Journal of the American Association for Laboratory Animal Science
Copyright 2007
by the American Association for Laboratory Animal Science

Vol 46, No 1
January 2007
Pages 35–41

Extra-auditory Effects of Noise in Laboratory Animals: The Relationship Between Noise and Sleep

Arnaud Rabat

Noise has both auditory and extra-auditory effects. Some of the most deleterious extra-auditory effects of noise are those leading to sleep disturbances. These disturbances seem to be related to both endogenous (physical parameters) and exogenous (sex, age) factors of noise. Despite correlative relations between noise level and awakenings, the scientific community has not reached consensus regarding a specific action of these factors on the different sleep stages. In animal research, 2 complementary main fields of research exist. One is focused on the positive modulation of sleep by repeated tone stimulation. The other concerns noise-related sleep disturbances. The few studies that have investigated noise-related sleep disturbances suggest the following conclusions. First, sleep disturbances are greater upon exposure to environmental noise, whose frequency spectrum is characterized by high and ultrasonic sounds, than white noise. Second, unpredictability and pattern of noise events are responsible for extractions from both SWS and PS. Third, chronic exposure to noise permanently reduces and fragments sleep. Finally, in chronic noise exposure, an inter-individual variability in SWS deficits is observed and correlated to a psychobiological profile related to an incapability to face stressful situations. Based on results from other research, acute noise-related sleep perturbations could result from an imbalance in the sleep–wake cycle in favor of arousing ascending systems. Chronic noise-related sleep disturbances may arise due to imbalance of the sleep-wake cycle and malfunctioning of the hypothalamo-pituitary-adrenal axis which may both contribute to the development of pathology.

Abbreviations: PS, paradoxical sleep; SWS, slow-wave sleep

Despite great efforts to reduce noise, it remains one of the main environmental problems of modern society.[48,71] This problem emerged during the end of the 20th century in parallel with the huge development of human activities (airway, railway, and road traffic). According to the World Health Organization, in contrast to many other environmental problems, noise pollution continues to grow, accompanied by an increasing number of complaints from affected individuals.[13] Noise is not simply a local problem—it remains a global dilemma that disturbs everyone and calls for precautionary actions in any environmental planning situation.[13] After briefly summarizing the effects of noise in humans (especially effects on sleep), I will discuss 1) effects of noise on sleep in animals and 2) the neurobiological mechanisms that explain how noise disturbs sleep.

Effects of Noise in Humans

In humans, noise is now recognized to cause important health problems.[73,92] Noise effects are divided into auditory and extra-auditory changes.[93] Although the auditory effects of noise have long been studied,[15,42] they are not responsible for most of the effects of noise on organisms.[17,92] Noise-associated problems are mainly extra-auditory perturbations, which can appear after exposure to noise as low as 50 dB.[48] These problems include physiologic (cardiovascular, endocrine), psychologic (mood, attention, memory), and sleep disturbances and can lead to psychiatric problems.[92,93] Further, sleep is altered by acute and chronic exposure to noise.[35,65,66,70] Because of the known restorative function of sleep,[31,113] noise-induced sleep disturbances are the most deleterious effects of noise,[35,38] and many studies in humans have focused on this problem. Both field and laboratory studies have addressed the relation between environmental noise and sleep disturbances. In human subjects in response to peak noise, K complexes on electroencephalograms are accompanied by increases in heart rate, constriction of peripheral blood vessels, and body movements.[38] This initial and typical reaction is followed by more or less long-lasting electroencephalogram desynchronization indicative of either lightening of sleep or awakening.[38,66] In field studies, correlative relations have been established between complaints or awakenings and noise levels from aircraft or road traffic.[59] Recently, Spreng[90] has proposed a physiological model to link indoor maximal levels of noise with the number of tolerable noise events during an 8-h night period.[38] Noise-induced sleep disturbances are related to other endogenous factors of noise, such as the predictability and frequency content of noise events, and to exogenous factors such as gender, age, information content of noise, individual and situational factors.[35,37,38,65] Indeed, noise-induced sleep disturbances increase with age[59,65,114] and sensitivity to noise.[20] With the same overnight equivalent sound level (that is, $L_{Aeq,\,T,}$ which is defined as $10 * \mathrm{Log}\,(\frac{1}{T})\int_0^T 10^{L(t)/10} * dt$, where T is time), sleep is more affected by intermittent noises than continuous ones.[20] In addition, sleep disturbances may be linked to the number of noise events.[67] However, there is no real consensus regarding the contribution of each attribute of noise on different sleep stages.[20] In fact, some studies have shown either slow-wave sleep (SWS)[84] or paradoxical sleep (PS) disturbances[30,34,52,97,103] in humans after continuous exposure to noise, whereas others have demonstrated both SWS and PS perturbations.[24,41,105] Some authors found SWS disturbances in human subjects exposed to intermittent noise,[30,36,101] whereas others demonstrated disrup-

Received: 24 Aug 2006. Revision requested: 23 Sept 2006. Accepted: 27 Sept 2006.
Research Department, Institute of Naval Medicine for the French Health Service of Armed Forces, Army Teaching Hospital, Saint Anne, France. Email: a.rabat@imnssa.net

tions in either PS only[33,86] or both PS and SWS.[52,98] What happens in laboratory animals that are exposed to noise? Can we draw the same conclusions as for humans?

Noise and Sleep: Studies in Laboratory Animals

Traditionally, research using animal models delves deeply into questions that arise during research involving human subjects. In noise research, laboratory animals have been used to determine how noise disturbs body and brain functions, [25] with the majority of works focusing on auditory damage. As in humans, auditory damage in laboratory animals appears upon prolonged or repetitive exposure to intense noise (that is, greater than 85 dB sound pressure level). However, few animal studies have addressed noise-related sleep disturbances.

