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Elemental Mercury Exposure and Sleep Disorder

Alfred Bogomir Kobal¹ and Darja Kobal Grum²

¹*Department of Occupational Medicine, Idrija Mercury Mine, Idrija,*

²*Department of Psychology, Faculty of Arts, University of Ljubljana, Ljubljana, Slovenia*

1. Introduction

The sleep-wake rhythms cycle coincides with the solar 24-hour schedule. Most adult subjects in nontropical areas are comfortable with 6.5 to 8.0 hours of daily sleep, taken in a single period. It is known that normal sleep consists of four to six behaviourally and electrophysiologically (EEG) defined cycles. Sleep is divided in two main types: REM (rapid eye movements) sleep and non-REM sleep. In the general population, sleep disorders are common and usually associated with some illness, psychological and social disturbances. Insomnia as the most common sleep disorder is most often the consequence of psychological disturbances. It is characterized by the inability to fall asleep quickly. Sleepwalking, night terrors and nightmares are parasomnias which often reflect significant stress or physiopathology. Restless legs syndrome and periodic limb movements are a type of motor disorders. Restless legs usually occur before sleep onset, while periodic limb movements can fragment the sleep. Transient sleep disturbances are mostly associated with variety of factors including stress, life changes, shift work, jet lag, and some acute health disorders. The most popular drugs, such as alcohol, nicotine and caffeine, can adversely affect the quality and quantity of sleep (Hornyak et al., 2006; Lee & Douglass, 2010; Pinel, 2009; Vgontzas et al., 2010).

Occupational exposure to heavy metals, such as cadmium, lead, manganese and mercury, was very frequent in the 20th century. Many epidemiological studies show that these heavy metals can cause serious functional disability among exposed workers (World Health Organization [WHO], 1980). Inorganic lead, manganese and inorganic-elemental mercury (Hg⁰) exposure can, among others, cause neurotoxic effects with a typical, but different, clinical picture associated with sleep disorder.

Hg⁰ a silvery-white liquid metal is quite attractive and very widespread which, despite being highly toxic, was used by humans as a medicine for thousands of years. We shall discuss its neurotoxic effects and the sleep disorders it can cause at increased occupational exposure. Hg⁰ was first described by Aristotle in the 4th century A.D., and the alchemist's concept of Hg⁰ leaned on his system of natural phenomena, which dominated all of science until the 17th century. For this reason Hg⁰ was attributed with all those qualities of nature that accelerate development, growth and maturation. The famous Arabian physician Avicena, who was active in the 11th century, wrote that Hg⁰ vapours cause paralysis, tremor

and frequent limb spasms. In Columbus' time began to be used to treat syphilis. The use of its compounds was still widespread in the United States in the 19th century, and was among others also used to treat depression (Goldwater, 1972). The popularity of Hg at the time was considerable, for even President Abraham Lincoln found relief for his health problems in a pharmacy-prepared drug called "blue pills", which contained elementary Hg⁰ (Hirschhorn et al., 2001). Various, mostly organic Hg compounds were still widely used in the 20th century, and even to a smaller extent today (Clarkson & Magos, 2006).

The Roman historian Pliny speaks of the first occupational Hg⁰ intoxications – *hydrargyrismis*, or mercurialism, in slaves who mined and smelted Hg ore for several centuries in the Sisapo-Almaden mine. Occupational exposure to Hg⁰ did not receive any noticeable attention until the 15th century, when Ulrich Ellenenborg described occupational exposure for the first time in his book, which was published posthumously in 1524. In a very extensive work entitled »The morbis artificum diatribe« (1700), Bernardo Ramazzini presented several occupational illnesses, among which he also described occupational intoxications with Hg⁰ vapours (Goldwater, 1972). In the 16th century, several physicians described the symptoms and signs of Hg⁰ intoxication in miners of the Idrija Mercury Mine, the most famous among them being Theophrastus von Hohenheim, otherwise known as Paracelsus, and Pierandrea Mattioli, a reputed botanist and physician who worked in the town of Gorica at the time (1544).

In his book *Von der Bergsucht und anderen Krankheiten*, published in 1527, Paracelsus described the serious condition of sick miners whom he had met during his visit to the Idrija Mine: "All the people who live there are deformed and paralyzed, asthmatic and benumbed, without any hope of ever getting well" (Lesky, 1956, p. 8). Hg⁰ intoxication in mercury miners of the Idrija Mercury Mine was well-described by Joannes Antonius Scopoli, the first physician appointed to the Idrija Mercury Mine in 1754. Along with the symptoms of Hg⁰ intoxication observed in miners, he also described their personality traits as well the characteristics of sleep disorders that usually appear in Hg⁰ intoxication. Sleep disorders were also mentioned in the monographs on inorganic mercury published by WHO (1976, 1991) and the Agency for Toxic Substances and Disease Registry [ATSDR] (1999).

