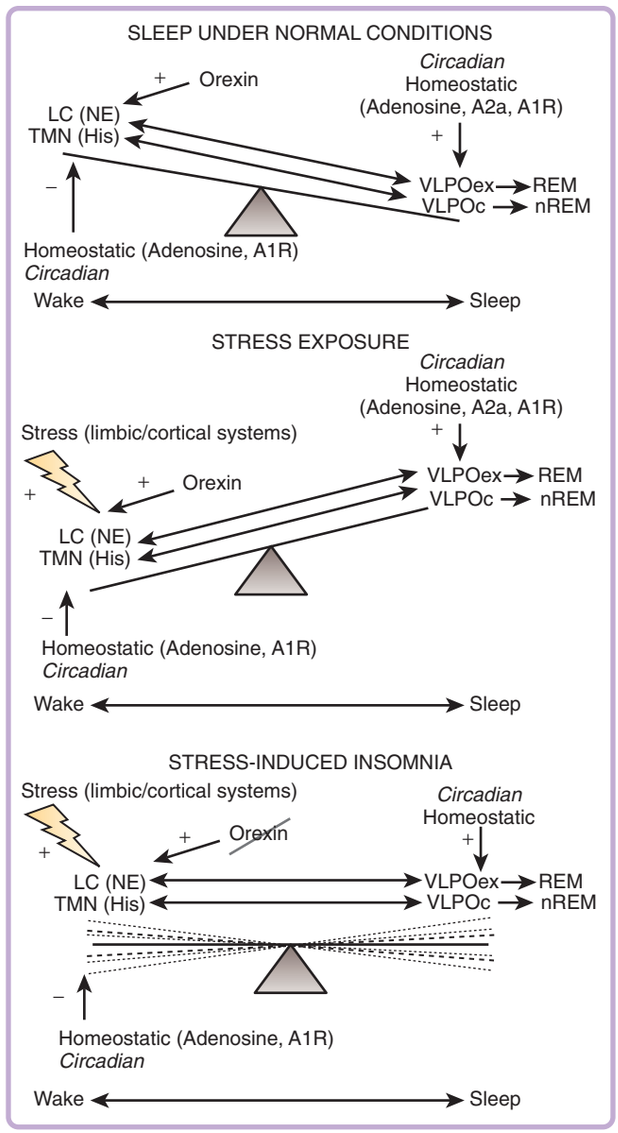

Figure 78-7 During normal sleep, the circadian and homeostatic drives enhance the activity of the sleep-promoting areas and simultaneously inhibit the arousal system, favoring the sleep state (the homeostatic effect is mediated in part by adenosine acting on A_1 and A_{2a} receptors). Stress activates part of the arousal system via cortical and limbic inputs, and this activation opposes the direction of the circadian and homeostatic drives. In stress-induced insomnia, the cortical, limbic, and arousal activation persists, but the homeostatic pressure is stronger than usual because the rats are partially sleep deprived; the circadian drive still favors the sleep state. Because these two forces are opposing and strong, the sleep–wake switch is forced into an unstable position, allowing the emergence of an intermediate state in which both sleep and wake circuitries are activated simultaneously, but each state is unable to sufficiently inhibit the other to prevent it from firing. His, histamine; LC, locus coeruleus; NE, norepinephrine; TMN, tuberomammillary nucleusVLPOc, ventrolateral preoptic nucleus core; VLPOex, ventrolateral preoptic nucleus extended.

Strengths and Weaknesses

The rat model's cage exchange paradigm has several strengths. One is the conceptualization of insomnia as part of, or precipitated by, the flight-or-fight response. It uses a psychosocial stressor (perceived territorial threat) to induce sleep continuity disturbance, and it successfully produces a form of acute insomnia that includes both initial and late subtypes. It identifies specific neuronal effects within regions implicated in the regulation of sleep and wakefulness and produces quantitative EEG findings that are consistent with those found in human insomnia. Its overall findings are consistent with the conceptualization of insomnia as a disorder of hyperarousal, and it neuronal findings suggest that acute insomnia is a hybrid state resulting from the co-activation of systems that normally function in bistable fashion.

The characterization of acute insomnia as part of (or as a consequence of) the flight-or-fight response is particularly useful. This suggests that insomnia may be, as a transitory phenomenon, an adaptive response to perceived threat[94] and is consistent with Richardson's[95] proposal that insomnia reflects the overactivity of systems extrinsic to the sleep–wake circuitry that can temporally override normal sleep–wake control to facilitate a more imperative function, the stress response. The suggestion that acute insomnia exists as a hybrid state represents an important refinement of the concept of hyperarousal and is consistent with the transition probability model described by Merica and colleagues [96,97] and with Espie's concept that insomnia occurs in association with a failure to inhibit wakefulness.[4,58]

The rat model of acute insomnia does have some limitations. As with the *Drosophila* model, it is unable to establish the subjective complaint of insomnia, and as an analogue of acute insomnia, it might not be relevant for assessing chronic insomnia, which many would argue is the more clinically relevant condition. Although there is no question that modeling chronic insomnia (e.g., using a conditioning paradigm) would be useful, the acute model might nevertheless serve as a guide for what to expect in chronic insomnia. For example, the model clearly identifies brain regions of interest and clearly delineates one kind of pathology that may be characteristic of both acute and chronic insomnia, namely, the co-activation of both sides of the flip-flop switch. Another limitation of the model may be its reliance on the Fos measure. Not all neuronal groups express Fos in association with action potential activity. Thus, this might limit the resolution of the neurobiological effects of the cage-exchange paradigm to regions that express Fos.