Khazan and Sawyer[53] were the first to demonstrate, in rabbit, a disruption of PS upon continuous exposure to white noise (78 dB). Initially, the purpose was to demonstrate a PS rebound effect after PS deprivation. Van Twyver and colleagues[108] demonstrated PS disturbances in rats continuously exposed to intense white noise (that is, 92 dB). These 2 studies revealed a direct and specific effect of continuous exposure to white noise on PS that leaves SWS intact. These results were not confirmed in a recent study with rats in which the authors compared the effects on sleep of acute exposure (24 h) to either environmental noises or to different kinds of white noises (continuous, intermittent).[78]

Many other studies have used noise or tones to disturb sleep in laboratory animals, but their purposes were not to determine how the noise in laboratory animal facilities disturbs sleep. For example, Van Twyver and Garrett[107] determined, using a meaningful tone (associated with electric footshock), that arousal thresholds were highest during PS, low during SWS, and lowest during waking; these results were partially comparable to those of humans studies.[16,81] Drucker-Colin and colleagues[29] wanted to determine whether ponto-geniculo-occipital spikes play a role in triggering or maintaining sleep. To this end the researchers repetitively exposed (every 20 s) cats to a high-intensity tone (2 kHz at 90 dB) and noted that the tones had a stimulating effect on these spikes, accompanied by increases in the duration and number of PS epochs. The same researchers later demonstrated, using similar experimental conditions, a direct stimulating effect of tones on the duration of PS epochs,[4] with no habituation effect.[109] The increase in the duration of PS epochs after tone stimulation was shown to be dependent on activation of the medial pontine reticular formation.[3] Ball and colleagues showed a dose-related effect of tone intensity on the ponto-geniculo-occipital waves elicited in cats.[9] These results were confirmed in 2 human studies[64,87] and in a study using young and aged rats.[5]

Other recent studies in rats yielded more detailed conclusions. Amici and colleagues[1,2] found that auditory stimulation with repetitive tones (1 kHz during 20 ms every 20 s with different intensities from 50 to 100 dB) induced a significant increase in the duration of PS epochs. This effect was induced with a lower intensity threshold when tone stimulation was applied during SWS than during PS.[2] In a complementary way, Velluti and Pedemonte studied the interaction between sleep regulation and auditory perception.[110,111] Pedemonte and colleagues demonstrated an increase in both SWS and PS epochs after deafness in guinea pigs[74] and concluded that the auditory system may influence central nervous system structures implicated in sleep regulation and thus may contribute to homeostasis of the sleep–wake cycle.[74]

Regarding interactions between noise and sleep in laboratory animals, one broad area of research addresses the positive modulation of sleep, especially PS, by repeated tone stimulations. Such stimulation increases sleep, particularly PS, with no habituation.[3-5,29] PS increases most when stimuli are applied during SWS epochs.[1,2] Amici and colleagues interpreted these results to indicate differences in sensory processing between the sleeping brain in a SWS state and the sleeping brain in a PS state.[2] This result is not surprising since awakening thresholds in rats are lower during SWS than during PS.[107] This hypothesis is consistent with human studies demonstrating that 1) the sleeping brain can process auditory stimuli and detect meaningful events[77,109] and 2) awakenings thresholds are lower during SWS than during PS.[16,81]

Another key area of noise research in laboratory animals concerns noise-related sleep disturbances.[53,78,79,108] Until very recently,[78,79] no studies had addressed this problem. In a pilot study, Rabat and colleagues[78] found that sleep in rats was disturbed to a greater extent under exposure to environmental noise (EN)—which (once adapted to rat audition) is very close to noise encountered in laboratory animal facilities[104]—than under white noise. Indeed, with continuous white noise, intensity shortens the duration of SWS epochs and indirectly the number of PS ones whereas intermittent noise events extract rats from both SWS and PS epochs and induce a stronger and longer effect than does continuous noise. These findings do not agree with animal[53,108] and human[30,34,52,97,103] studies according a direct role of continuous noise exposure in PS deficits but agree with human studies involving continuous noises in both SWS and PS perturbations[24,41,105] and intermittent noises in either SWS disturbances[30,36,101] PS ones[33,86] or in both PS and SWS deficits.[52,98]

From these animal studies the following 3 conclusions can be proposed. First, both environmental and white noise disturb sleep,[53,78,108] but environmental noise is more deleterious to sleep than is white noise even if its global noise level (L_{Aeq}) is higher than that of environmental noise.[78] Two physical components of environmental noise are responsible for its effect on sleep:[78] the unpredictability of noise events and their pattern, such as frequency content and the ratio between background and peak levels. These 2 physical components do not prevent rats from entering SWS and PS, as does continuous white noise, but awakens them from all sleep stages. Interestingly, Stanchina and colleagues[91] recently demonstrated that arousal decreased substantially in an environment with intensive care unit noises combined with continuous moderated white noise (62 dB) compared with this type of environmental noise alone. The authors concluded that the difference in intensities between peak and background noise (known as 'delta dB') must be higher than the arousal threshold for waking to occur. As suggested by Ising and Kruppa[48] and confirmed experimentally,[78,79] most important to tone intensity is the unpredictability of noise peak and the pattern of noise especially with its information content, such as the presence of high and ultrasonic frequencies, often present in many laboratory animal rooms.[63,85]

The second conclusion regarding sleep and exposure to noise in laboratory animals is that upon chronic exposure to environmental noise, both SWS and PS are altered permanently.[79] Again the unpredictability and pattern of noise events seem to be implicated in these effects.[79] Some human studies have paralleled these findings, showing a stronger and longer deleterious effect of intermittent noise events on sleep compared with those of continuous noise.[20,30,68,101,102]

The third conclusion regarding sleep and exposure to noise is that extra-auditory noise effects do not affect all animals equally. Indeed Rabat and colleagues[79,80] recently showed that under chronic exposure to noise, some rats accumulated a bigger SWS debt with greater fragmentation of the remaining