The observations of J. A. Scopoli in the 18th century, our observations of workers exposed to Hg⁰ in the Idrija Mercury Mine, as well as certain biochemical interactions of Hg⁰ in central nervous system (CNS) that were studied by many researchers in the late 20th and early 21st centuries, help to throw light on those biochemical effects of Hg in CNS that could hypothetically disturb the regulation of sleep and cause the sleep disorders occurring in occupational intoxications or increased Hg⁰ absorption in exposed miners and smelters. In this chapter, we shall briefly present the subjective characteristics of sleep disorder observed in occupational Hg⁰ intoxication and increased absorption, the interaction of Hg⁰ in the body and its toxic effects in the CNS, the basic neurobiological and biochemical characteristics of sleep-wake cycles and, finally, its hypothetical interactions with Hg⁰.

2. Sleep disorder in occupational exposure to Hg⁰ vapours

J. A. Scopoli presented his knowledge on occupational Hg⁰ exposure of miners and smelters in the Idrija Mercury Mine in his book entitled *DE HYDRARGYRO IDRIENSI TENTAMINA Phisico – Chimico – Medica*, which was printed in Venice in 1761, and reprinted in 1771. In the third part of this book, *De Morbis Fossorum Hydrargyri*, he presents an in-depth description of

the symptoms of mercury intoxication - mercurialism among pit and smeltery workers. He classifies mercurialism according to those symptoms that are the most pronounced in the disease pattern. Scopoli describes acute, sub-acute and chronic Hg intoxication appearing during work in the smelting plant and in the pit, in poorly ventilated sites with native ore where, according to our present-day knowledge (Kobal, 1994), mercury vapour concentrations were extremely high. Among the symptoms accompanying chronic intoxication, Scopoli mentions changes in some personality traits, such as bad temper, irritability and sadness, as well as sleep disorder. "...*somnus inquietus, somnia terrifica, artuum agitatio...*" are the key words which Scopoli uses (1771, p. 80). He finds that mercury intoxication is accompanied by restless sleep, terrible dreams with nightmares, sleep terrors, and strange, periodic contractile movements of the legs (Kobal & Kobal-Grum, 2010). The reputed clinical toxicologist, Adolph Kussmaul, presented in his book (1861, p. 227) an occupational clinical picture of mercurial intoxication in miners. Among the symptoms of eretism-increased irritability, he also mentions "restless sleep, terrible dreams and frighten awakenings".

Our observations are based on data collected from the program of health surveillance of workers exposed to Hg⁰ in the Idrija Mercury Mine. In the first 20 years following the Second World War, the number of Hg⁰ intoxicated workers was very high (ranging from 10 to 14% of workers in the mine and smelting plant). After 1975, no new cases of intoxication were observed thanks to the introduction of preventive-target medical examinations, which, after 1968, also included biological monitoring of exposure. Subjective descriptions of sleep disturbances and other potential, known, subjective troubles associated with Hg⁰ exposure were always evaluated directly by the physician during contact with intoxicated or exposed workers in the course of preventive target examinations. No polysomnographic recording was used to define the stages of sleep in intoxicated workers, or in workers with increased Hg⁰ absorption. Some disordered sleep, such as fragmentation of sleep accompanied with dreaming and awakening, as well as periodic leg contractile movements, were often observed as some important early symptoms that announced the critical absorption of Hg⁰ vapours in miners working in the pit where native Hg ore was mined, with substantially elevated air Hg⁰ vapour levels. During the target medical surveillance and biological monitoring of miners intermittently exposed to native Hg, the previously mentioned sleep disorder appeared in 30% of exposed miners, associated with increased urinary Hg excretion. In these miners, the urine Hg concentrations were usually within a range of 100-400 µg/L, which is, at intermittent type of exposure, associated with blood Hg levels from 60 to 260 µg/L (Kobal, 1975a, 1991), which are substantially above the blood Hg level of 35 µg/L usually accompanied with the earliest nonspecific symptoms (WHO, 1976). In cases of subacute mercurialism with classical signs of intoxication, such as stomatitis, limb tremor, and other known symptoms and signs, the sleep disorders were much more pronounced, and the urinary Hg excretions were very high, in some cases even over 700 µg/L (Kobal, 1975b, 1991). The periodic leg movement index was not evaluated in these miners (calculated by dividing the total number of periodic leg movements by sleep time in hours). In the cases of increased Hg⁰ absorption, the sleep disorder decreased usually in one to two months after the interruption of exposure associated with decreased urine Hg level. In the cases of Hg⁰ intoxication, sleep disorders with terrible dreams and and periodic leg movements were much more obstinate and disappeared very slowly in association with other symptoms and clinical signs of mercurialism; the urine Hg level decreased after 3 to 6 months. A subclinical peripheral nerve function with lower motor conduction velocities of

the median nerve and lower sensory conduction velocities of the ulnar nerve was observed in the subgroup of miners with long-term intermittent exposure and increased Hg^0 absorption (urine Hg excretion $> 100\mu\text{g/L}$). In contrast to sleep disorder, these subclinical peripheral nerve function changes usually persist many years after the cessation of exposure (Gabrovec-Nahlik et al., 1977; Kobal et al., 2004), which is also in agreement with some other observations (Albers et al., 1982).