Implications for Current and Future Research and Therapeutics

Observations from the rat model might help to identify putative targets for pharmacologic manipulation that can guide the development of new therapies. One essential finding is that the sleep-promoting neuronal groups are fully active in the rat model, and the problem seems to be the anomalous residual activation of the arousal and limbic systems at a time they should be completely off. This suggests that shutting down the residual activity of these systems might be a better approach to treat stress-induced insomnia (and perhaps chronic insomnia) rather than potentiation of the sleep system. Further, identifying the phenotype of these neurobiological abnormalities may be helpful in the search for more-specific pharmacologic treatments, which may, in turn, yield fewer unwanted side effects.

CONCLUSION

The neurocognitive model, psychobiological inhibition model, and the Cano-Saper rodent model share at least two central tenets: Stress (threat or perceived threat) is a major precipitant of acute insomnia, and chronic insomnia involves a hybrid state where there are simultaneously higher than normal levels of CNS activation and a failure to inhibit processes normally associated with wakefulness.

The neurocognitive model and the psychobiological inhibition model differ with respect to the role of cognitive processes as they occur in chronic insomnia. The psychobiological inhibition model allows mental activity and cognitive processes to assume a central role in perpetuating insomnia: The person is awake because he or she is worrying or is attending to not sleeping. The neurocognitive model takes into account cognitive processes but does not ascribe a primary role to such phenomena: One is worrying or is attending to not sleeping because he or she is awake. Thus, cognitive phenomena serve as the flame for the psychobiological inhibition model and wind to the flame for the neurocognitive model.

The Cano-Saper model differs from the human models, at the conceptual level, because of its mechanistic emphasis on the sleep switch (as opposed to functional or environmental factors) and dysregulation of the sleep switch as it occurs acutely with homeostatic and circadian dysregulation. This difference is, however, not as profound as one might think. The question is what happens over time? Is it possible that rodents can develop chronic insomnia, and if so does this occur in a fashion that is analogous to, or relevant for, the human condition ? In the absence of data, it stands to reason that the conditioning factors that appear to be operative with human insomnia are also likely to be operational in the rodent. If true, an animal model of chronic insomnia is possible and may be used to explore the effects of conditioned arousal or conditioned wakefulness on brain function, physiology, and anatomy.

In the end, the differences in emphasis among the neurocognitive model, the psychobiological inhibition model, and the Cano-Saper model might not be a matter of which is correct but rather at what point the various models are more or less relevant. The assessment of such a proposition awaits empirical assessment, such as a large-scale natural history study focused on the factors that mediate the transitions from good sleep to acute insomnia and from acute insomnia to chronic insomnia. It stands to reason that stress response, attention bias, conditioning, and altered neurobiology all play a role across the trajectory from acute to chronic insomnia.

Finally, there is the *Drosophila* model. At first glance it appears that this model highlights an entirely different component or phase of the disease process (genetic predisposition) and as such is potentially more relevant for idiopathic insomnia and has little overlap with models that are almost entirely focused on the precipitation and perpetuation of insomnia in the context of psychophysiologic or paradoxical insomnia. This, however, might not be the case.

The Shaw *Drosophila* model might also be relevant for issues pertaining to the precipitation and perpetuation of insomnia. This may be true because the selective breeding paradigm might have resulted in a fundamental alteration of the strength and plasticity of the sleep system, the trigger threshold for and intensity of the flight-or-fight response, or the robustness of sleep or circadian processes. It is also possible that the selective breeding paradigm (particularly the short sleep aspect) might have itself directly predisposed the animals to insomnia. That is,

Shaw and colleagues bred short sleepers without altering the environment (duration of the light–dark cycles) in such a way as to be compatible with short sleep. Thus, as with humans, it is possible that the insomnia was expressed as a result of a mismatch between sleep ability and sleep opportunity.

In humans with psychophysiologic (and potentially paradoxical) insomnia, this mismatch is posited to result from sleep extension (activities enacted to recover lost sleep). In the *Drosophila* model the mismatch might occur because the animal cannot escape the environmental imperative for sleep. As with the above speculation, this concept also awaits an empirical evaluation; in this case one where the light–dark cycles may be altered to match sleep–wake propensity or where an opportunity is provided for the fly to manipulate its environment so as to allow light and dark exposure on demand. Under such conditions, if negative consequences are attenuated, this would suggest that the *Drosophila* model is also relevant for the primary insomnias.

Acknowledgement

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❖ Clinical Pearls

While many consider theory and experimental models of clinical entities to be largely academic enterprises, this is far from the case for the models summarized in the present chapter. Each model clearly suggests one or more targets for treatment, which might or might not be currently addressed by current therapeutics.

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