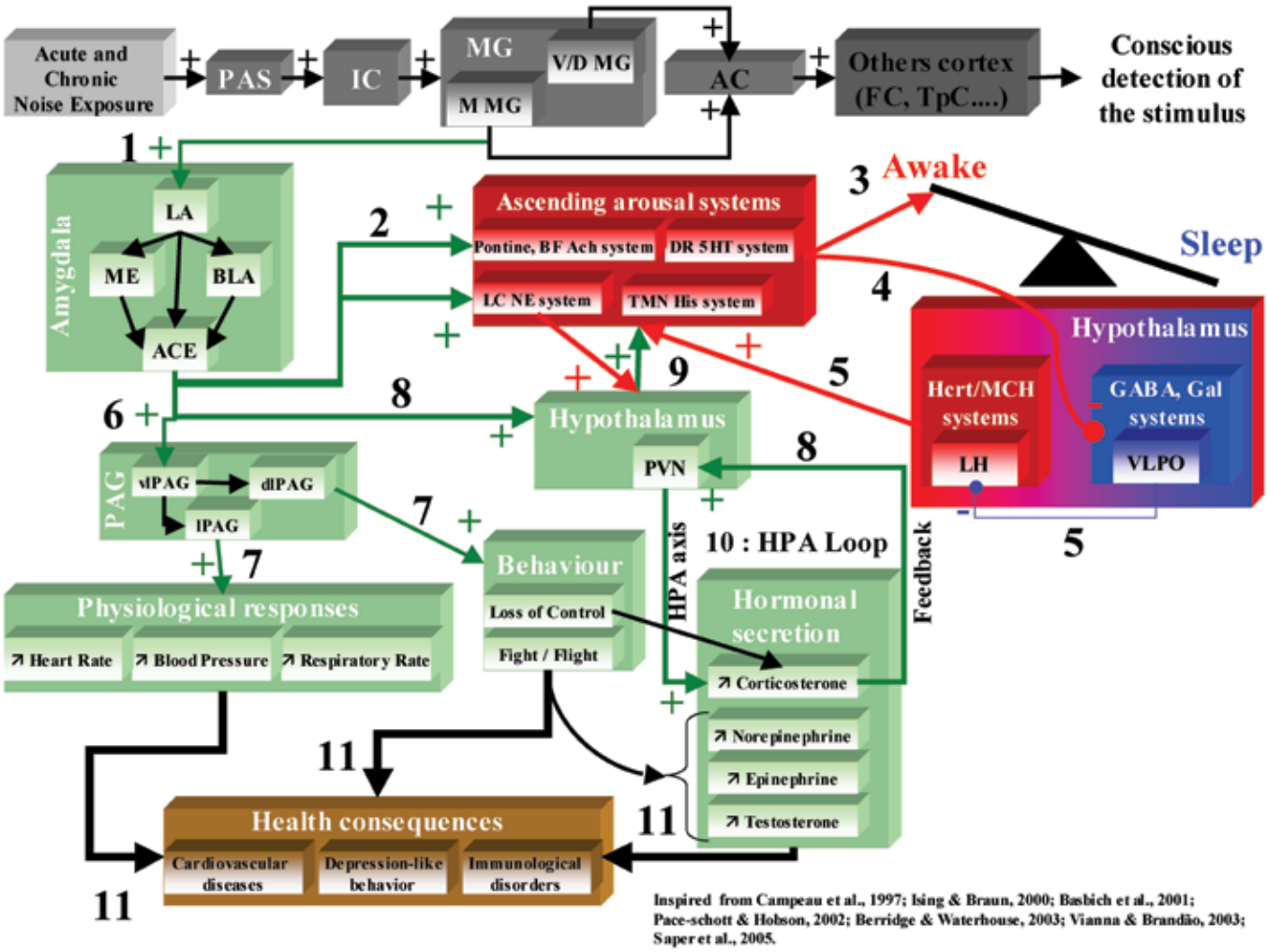

Figure 1. A simplified theoretical model of how acute and chronic exposure to noise induces sleep disturbances. Noise interacts with auditory systems (gray boxes; PAS, peripheral auditory system; IC, inferior colliculus; MG, medial geniculate body; AC, auditory cortex; FC, frontal cortex; TpC, temporal cortex) to produce both conscious detection of the stimulus and auditory effects if noise is too loud or prolonged. Concurrently, acute and chronic noise activate, in the thalamus, the medial division of the medial geniculate body (MMG). This nucleus, which connected to the lateral nucleus (LA) of the amygdala (1, green line), the gateway of noise into neuronal systems implicated in wake–sleep regulation (red and blue boxes) and adaptive responses to emotional and stressful stimuli (green boxes).

The first consequence of acute exposure to noise is the activation of the central nucleus of amygdala (ACE) of both the locus coeruleus (LC) and of 3 cholinergic nuclei (pedunculopontine [PPT], laterodorsal [LDT], and basal forebrain [BF] nuclei; 2, green lines). These serotoninergic (5HT) and cholinergic (Ach) neuronal systems promote wakefulness to the detriment of sleep (3, red line). This wake-promoting effect is amplified by inhibition of the ventrolateral preoptic nucleus (VLPO) of the posterior hypothalamus by monoaminergic nuclei (LC, DR, and TMN) of the ascending arousal system (4, red line). This inhibition (see Figure 2 for additional details) relieves inhibition of the lateral hypothalamus (LH; 5, blue line) that exerts, through hypocretins (Hcrt) and melanoconcentrating hormone (MCH) neurons, a reinforcing effect on all ascending arousal systems (5, red line). All of these factors contribute to increase wakefulness in animals exposed to noise.

The second consequence of acute exposure to noise is activation of the ventrolateral part of the periaqueductal gray (vlPAG) by ACE (6, green line). This nucleus connected to the lateral (lPAG) and dorsolateral (dlPAG) parts of the PAG, induces many body and brain responses (7, green lines), including physiologic (increases in heart and respiratory rates and blood pressure), behavioral (fight-or-flight response to acute exposure to noise and loss of control in a chronic exposure to noise), and endocrine (secretion of catecholamines, epinephrine, norepinephrine, corticosterone, and testosterone) effects. With ACE, corticosterone activates the paraventricular nucleus (PVN) of the hypothalamus (8, green lines). This nucleus contributes to increasing wakefulness to the detriment of sleep by activating LC (9, green line). In a reciprocal manner, LC activates PVN (9, Red line).