As already mentioned above, sleep disorders were also mentioned in the monographs on inorganic-elemental mercury published by WHO (1976, 1991) and ATSDR (1999), which place them among the symptoms of erethism. However, no disorders of sleep structure or any possible neurobiological or biochemical mechanisms and EEG changes that could accompany sleep disorders in intoxicated subjects exposed to Hg^0 are described in these monographs.

3. The toxicology of elemental mercury- Hg^0

3.1 Absorption, disposition in the body, and elimination

Hg^0 is the only metal that takes the form of liquid at room temperature, and releases monoatomic vapours (Hg^0 vapours) that are very stable and may remain in the atmosphere for months or even years on end. Their pressure is in equilibrium with the metal, and their concentrations attain a value of 18.3 mg/m^3 at a room temperature of 24°C , which is 360 times above the “permissible level” for occupational exposure ($0.05 \text{ mg Hg}^0/\text{m}^3$) prescribed in the Environmental Health Criteria 1, Mercury (WHO, 1976). We know today that Hg^0 vapours enter the body mainly through inhalation. As much as 80% of the inhaled amount of Hg^0 is absorbed in the lungs and then passes across the alveolar membrane very quickly into the plasma and erythrocytes, and through blood circulation into CNS, kidneys and other organs. In the tissue, Hg^0 oxidizes into the ionic divalent form (Hg^{++}), which takes place by way of the hydrogen peroxide-catalase compound I enzyme system. The oxidation of Hg^0 in blood, although rapid, is sufficiently prolonged so that the Hg^0 dissolved in blood can be conveyed to the brain, where it passes the blood-brain barrier and cell membranes. Only a small amount of Hg^0 is oxidized during the transit time from the lungs to the brain, so that over ninety percent of dissolved Hg^0 arrives in the brain unoxidized. It is then oxidized in brain cells and complexed to the SH-group of the cell (Hursh et al., 1988; Magos et al., 1978). The divalent ionic Hg^{++} accumulates primarily in astrocytes, where it mostly binds to reduced glutathione (GSH), cysteine, and metallothioneins (MTs) (Aschner, 1997; Tušek-Žnidarič et al., 2007). After Hg^0 vapour exposure of animals, a marked accumulation of Hg was observed in the cerebellum, nucleus olivarius inferior in the brainstem, and in the nucleus subthalamicus (Berlin et al., 1969). In autopsy samples of retired and ex-miners previously intermittently exposed to Hg^0 , substantially higher accumulations and retention of Hg were observed in the pituitary gland, pineal gland, hippocampus, nucleus dentatus, and in the cerebellar cortex in comparison with the control group (Falnoga et al., 2000; Kosta et al., 1975) (Tab.1). Hg is eliminated in the urine, feces, expired air, sweat, saliva, and milk. In long-term occupational exposure, the kidneys are the major pathway of Hg excretion, and are not only an indicator of kidney burden, but may also be a rough indicator of total body burden. The retention of Hg in the brain observed several years after remote exposure in retired mercury miners suggests that the brain does not follow the same kinetics of elimination as the kidneys (Falnoga et al., 2000; Kosta et al., 1975; WHO, 1991). In the case of intermittent exposure to Hg^0 , blood Hg was very positively correlated with the spot urine

Hg mercury concentration ($r=0.68$, $p < 0.001$), which, in such types of exposure, allows use of urine Hg as a biological indicator of recent exposure (Kobal, 1991).

	Ex-miners	Controls
Pituitary gland (ng/g)	39100 (N-1)	36.9 ± 62 (N-13)
Piniel gland (ng/g)	1109 (N-1)	9.5 ± 9.2 (N-15)
Hyppocampus (ng/g)	251, 309, 337 (N-3)	3.9 ± 1.6 (N-6)
Nucleus dentatus (ng/g)	2090, 2363, 4428 (N-3)	137 ± 77 (N-7)
Cerebellar cortex (ng/g)	43, 108, 110, 301 (N-4)	2.1, 2.5, 2.9 (N-3)

Table 1. Total Hg concentration in autopsy samples (homogenised tissue) of pituitary gland, pineal gland, hippocampus, nucleus dentatus and cerebellar cortex (ng/g fresh weight) in ex-miners of the Idrija Mercury Mine and controls (data adapted by Falnoga et al., 2000).