Under chronic exposure to noise, the effects described for acute exposure would be intensified. Decreased amounts and noise-induced fragmentation of sleep could result from chronic activation of ascending arousal systems and would be counteracted in part by circadian and sleep homeostatic input. Prolonged secretion of corticosterone may lead to malfunctioning of the hypothalamo-pituitary-adrenal (HPA) loop, as characterized by amplification of both corticosterone secretion and PVN activation (10, green lines). Consequently, activation of ascending arousal systems would be maintained and amplified in a feed-forward loop (9, green and red lines). Furthermore, chronic physiologic, hormonal, and behavioral changes (especially loss of control, because animals strive to free themselves from noise exposure) would contribute to many detrimental health consequences such as cardiovascular, depression-like, and immunologic effects (11, black lines). Inspired from references 8, 14, 19, 47, 72, 88, 112.

SWS than did other rats. In this work, locomotor reactivity of rats placed in a novel environment, before their exposure to noise, was correlated with both the intensity of SWS debt (a quantitative measure of sleep) and daily decrease of SWS bout duration (a qualitative parameter). Behavioral reactivity to novelty predicted quantitative and qualitative characteristics of SWS disturbances related to environmental noise and reflected the existence of separate psychobiological profiles (high-reactive versus low-reactive) in rats[27,28] with neurochemical, neuroadaptative, and neuroendocrine characteristics.[44,51,57,75]

Interindividual vulnerability to noise-induced sleep alterations may reflect these specific neurochemical and neuroendocrine profiles. Indeed, noise exposure modifies neurochemical transmission in the brain.[6,55,56,100] Furthermore, high-reactive and low-reactive rats showed distinct basal modifications in cholinergic, dopaminergic, and serotoninergic systems in the brain.[44,75,99] Some authors previously had suggested interindividual vulnerability in humans to auditory[26] and extra-auditory damage.[10,11,20,49,114] This last point brings us to the last question addressed in this review: how does noise act on the brain to cause the described sleep disturbances?

An Experimental Hypothesis to Explain How Noise Disturbs Sleep

As a sensory stimulation, noise can induce a wide range of responses that allow the organism to gather information from the source of the stimulation and to develop an adapted behavioral response. Thus noise engages peripheral auditory system and, in a general way, the central nervous system (Figure 1).

Lai and colleagues[55,56] demonstrated that when rats were exposed acutely to white noise of low intensity (70 dB), choline recapture in the frontal cortex and hippocampus of rats was increased, but this recapture was decreased with white noise of higher intensity (100 dB). Choline recapture is a direct reflection of acetylcholine (Ach) transmission.[39,40,60]

In addition, pontine structures, such as the reticular formation and pedunculopontine nucleus, receive auditory input[82] and modulate neurotransmission activities of basal forebrain, limbic, thalamic, and hypothalamic structures,[54,76,89] all of which are implicated in sleep regulation.[12,43] Perturbations of neurotransmission in pontine and hypothalamic structures and in basal forebrain thus might contribute to disturbing sleep during acute exposure to noise (Figure 1). A recent study found that after total sleep deprivation for 6 h, mice null for the dopamine β-hydroxylase gene, which encodes an enzyme involved in the production of norepinephrine in the brain, show a significant increase in acoustic arousal threshold compared with that in a wild-type mice.[46] The authors hypothesized that norepinephrine-containing neurons of the locus coeruleus, one of the wake-promoting regions[88] activated by noise,[18] in the knockout mice would be inefficient and thus contribute to imbalance the sleep-wake cycle in favor of sleep.[46] NE therefore may be another neurotransmitter responsible for noise-related sleep disturbances (Figure 1). Because noise promotes waking by activating many pontine and brainstem arousal systems,[45,89] acute sleep disturbances could be due to a temporary and reversible imbalance of sleep neurotransmissions in favor to wakefulness (Figure 1). In the situation of chronic noise exposure, this hypothesis is necessary but not sufficient to explain long-lasting sleep disturbances.[50,72]

Repetitive or chronic noise exposure induces a neurotropic response with corticosterone secretion.[7,32,47] This hormone exerts inhibitory effects on SWS state,[21-23] and sleep-deprived human subjects have elevated levels of glucorticoids.[58] In addition differing corticosterone responses to stressful situations have been related to distinct psychobiological profiles.[27] In a recent work, feedback regulation of the hypothalamo-pituitary-adrenal axis under basal conditions was quite different between high-locomotor-responder-to novelty and low-locomotor-responder-to novelty rats.[51] Further, Rabat and colleagues[79] showed that inter-individual vulnerability of SWS to chronic noise exposure were predicted by this psychobiological profile. Taken together these results suggest that, in situations of chronic noise exposure, malfunctioning of hypothalamo-pituitary-adrenal axis could occur and, when accompanied by disruption of sleep–wake neurotransmissions, could be sufficient to induce chronic sleep disturbances and explain interindividual vulnerability. Figure 1 provides a more detailed explanation of how acute and chronic exposure to noise disrupts sleep. Figure 2 presents the flip–flop switch model which highlights the delicacy balance in the regulation of the sleep–wake cycle.