3.2 Toxic effects of Hg°

Various Hg species, as Hg°, methyl-Hg ore ethyl-Hg, accumulates in the central nervous system (CNS) and has extremely neurotoxic effects, including the appearance of well-known clinical symptoms and signs. In case of occupational exposure to Hg°, the most frequent symptoms and signs include “erethism”, increased irritability, depression and other neurobehavioral changes, sleep disturbances, oral disturbances, gingivitis and stomatitis with excessive salivation, intentional tremor, peripheral neuropathy (lower sensor and motor conduction velocities), and renal impairment. In vitro and in vivo studies showed that Hg can stimulate free radical generation as a catalyst in Fenton-type reactions and through some other mechanisms, and can promote oxidative stress, peroxidation of lipids and DNA bases, disturbances in cell membrane permeation and calcium homeostasis in cells, impairment and even apoptosis of monocytes, T cells, glial cells and neurons, disturb the functioning of neurotransmitters, and cause immune disorders (Aschner, 2000; ATSDR, 1999; Castoldi et al., 2001; Clarkson & Magos, 2006; Kobal et al., 2004; Kobal-Grum et al., 2006; Lund et al., 1993; Magos, 1997; Pollard & Hultman, 1997; Schara et al., 2001; WHO, 1991).

3.2.1 Interaction with neurotransmitters

Various Hg species presynaptically blocks sodium and calcium channels and thus inhibits the uptake of some neurotransmitters, especially *glutamate* into astrocytes, which increases their extracellular concentration, thus increasing the sensitivity of neighbouring neurons for *stimulating excitotoxic effects* (Aschner et al., 2007; Brookes, 1996; Castoldi et al., 2001; Sirois & Atchison, 1991; Trotti et al., 1997). Many studies reviewed by Mottet et al. in 1997 showed

that astrocytes, which accumulate a high level of Hg^{++} , play a fundamental role in regulating glutamate level. In cases of methyl-Hg exposure, it seems that the Hg^{++} ions formed after the demethylation of methyl-Hg may also be responsible for the disruption of normal Ca^{++} ion channels.

Hg may affect sleep because it can: (i) increase extra-cellular glutamate concentrations associated with the activation of some cytokines, which can reduce the serotonin level by lowering the availability of its precursor, tryptophan, through the activation of its metabolizing enzyme, indoleamine 2,3-dioxygenase (McNally et al., 2008); (ii) increase the production of nitrogen oxide (NO) (Ikeda et al., 1999), which can directly, or in interaction with melatonin, decrease the active form of serotonin (Fossier et al., 1999; Kopczak et al., 2007); and (iii) Hg can also increase the consumption of serotonin and melatonin because of its potential oxidation in interaction with the increased production of free radicals observed in microglial cell cultures (Huether et al., 1997; Tan et al., 2000).

It is suggested that inorganic Hg potentiate and inhibit the neuronal nicotinic acetylcholine receptors, depending on its concentration (Mirzoian & Luetje, 2002). Another animal study shows that up-regulation of cerebral acetylcholine receptor can occur in chronic methyl-Hg exposure to compensate the early stage reduction of brain acetylcholine, as a consequence of acetylcholinesterase inhibition (Basu et al., 2006). It is evident from some studies on occupationally and environmentally Hg^0 -exposed subjects that Hg enhances the *dopaminergic effect* in CNS, which otherwise leads to cortical hyperexcitability and changes in the control of locomotor function, emotions, and behaviour (Burbure et al., 2006; Entezari-Taher et al., 1999; Lucchini et al., 2003; Missale et al., 1998).

3.2.2 Subcellular protective mechanism

Particularly significant in reducing the effects of Hg binding with SH groups of GSH and its biochemical precursors, cystine and cysteine, as well as its binding with MTs a cysteine rich low molecular weight proteins and with selenium (Se) an essential element and an integral part of a type of Se-proteins. The two major thiols, GSH and MTs, appear to be most important in regulating the accumulation and detoxification of Hg in CNS. The induction of GSH and MTs in astrocytes leads to greater detoxification of Hg and protection of CNS. Astrocytes represent the first line of CNS's defence against Hg (Aschner et al., 2007; Dringen et al., 2000). GSH (L- γ -glutamyl-L-cysteinyl-glycine) is synthesized from its precursors, glutamate, cysteine and glycine, in the cytosol of cells by the ATP-requiring enzymes γ -glutamylcysteine ligase and GSH synthetase (Meister & Andersen, 1983). Most of the free intracellular GSH (98%) is in thiol-reduced form (GSH) rather than in disulfide form (GSSG). From the cytosol, GSH is delivered into the mitochondria, endoplasmic reticulum and nucleus, but much of it is delivered to extracellular spaces, where its degradation begins to occur on the surface of cells that express the enzyme γ -glutamyl transpeptidase. GSH, as a nonenzymatic antioxidant, participates in a variety of detoxification, transport, and metabolic processes (Ballatri et al., 2009; Rossi et al., 2002). It is speculated that GSH may also function as a neuromodulator and neurotransmitter, since the degradation of extracellular GSH by γ -glutamyl transpeptidase liberates glutamate and, subsequently, the hydrolysis of cysteinylglycine liberates cysteine and glycine, which function as a source of neuroactive amino acid (Oja et al., 2000).

Some other protective mechanisms, such as Se, antioxidative enzymes and melatonin, are also important in the detoxification of Hg and its peroxidative effect on the body, and

particularly CNS. Se that binds with Hg in CNS in a molecular ratio of 1:1 into a nontoxic complex, which in lysosomes represents the last stage of detoxification of Hg (Falnoga et al., 2002; Kosta et al., 1975;).

It is evident from the study of ex-mercury miners that the Hg accumulated in the pineal gland and bound to Se did not impair its function, while the blood melatonin level was still high, probably due to the slow release of Hg from the gland and the adaptive response to free radical production induced by Hg (Kobal et al., 2004). Melatonin and free radicals form stable secondary and tertiary products, biogenic amines, which also enter into reactions with free radicals. So melatonin inhibits the excessive formation of NO and its free radicals, peroxinitrites, and in this way also reduces the excitotoxic effects of glutamate (Sener et al., 2003; Tan et al., 2000).

The main enzymes that provide cellular protection against damage by reactive oxygen species mediated by Hg^{++} are Cu/Zn superoxide dismutase, catalase and the selenoenzyme glutathion peroxides, which transform the superoxide anion radical into hydrogen peroxide and then into oxygen and water (Lund et al., 1993). It is evident from some studies that repeated-intermittent occupational Hg^0 exposure induced an adaptive response and increase of GSH and catalase activity in erythrocytes, as well as the melatonin level in blood. The actual levels of GSH and catalase in erythrocytes depend on the actual level of blood Hg, both of these decreasing at higher blood Hg concentrations during actual exposure (Kobal, 1991; Kobal et al., 2004, 2008).

4. Some basic neurobiological characteristics of sleep-wake cycles

A study conducted by Qiu and colleagues in 2010 presented the main overall neurobiological activity of basal ganglia neurons associated with the sleep-wake state. The differences in firing patterns across the basal ganglia suggest multiple input sources, such as the cortex, thalamus, and the dopamine system, as well as some other intra basal ganglia inputs, such as the globus pallidus-subthalamic nucleus, and striatum-globus pallidus interactions. The largest nucleus striatum of the basal ganglia is mostly comprised of γ -aminobutyric acid ergic spiny neurons, whose activity is influenced by excitatory glutaminergic projection from the neocortex and thalamus, and dopaminergic projection from the midbrain ventral tegmental area and other known parts. The striatum receiving cortical inputs projects to the globus pallidus, which then projects to the cerebral cortex directly or by the thalamus (mainly the mediodorsal thalamic nucleus). It was suggested that the lesion of globus pallidus produced a higher increase in wakefulness and frequent sleep-wake transitions, as well as a concomitant decrease in non-REM sleep duration. The results of the study also suggest that the cortico-striato-pallidal loop may be critically involved in the basal ganglia control of arousal.

There are four stages of sleep, which include the brain-active period associated with rapid eye movements called REM sleep (emergent stage 1 EEG), preceded by progressively deeper sleep stages (stages 2, 3, 4) graded on the basis of increasingly slower EEG patterns, called non-REM sleep. Stages 3 and 4 are referred to as slow-wave sleep (SWS) characterized by delta waves (high amplitude and low-frequency). REM sleep and wakefulness are characterized by increased activity in the cerebral cortex with low-amplitude and high-frequency EEG (alpha waves) and in REM by the inhibition of peripheral neurons displayed in the postural muscle atonia. Increased cerebral activity during REM sleep is associated with higher oxygen consumption, blood flow and neural firing (Madsen et al., 1991).

Acetylcholine, norepinephrine, serotonin, histamine and hypocretin levels are increased in wakefulness and low in non-REM sleep, whereas during REM sleep the noradrenergic, serotonergic and histaminergic cells become silent (Jones, 2005). A high cholinergic tone in the pontine reticular formation combined with a low GABAergic tone contributes to the generation of REM sleep (Vanini et al., 2011). Animal studies showed that the neurotransmitter glutamate enhances REM sleep by activation of the kainite receptor within the cholinergic cell compartment of the brainstem pedunculo pontine tegmentum of cat and rat (Datta, 2002). During REM sleep and waking, the release of acetylcholine activated dopamine in the ventral tegmental neurons, which were higher in the prefrontal cortex and nucleus accumbens. It was also suggested that glutamate and aspartate release can reciprocally affect dopamine release (Forster and Blaha, 2000; Morari et al., 1998). The animal study of Lena and colleagues in 2005 also showed elevated levels of dopamine during waking and REM sleep in the medial prefrontal cortex and nucleus accumbens.