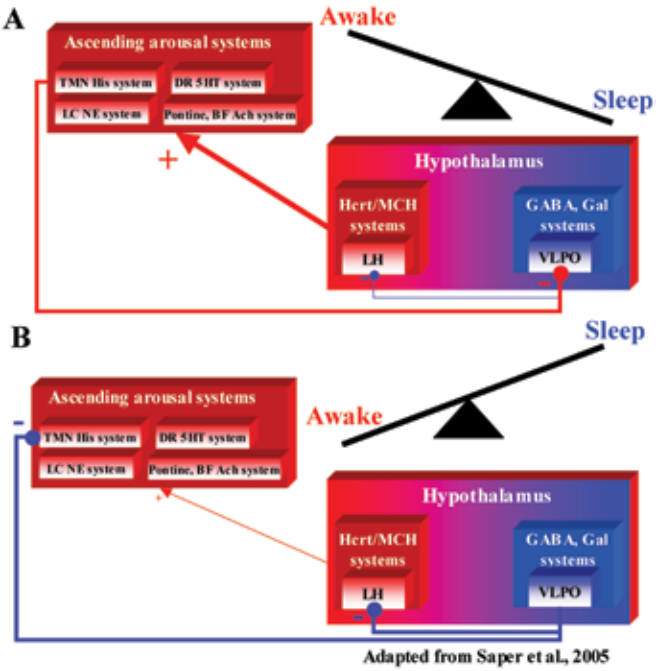

Figure 2. A simplified description of the flip–flop switch model proposed by Saper and colleagues.[88] (A) In this model, wakefulness emerges after inhibition of the ventrolateral preoptic nucleus (VLPO) by monoaminergic nuclei (locus coeruleus [LC], dorsal raphe [DR], and tuberomammillary nucleus [TMN]). This inhibition relieves inhibition from VLPO to the lateral hypothalamus (LH), which has hypocretins (Hcrt) and melanoconcentrating hormone (MCH) neurons that exert a reinforcing effect on all of the ascending arousal system (pontine and brainstem system). (B) During sleep, firing of VLPO neurons leads to production of γ-aminobutyric acid (GABA) and galanine (Gal); these neurotransmitters inhibit monoaminergic nuclei (LC, DR, and TMN) to counteract VLPO inhibition. In addition, VLPO neurons inhibit the Hcrt and MCH systems of the LH, thus preventing monoaminergic activation that might interrupt sleep.

Conclusions, Recommendations, and Perspectives

Despite the paucity of research, noisy environments, such as those encountered in laboratory animal facilities,[104] potentially contribute to sleep disturbances in animals. Recent studies argue against habituation to such exposure to environmental noise. Two physical components are mainly responsible: the unpredictability of noise events and their spectral composition (especially when they are high-frequency [greater than 4 kHz]). Furthermore, individual laboratory animals may not be affected equally by noise-related sleep disturbances. Offline information processing occurs during both SWS and PS,[12,43,83,95,96] as does a restorative brain process during SWS;[113] therefore noise-induced sleep restriction might lead to interindividual vulnerability in cognitive deficits. Recent data from rats,[80] confirmed by studies in humans,[106] support this hypothesis.

Because SWS is intimately linked to both activity of the hypothalamo-pituitary-adrenal axis[94] and of the immune system,[61,69] animals chronically exposed to noisy laboratory animal facilities

may develop pathology.[62] To avoid such health problems, managers and veterinarians should ensure that acoustic environment of laboratory facilities does not contain excessive high-frequency noises. These personnel also should ensure that the absolute difference between peak and background levels (delta dB) does not exceed 30 dB. Future research should verify the accuracy of described hypotheses regarding noise-induced pathology and identify measures to limit or counteract such consequences.

Acknowledgments

This review is dedicated to Jean-Jacques Bouyer. Thanks to Martine Kharouby for her technical assistance. Thanks to Olivier George, Jean-Marie Aran, Muriel Koehl, Monique Vallée, Alain Courtière, Willy Mayo, Pier-Vincenzo Piazza and Michel Le Moal, who contributed in varying degrees to the works cited.[78-80] All of the work described was completed in the following research units: "Psychopathologie des comportements adaptatifs" (Inserm U259) and "Physiopathologie du comportement" (Inserm U588) at Bordeaux and was supported by grants from Inserm, Université Victor Segalen Bordeaux 2, and Délégation Générale pour l'Armement (D.G.A.).