The impairment of the subcortical dopaminergic system may cause disinhibition of the GABAergic inhibitory circuitry at the motor cortex level (Entazry-Taher et al., 1999; Ziemann et al., 1996). It is suggested that the diencephalon-spinal dopaminergic tract could be important as a potential anatomic site of dopaminergic dysfunction in restless leg syndrome, and of periodic leg contractile movements in sleep. The diencephalon-spinal dopaminergic tract projects to the limbic system, sensory cortex and spinal cord (Ondo et al., 2000). The periodic leg contractile movements occur mainly during non-REM sleep. The results of the study of Rijsman et al. in 2005 indicate diminished inhibition at spinal level in subjects with periodic leg movements disorder, probably because of the altered function of the descending spinal tracts and peripheral changes in the inter-neural circuitry at the spinal level. Dreams and nightmares occur usually at the end of the night, when REM sleep is longer. On the other side, sleep terrors occur more often in children than in adults, while children have more delta sleep (Pinel, 2009; Lee & Douglass, 2010).

Another recent animal study (John et al., 2008) showed a rapid increase in the glutamate level during REM sleep and awakening in the histamine-containing posterior hypothalamic region and the perifornical-lateral hypothalamus, and its reduction shortly after the termination of REM sleep and awakening. In the animal study of Dash and colleagues conducted in 2009, which employed a very sensitive method (in vivo amperometry) to measure cortical extracellular glutamate, a progressive increase was observed in the cortical extracellular glutamate concentration during REM sleep and waking. It was suggested that extrasynaptic glutamate is released from astrocytes and neurons in extracellular space, where it is accumulated, and then declines during non-REM sleep due to the intracellular re-uptake mediated by glutamate/aspartate transporters. The rate of glutamate decline during non-REM sleep positively correlated with the levels of slow wave activity (SWA) (Fig. 1). The authors of the study concluded that perhaps the glutamate-decreasing effect of non-REM sleep is especially relevant in a pathological condition.

It is thought that the pineal gland itself takes part in regulating the rhythm of sleep and wakefulness, entrained by the light/dark cycle. Neural impulses from the retina enter the pineal gland, which coordinates the formation and secretion of serotonin and melatonin, through the suprachiasmatic nuclei (SCN) of the hypothalamus. Light induces serotonin secretion, while melatonin is produced at night directly from serotonin by acetylation. However, melatonin production can be acutely interrupted by light exposure during the night. Norepinephrine, which is released at night in response to stimulatory signals

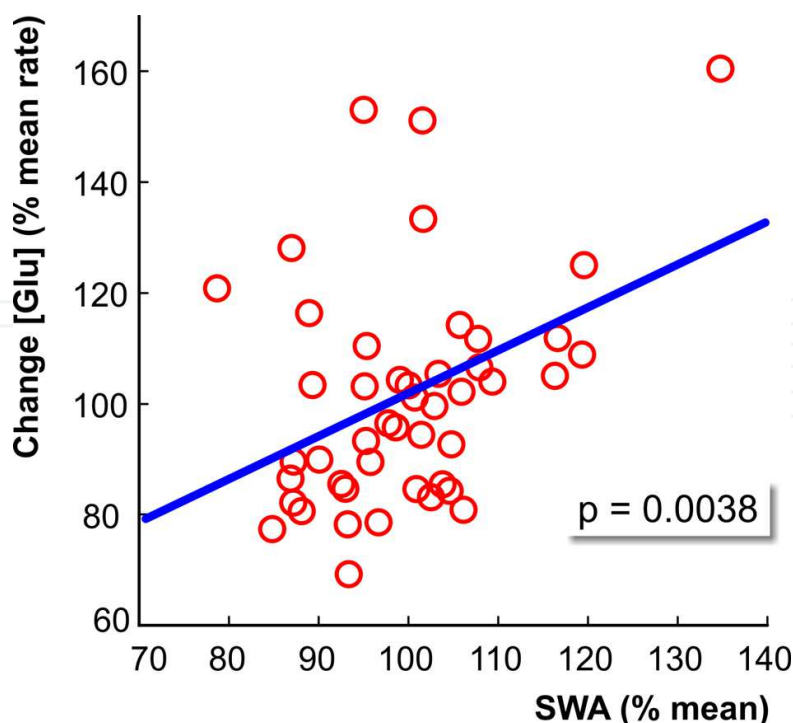


Fig. 1. The rate of glutamate decline during non-REM sleep positively correlated ($r = 0.41$, $p < 0.01$) with the amount of SWA. Each data point represents the average SWA and the change in glutamate concentration during non-REM sleep (Adapted from Dash, et al. 2009, *The Journal of Neuroscience*, Vol. 29, No. 3, pp. 620-629. Copyright 2009, Society for Neuroscience. Adapted with permission.)

originating in SCN, also regulates pineal gland activity. Melatonin can influence the sleep-promoting and sleep-wake rhythm regulating actions through the specific activation of melatonin receptors type 1 and 2, which are highly concentrated in SCN, and are also expressed in the peripheral organs and cells regulating other physiological functions of the so-called circadian 24-hour rhythms. The activation of type 1 occurs by inducing a receptor-suppressed neuronal firing rate in CNS, while type 2 induces a circadian phase shift. The increased secretion of melatonin is also accompanied by other circadian 24-hour rhythms of humans, and in rats studies associated with decreased production of neurotransmitter nitric oxide (NO) (Fig. 2) (Dubocovich et al., 2003; Ebadi, 1992; Geoffriau et al., 1998; Leon et al., 1998; Murphy & Delanty, 2007; Starc, 1998). Some studies do not confirm the influence of melatonin on the duration of sleep (Hughes et al., 1998), while others support the effect of melatonin on the duration and quality of REM sleep because they assume that it either directly influences cholinergic activity in REM sleep, or indirectly influences REM sleep by the elimination of serotonergic or aminergic activity (Jones, 1991; Kunz et al., 2004). It seems that melatonin modulates the release of acetylcholine in the nucleus accumbens and the motor activity of rats (Paredes et al., 1999). Some animal studies suggest that the daily changes in melatonin production may regulate the day-night variation in glutamate and GABA in the neostriatum (Marquez de Prado et al., 2000). It seems that the glutaminergic system negatively regulates norepinephrine-dependent melatonin synthesis in the rat's pineal gland (Yamada et al., 1998). In rats studies melatonin inhibits the glutamate-mediated response of the striatum to motor cortex stimulation and decrease NO content in parieto-temporal cortex, striatum and brainstem of rats due to the inhibition of neuronal nitric oxide

synthase activity. On the other site the administration of high doses of melatonin have paradoxal effect and can decrease GABA and increase glutamate levels (Bikjdaouene et al., 2003; Leon et al., 1998). The synaptically released glutamate is taken up into astrocytes, where it is degraded into glutamine by the glutamate-metabolizing enzyme, glutamate synthetase. It is suggested that astrocytes are primarily responsible for controlling the extracellular level of glutamate, and melatonin seems to have a direct effect on astrocytes (Marquez de Prado et al., 2000; Segovia et al., 1999).

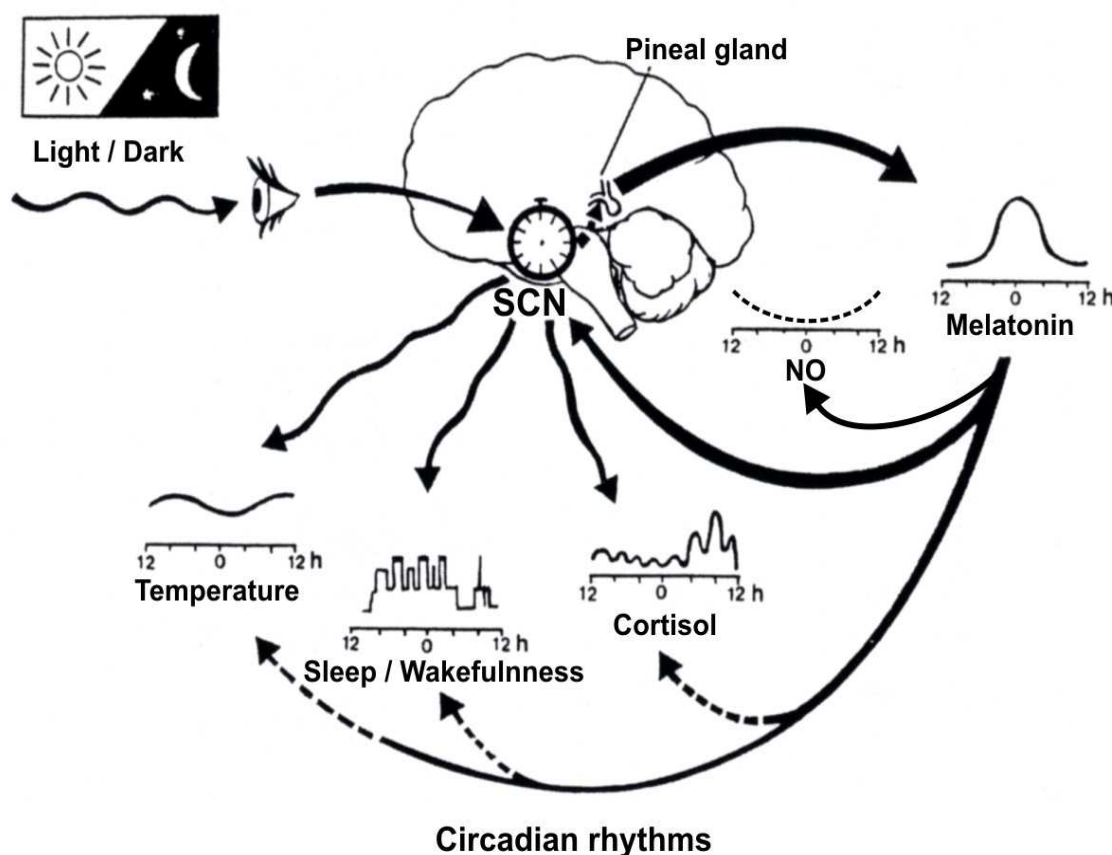


Fig. 2. Melatonin rhythm acts as an endogenous synchroniser adjusted to the 24-hour light/ dark cycle, which (rats studies) regulates also the NO production (Adapted from Geoffrieau et al., 1998 ; Leon et al., 1998, *Hormone Research*, Vol. 49, pp. 136-141. Copyright 1998, S. Karger AG, Medical and Scientific Publishers. Adapted with permission.)