References

1. **Amici R, Domeniconi R, Jones CA, Morales-Cobas G, Perez E, Tavernese L, Torterolo P, Zamboni G, Parmeggiani PL.** 2000. Changes in REM sleep occurrence due to rhythmical auditory stimulation in the rat. Brain Res **868:**241–250.
2. **Amici R, Morales-Cobas G, Jones CA, Perez E, Torterolo P, Zamboni G, Parmeggiani PL.** 2001. REM sleep enhancement due to rhythmical auditory stimulation in the rat. Behav Brain Res **123:**155–163.
3. **Aranskowsky-Sandoval G, Garcia-Hernandez F, Aguilar-Roblero R, Drucker-Colin R.** 1989. REM sleep enhancement induced by auditory stimulation is prevented by kainic acid lesion of the pontine reticular formation. Brain Res **494:**396–400.
4. **Aranskowsky-Sandoval G, Prospero-Garcia O, Aguilar-Roblero R, Drucker-Colin R.** 1986. Cholinergic reduction of REM sleep duration is reverted by auditory stimulation. Brain Res **375:**377–380.
5. **Aranskowsky-Sandoval G, Stone WS, Gold PE.** 1992. Enhancement of REM sleep with auditory stimulation in young and aged rats. Brain Res **589:**353–357.
6. **Arnsten AF, Goldman-Rakic PS.** 1998. Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism. Arch Gen Psychiatr **55:**362–368.
7. **Babisch W.** 2002. The noise–stress concept: risk assessment and research needs. Noise Health **4:**1–11.
8. **Babisch W, Fromme H, Beyer A, Ising H.** 2001. Increased catecholamine levels in urine in subjects exposed to road traffic noise. The role of stress hormones in noise research. Environ Int **26:**475–481.
9. **Ball WA, Hunt WH, Sanford LD, Ross RJ, Morrison AR.** 1991. Effects of stimulus intensity on elicited ponto-geniculo-occipital waves. Electroencephalogr Clin Neurophysiol **78:**35–39.
10. **Belojevic G, Jakovljevic B, Aleksic O.** 1997. Subjective reactions to traffic noise with regard to some personality traits. Environl Int **23:**221–226.
11. **Belojevic G, Jakovljevic B, Slepcevic V.** 2003. Noise and mental performance: personality attributes and noise sensitivity. Noise Health **6:**77–89.
12. **Benington JH, Frank MG.** 2003. Cellular and molecular connections between sleep and synaptic plasticity. Progr Neurobiol **69:**71–101.
13. **Berglund BL, Lindvall T, Schwela DH,** editors. 1999. Guidelines for community noise. Geneva: World Health Organization.
14. **Berridge C, Waterhouse BD.** 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Rev **42:**33–84.
15. **Boettcher FA, Gratton MA, Schmiedt RA.** 1995. Effects of noise and age on the auditory system. Occup Med **10:**577–591.
16. **Bonnet MH.** 1986. Auditory threshold during continuing sleep. Biol Psychol **22:**3–10.
17. **Buffe P.** 1992. [Noise and hearing. In French]. Bull Acad Natl Med **176:**363–370.
18. **Burow A, Day HE, Campeau S.** 2005. A detailed characterization of loud noise stress: intensity analysis of hypothalamo-pituitary-adrenocortical axis and brain activation. Brain Res **1062:**63–73.
19. **Campeau S, Akil H, Watson SJ.** 1997. Lesions of the medial geniculate nuclei specifically block corticosterone release and induction of c-fos mRNA in the forebrain associated with audiogenic stress in rats. J Neurosci **17:**5979–5992.
20. **Carter NL.** 1996. Transportation noise, sleep, and possible after-effects. Environ Int **22:**105–116.
21. **Chang FC, Opp MR.** 1998. Blockade of corticotropin-releasing hormone receptors reduces spontaneous waking in the rat. Am J Physiol **275(3 Pt 2):**R793–R802.
22. **Chang FC, Opp MR.** 1999. Pituitary CRH receptor blockade reduces waking in the rat. Physiol Behav **67:**691–696.
23. **Chang FC, Opp MR.** 2002. Role of corticotropin-releasing hormone in stressor-induced alterations of sleep in rat. Am J Physiol Regul Integr Comp Physiol **283:**R400–R407.
24. **Culpepper-Richards K.** 1988. A description of night sleep patterns in the critical care unit. Heart Lung **17:**35–42.
25. **Dancer AL.** 1995. Use of animal models in the study of the effects of noise on hearing. Occup Med **10:**535–544.
26. **Davis RR, Kozel P, Erway LC.** 2003. Genetic influences in individual susceptibility to noise: a review. Noise Health **20:**19–28.
27. **Dellu F, Piazza PV, Mayo W, Le Moal M, Simon H.** 1996. Novelty-seeking in rats—biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. Neuropsychobiology **34:**136–145.
28. **Dellu-Hagedorn F.** 2006. Relationship between impulsivity, hyperactivity and working memory: a differential analysis in the rat. Behav Brain Funct **28:**2–10.
29. **Drucker-Colin R, Bernal-Pedraza J, Fernandez-Cancino F, Morrison AR.** 1983. Increasing PGO spike density by auditory stimulation increases the duration and decreases the latency of rapid eye movement (REM) sleep. Brain Res **278(1-2):**308–312.
30. **Eberhardt JL, Strale LO, Berlin MH.** 1987. The influence of continuous and intermittent traffic noise on sleep. J Sound Vibrat **116:**445–464.
31. **Ferrara M, De Gennaro L.** 2001. How much sleep do we need? Sleep Med Rev **5:**155–179.
32. **Gesi M, Fornai F, Lenzi P, Natale G, Soldani P, Paparelli A.** 2001. Time-dependent changes in adrenal cortex ultrastructure and corticosterone levels after noise exposure in male rats. Eur J Morphol **39:**129–135.
33. **Globus G, Friedmann J, Cohen H.** 1973. Effects of aircraft noise on sleep recorded in the home. J Sleep Res **2:**116.
34. **Griefahn B.** 1986. A critical load for nocturnal high-density road traffic noise. Am J Ind Med **9:**261–269.
35. **Griefahn B.** 2002. Sleep disturbances related to environmental noise. Noise Health **4:**57–60.
36. **Griefahn B, Jansen G.** 1975. Disturbances of sleep by sonic booms. Sci Total Environ **4:**107–112.
37. **Griefahn B, Jansen G.** 1978. EEG responses caused by environmental noise during sleep their relationships to exogenic and endogenic influences. Sci Total Environ **10:**187–199.
38. **Griefahn B, Spreng M.** 2004. Disturbed sleep patterns and limitation of noise. Noise Health **6:**27–33.
39. **Guyenet P, Lefresne P, Rossier J, Beaujouan JC, Glowinski J.** 1973. Effect of sodium, hemicholinium-3 and antiparkinson drugs on (14C)acetylcholine synthesis and (3H)choline uptake in rat striatal synaptosomes. Brain Res **62:**523–529.
40. **Guyenet P, Lefresne P, Rossier J, Beaujouan JC, Glowinski J.** 1973. Inhibition by hemicholinium-3 of (^{14}C)acetylcholine synthesis and (^{3}H)choline high affinity uptake in rat striatal synaptosomes. Mol Pharmacol **9:**630–639.
41. **Hansell NR.** 1984. The behavioral effects of noise on man: the patient with 'intensive care unit psychosis.' Heart Lung **13:**59–65.
42. **Henderson D, Prasher D, Kopke RD, Salvi RJ, Hamernik RP.** 2001. Noise-induced hearing loss: basic mechanisms, prevention, and control. London: Noise Research Network Publications.