5. Conclusion

In the above-mentioned studies, we assumed that the increased uptake of Hg^0 into CNS could affect sleep: (i) due to the further increase of extracellular concentrations of glutamate, which leads to the induction of excitotoxic effects that can have an impact on disbalance of cholinergic, glutaminergic and dopaminergic activity and other neuronal activity which otherwise regulate non-REM sleep, REM sleep and awakening , and (ii) due to the decreased night-time melatonin level, which also seems to be involved in day-night glutamate regulation and sleep-wake regulating actions by the activation of melatonin receptors in SCN and in the peripheral organ cells regulating other circadian 24-hour rhythms.

In vitro and in vivo studies have shown that due to the increased production of free radicals as well as blocked sodium and calcium channels, Hg inhibits the uptake of some neurotransmitters, especially glutamate, into astrocytes, which increases their extracellular concentration, thus increasing the sensitivity of neighbouring neurons for stimulating excitotoxic effects (Aschner et al., 2007; Castoldi et al., 2001). The increased production of the neurotransmitter nitrogen oxide (NO) mediated by Hg (Ikeda et al., 1999) is also indirectly included in the excitotoxic effects of glutamate (Dawson et al., 1991). Hg^0 thus additionally increases the physiological level of extracellular glutamate and its glutaminergic activity during REM sleep and awakening. It is not expected that Hg^{++} -mediated glutamate accumulation in extracellular space can decline during non-REM-SWA sleep through intracellular-astrocyte uptake by glutamate/aspartate transporters and its degradation into glutamine, whose capacity is satisfactory in physiological conditions (Dash et al., 2009), but probably not in Hg^{++} -enhanced glutaminergic activity. It seems that the decrease of melatonin mediated by interaction with Hg^{++} can also decrease the uptake of glutamate in astrocytes, which additionally contributes to pathological glutaminergic overactivity at increased Hg^{++} concentrations in CNS.

Given the results of some animal studies (Lena et al., 2005; Morari et al., 1998) and human data (Burbure et al., 2006; Entezari-Taher et al., 1999; Lucchini et al., 2003; Missale et al., 1998), it is expected that Hg^{++} enhances the dopaminergic effect in CNS, otherwise associated with cortical hyperexcitability and changes in the control of locomotor function. The impaired subcortical dopaminergic system, which may cause disinhibition at motor cortex level, could be associated with periodic contractile movements of the legs in the sleep (Entezari-Taher et al., 1999; Ondo et al., 2000; Rijsman et al., 2005; Ziemann et al., 1996) observed in miners during increased Hg^0 absorption and intoxication. We can not completely exclude the potential additive effect of sub-clinical peripheral neuropathy observed in miners, which can trigger and modify the appearance of periodic leg contractile movements in sleep.

Melatonin is decreased in the night-time, either because of decreased synthesis under the influence of Hg-mediated, increased NO production, which in SCN operates similarly to a light signal (Ding et al., 1994; Ikeda et al., 1999), or by lowering its precursor tryptophan through its increased metabolizing, and because of its consumption in interaction with free radicals (McNally et al., 2008; Sener et al., 2003; Tan et al., 2000). A lower melatonin level is, at the same time, associated with the increased production of NO and its free radicals, peroxytrites, which also increase the excitotoxic effects of glutamate (Acuna-Castroviejo et al., 1995; Leon et al., 1998). However, it has been established in many studies that melatonin plays a role in mediation between the circadian pacemaker and sleep-wake behaviour, and may have soporific properties and induce sedation, as well as the decreased nocturnal melatonin level labilised circadian rhythm function (Rodenbeck & Hajak, 2001; Stone et al., 2000; Turek & Gillette, 2004).

Increased extracellular glutamate and its decreased uptake in astrocytes (Dash et al., 2009) could hypothetically lead to longer REM periods and more frequent awakening associated with more frequent dreaming during increased Hg^0 absorption or intoxication. Hypothetically, persistent glutaminergic activity can also disrupt delta wave sleep, which could be associated with the sleep terrors observed in intoxicated miners. Further animal studies would be very helpful in elucidating the potential effects of Hg on the uptake of

extracellular glutamate into astrocytes during the non-REM sleep, which could be relevant for sleep disorders observed in states of increased Hg^0 absorption or intoxication.

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Phone: +86-21-62489820
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