43. **Hobson JA, Pace-Schott EF.** 2002. The cognitive neuroscience of sleep: neuronal systems, consciouness, and learning. Nat Rev Neurosci **3:**679–693.
44. **Hooks MS, Jones GH, Smith AD, Neill DB, Justice JB.** 1991. Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse **9:**121–128.
45. **Horner KC.** 2003. The emotional ear in stress. Neurosci Biobehav Rev **27:**437–446.
46. **Hunsley MS, Palmiter RD.** 2004. Altered sleep latency and arousal regulation in mice lacking norepinephrine. Pharmacol Biochem Behav **78:**765–773.
47. **Ising H, Braun C.** 2000. Acute and chronic endocrine effects of noise: review of the research conducted at the Institute for Water, Soil, and Air Hygiene. Noise Health **7:**7–24.
48. **Ising H, Kruppa B.** 2004. Health effects caused by noise: evidence in the literature from the past 25 years. Noise Health **6:**5–13.
49. **Job, R. F.** 1999. Noise sensitivity as a factor influencing human reaction to noise. Noise Health **1(3):**57–68.
50. **Jones G, Cohen JD.** 2005. An integrative theory of locus coeruleus–norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci **28:**403–450.
51. **Kabbaj M, Devine DP, Savage VR, Akil H.** 2000. Neurobiological correlates of individual differences in novelty-seeking behavior in the rat: differential expression of stress-related molecules. J Neurosci **20:**6983–6988.
52. **Kawada T, Suzuki S.** 1999. Change in rapid eye movement (REM) sleep in response to exposure to all-night noise and transient noise. Arch Environ Health **54:**336–340.
53. **Khazan N, Sawyer CH.** 1963. Rebound recovery from paradoxical sleep deprivation in the rabbit. Proc Soc Exp Biol Med **114:**536–539.
54. **Kobayashi Y, Isa T.** 2002. Sensory-motor gating and cognitive control by brainstem cholinergic system. Neural Network **15:**731–741.
55. **Lai H.** 1987. Acute exposure to noise affects sodium-dependent high-affinity choline uptake in the central nervous system of the rat. Pharmacol Biochem Behav **28:**147–151.
56. **Lai H, Carino MA.** 1990. Acute white noise exposure affects the concentration of benzodiazepine receptors in the brain of the rat. Pharmacol Biochem Behav **36:**985–987.
57. **Lemaire V, Aurousseau C, Le Moal M, Abrous DN**. 1999. Behavioural trait of reactivity to novelty is related to hippocampal neurogenesis. Eur J Neurosci **11:**4006–4014.
58. **Leproult R, Copinschi G, Buxton O, Van Cauter E.** 1997. Sleep loss results in an elevation of cortisol levels in the next evening. Sleep **20:**865–870.
59. **Lukas JS.** 1976. Noise and sleep: a literature review and a proposed criterion for assessing effect. J Acoust Soc Am **58:**1232–1242.
60. **Maire JC, Wurtman RJ.** 1985. Effects of electrical stimulation and choline availability on the release and contents of acetylcholine and choline in superfused slices from rat striatum. J Physiol (Paris) **80:**189–195.
61. **Majde JA, Krueger JM.** 2005. Links between the innate immune system and sleep. J Allergy Clin Immunol **116:**1188–1198.
62. **McEwen BS, Wingfield JC.** 2003. The concept of allostasis in biology and biomedicine. Horm Behav **43:**2–15.
63. **Milligan SR, Sales GD, Khirnykh K.** 1993. Sound levels in rooms housing laboratory animals: an uncontrolled daily variable. Physiol Behav **53:**1067–1076.
64. **Mouze-Amady M, Sockeel P, Leconte P.** 1986. Modification of REM sleep behavior by rems contingent auditory stimulation in man. Physiol Behav **37:**543–548.
65. **Muzet A.** 1989. [The effects of noise on sleep. In French]. C R Seances Soc Biol Fil **183:**437–442.
66. **Muzet A.** 2002. The need for a specific noise measurement for population exposed to aircraft noise during night-time. Noise Health **4:**61–64.
67. **Öhrström E.** 1995. Effects of low levels of road traffic noise during the night: a laboratory study on numbre of events, maximum noise levels and noise sensitivity. J Sound Vibrat **179:**603–615.
68. **Öhrström ER.** 1982. Sleep disturbance effects of traffic noise. A laboratory study on after effects. J Sound Vibrat **84:**87–103.
69. **Opp MR.** 2005. Cytokines and sleep. Sleep Med Rev **9:**355–364.
70. **Ouis D.** 1999. Exposure to nocturnal road traffic noise: sleep disturbance and its after effects. Noise Health **1:**11–36.
71. **Ouis D.** 2001. Annoyance from road traffic noise: a review. J Environ Psychol **21:**101–120.
72. **Pace-Schott EF, Hobson JA.** 2002. The neurobiology of sleep: genetics, celullar physiology and subcortical networks. Nat Rev Neurosci **3:**591–605.
73. **Passchier-Vermeer W, Passchier WF.** 2000. Noise exposure and public health. Environ Health Perspect **108 Suppl 1:**123–131.
74. **Pedemonte M, Pena JL, Torterolo P, Velluti RA.** 1996. Auditory deprivation modifies sleep in the guinea-pig. Neuroscience Letters **223:**1–4.
75. **Piazza PV, Rouge-Pont F, Deminiere JM, Kharoubi M, Le Moal M, Simon H.** 1991. Dopaminergic activity is reduced in the prefrontal cortex and increased in the nucleus accumbens of rats predisposed to develop amphetamine self-administration. Brain Res **567:**169–174.
76. **Pollak GD, Burger RM, Klug A.** 2003. Dissecting the circuitry of the auditory system. Trends in Neurocience. **26:**33–39.
77. **Portas CM, Krakow K, Allen P, Josephs O, Armony JL, Frith CD.** 2000. Auditory processing across the sleep-wake cycle: simultaneous EEG and fMRI monitoring in humans. Neuron **28:**991–999.
78. **Rabat A, Bouyer JJ, Aran JM, Courtiere A, Mayo W, Le Moal M.** 2004. Deleterious effects of an environmental noise on sleep and contribution of its physical components in a rat model. Brain Res **1009(1-2):**88–97.
79. **Rabat A, Bouyer JJ, Aran JM, Le Moal M, Mayo W.** 2005. Chronic exposure to an environmental noise permanently disturbs sleep in rats: inter-individual vulnerability. Brain Res **1059(1):**72–82.
80. **Rabat A, Bouyer JJ, George O, Le Moal M, Mayo W.** 2006. Chronic exposure of rats to noise: relationship between long-term memory deficits and slow wave sleep disturbances. Behav Brain Res **171:**303–312.
81. **Rechtschaffen AH, Hauri P, Zeitlin M.** 1966. Auditory awakeing threshold in REM and NREM sleep stages. Percept Mot Skills **22:**927–942.
82. **Reese NB, Garcia-Rill E, Skinner RD.** 1995. The pedunculopontine nucleus-auditory input, arousal and pathophysiology. Prog Neurobiol **42:**105–133.
83. **Ribeiro S, Nicolelis MA.** 2004. Reverberation, storage, and postsynaptic propagation of memories during sleep. Learn Mem **11:**686–696.
84. **Roth T, Kramer M, Trinder J.** 1972. The effect of noise during sleep on the sleep patterns of different age groups. Can Psychiatr Assoc J **17(Suppl 2):**SS197-201.
85. **Sales GD, Wilson KJ, Spencer KE, Milligan SR.** 1988. Environmental ultrasound in laboratories and animal houses: a possible cause for concern in the welfare and use of laboratory animals. Lab Anim **22(4):**369–375.
86. **Saletu B, Grunberger J.** 1981. Traffic noise-induced sleep disturbances and their correction by an anxiolytic sedative, OX-373. Neuropsychobiology **7:**302–314.
87. **Salin-Pascual R, Granados-Fuentes D, De la Fuente JR, Drucker-Colin R.** 1991. Effects of auditory stimulation during rapid eye movement (REM) sleep in healthy volunteers and depressed patients. Psychiatr Res **38:**237–246.
88. **Saper CB, Scammell TE, Lu J.** 2005. Hypothalamic regulation of sleep and circadian rhythms. Nature **437:**1257–1263.
89. **Spreng M.** 2000. Central nervous system activation by noise. Noise Health **2:**49–57.
90. **Spreng M.** 2002. Cortical excitation, cortisol excretion, and estimation of tolerable nightly over-flights. Noise Health **4:**39–46.
91. **Stanchina ML, Abu-hijleh M, Chaudhry BK, Carlisle CC, Millman RP.** 2005. The influence of white noise on sleep in subjects exposed to ICU noise. Sleep Med **6:**423–428.
92. **Stansfeld S, Haines M, Brown B.** 2000. Noise and health in the urban environment. Rev Environ Health **15:**43–82.
93. **Stansfeld S, Matheson MP.** 2003. Noise pollution: nonauditory effects on health. Br Med Bull **68:**243–257.
94. **Steiger A.** 2002. Sleep and the hypothalamo-pituitary-adrenocortical system. Sleep Med Rev **6:**125–138.

95. **Stickgold R.** 2005. Sleep-dependent memory consolidation. Nature **437:**1272–1278.
96. **Stickgold R, Walker MP.** 2005. Memory consolidation and reconsolidation: what is the role of sleep. Trends Neurosci **28:**408–415.
97. **Suzuki S, Kawada T, Ogawa M, Aoki S.** 1991. Sleep deepening effect of steady peak noise. J Sound Vibrat **151:**407–413.
98. **Terzano MG, Parrino L, Fioriti G, Orofiamma B, Depoortere H.** 1990. Modifications of sleep structure induced by increasing levels of acoustic perturbation in normal subjects. Electroencephalogr Clin Neurophysiol **76:**29–38.
99. **Thiel CM, Müller CP, Huston JP, Schwarting RK.** 1999. High versus low reactivity to a novel environment: behavioural, pharmacological and neuorchemical assessments. Neuroscience **93:**243–251.
100. **Thiel CM, Müller CP, Huston JP, Schwarting RK.** 2000. Auditory noise can prevent increased extracellular acetylcholine levels in the hippocampus in response to aversive stimulation. Brain Res **882:**112–119.
101. **Thiessen GJ, Lapointe AC.** 1978. Effect of intermittent truck noise on percentage of deep sleep. J Acoust Soc Am **64:**1078–1080.
102. **Thiessen GJ, Lapointe AC.** 1983. Effect of continuous traffic noise on percentage of deep sleep, waking, and sleep latency. J Acoust Soc Am **73:**225–229.
103. **Topf M, Davis JE.** 1993. Critical care unit noise and rapid eye movement (REM) sleep. Heart Lung **22:**252–258.
104. **Turner JG, Parrish JL, Hughes LF, Toth LA, Caspary DM.** 2005. Hearing in laboratory animals: strain differences and nonauditory effects of noise. Comp Med **55:**12–23.
105. **Vallet M, Gagneux JM, Blanchet V, Favre B, Labiale G.** 1983. Long-term sleep disturbances due to traffic noise. J Sound Vibrat **90:**173–191.
106. **Van Dongen HPA, Baynard MS, Maislin G, Dinges DF.** 2004. Systematic inter-individual differences in neurobehavioral impairment from sleep loss: evidence of trait-like differential vulnerability. Sleep **27:**423–433.
107. **Van Twyver H, Garrett W.** 1972. Arousal threshold in the rat determined by meaningful stimuli. Behav Biol **7:**205–215.
108. **Van Twyver H, Levitt R, Dunn R.** 1966. The effects of high intensity white noise on the sleep pattern of the rat. Psychon Sci **6:**355–356.
109. **Vazquez J, Merchant-Nancy H, Garcia F, Drucker-Colin R.** 1998. The effects of sensory stimulation on REM sleep duration. Sleep **21:**138–142.
110. **Velluti RA, Pedemonte M.** 1997. Interactions between sleep and sensory physiology. J Sleep Res **6:**61–77.
111. **Velluti RA, Pedemonte M.** 2002. In vivo approach to the cellular mechanisms for the sensory processing in sleep and wakefulness. Mol Neurobiol **22:**501–516.
112. **Vianna DML, Brandão ML.** 2003. Anatomical connections of the periaqueductal grey: specific neural substrates for different kinds of fear. Brazil J Med Biol Sci **36:**557–566.
113. **Wesensten NJ, Balkin TJ, Belenky G.** 1999. Does sleep fragmentation impact recuperation? A review and reanalysis. J Sleep Res **8:**237–245.
114. **Wilkinson RT, Campbell KB.** 1984. Effects of traffic noise on quality of sleep: assessment by EEG, subjective report, or performance the next day. J Acoust Soc Am **75:**468–475.