High pressure neurological syndrome

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HIGH PRESSURE NEUROLOGICAL SYNDROME

Summary. Introduction. *Pressure is a thermodynamic variable that, like temperature, affects the states of matter. High pressure is an environmental characteristic of the deep sea. Immersion to depth brings about an increase in pressure of 0.1 MPa (1 atm) for each 10 m of seawater. Humans exposed to high pressure, mostly professional divers, suffer effects that are proportional to their exposure.* Development. *The nervous system is one of the most sensitive targets of high pressure. The high pressure neurological syndrome (HPNS) begins to show signs at about 1.3 MPa (120 m) and its effects intensify at greater depths. HPNS starts with tremor at the distal extremities, nausea, or moderate psychomotor and cognitive disturbances. More severe consequences are proximal tremor, vomit, hyperreflexia, sleepiness, and psychomotor or cognitive compromise. Fasciculations and myoclonia may occur during severe HPNS. Extreme cases may show psychosis bouts, and focalized or generalized convulsive seizures. Electrophysiological studies during HPNS display an EEG characterized by reduction of high frequency activity (alpha and beta waves) and increased slow activity, modification of evoked potentials of various modalities (auditory, visual, somatosensory), reduced nerve conduction velocity and changes in latency. Studies using experimental animals have shown that these signs and symptoms are progressive and directly dependent on the pressure. HPNS features at neuronal and network levels are depression of synaptic transmission and paradoxical hyperexcitability.* Conclusion. *HPNS is associated with exposure to high pressure and its related technological means. Experimental findings suggest etiological hypotheses, prevention and therapeutic approaches for this syndrome. [REV NEUROL 2007; 45: 631-6]*

Key words. *Calcium channels. Epilepsy. HPNS. Hyperexcitability. Neuronal networks. Synaptic release.*

INTRODUCTION

High environmental pressure exerts critical effects on the nervous system. Humans exposed to it, mostly professional deep divers, suffer the high pressure neurological syndrome (HPNS), which is characterized by disorders of motor, sensory, vegetative and cognitive functions [1]. The consequences of HPNS may be so severe that they not only impair divers' regular activities and increase their risks, but they may also be the main limiting factor for deep diving. Evidences of HPNS have been obtained in neurological and psychiatric examinations, and also in clinical neurophysiological studies [2]. This characterization allowed reproduction of HPNS in experimental models in human and laboratory animals [3]. Various studies have shown that during HPNS the central nervous system (CNS) paradoxically combines systemic hyperexcitability with reduction in the conduction velocity of axons and depression of synaptic activity [4]. In extreme cases, HPNS may be seen as a model for epilepsy [5] or for acute psychosis [6]. These events contrast with other notorious effect of pressure at CNS level: the pressure reversion of anaesthesia [7]. This review describes HPNS, correlates its signs with experimental findings at cellular and molecular levels, and tries to establish etiological causes.

PRESSURE AND HYPERBARIC ENVIRONMENTS

The depths of the sea are the most significant instances of hyperbaric environments, in which pressure increases at a rate of 0.1 MPa (1 atm) per each 10 m depth in seawater. Thus, sport (scuba) divers descending until 40 m are exposed to pressures around 0.5 MPa (including the atmospheric pressure on the water surface). Deep divers used to carry out work at more than 250 m under seawater (i.e: during the construction and maintenance of oil wells in the North Sea). Due to the occurrence of HPNS's signs and its increased risk, underwater work is now restricted to 180 m (though these depths are occasionally surpassed). Experimental submersions reached 600-800 m revealing the most serious consequences of HPNS. The extremely long compression (and decompression) times needed to reach (or leave from) great depths determined that divers cannot ascend to surface in a daily base. Therefore, they may remain under pressure at a medium depth (140-150 m) for more than a week, from which they descend to greater depths for work (180-250 m). Figure 1 describes frequent hyperbaric conditions in these missions, in which divers are exposed to pressures that vary between 1.5 and 2.6 MPa. Because nitrogen in the air turns narcotic at high pressure, and increases the risk of embolism, deep divers (saturation divers) breathe either heliox (a mixture of helium and oxygen) or trimix (heliox plus a fraction of a third gas: nitrogen or hydrogen) during their stay at the depth [2]. HPNS occurs within this conjunction of technological means and exposure to high pressure.

Animals that are natural divers, such as cetaceans odontocetes and elephant seals, reach much greater depths than humans (i.e.: 2000 m for 40 min) and ascend from them frequently to breathe at the surface [9]. There are no records of HPNS in these animals, but recent research suggest that their CNS might be more labile to other environmental alterations, like excess of noise during deep diving [10].

HIGH PRESSURE NEUROLOGICAL SYNDROME

High pressure exerts its effects on the various systems of the human body, but the most sensitive seems to be the nervous system. HPNS has been described many years ago, as a syndrome mostly characterized by hyperexcitability of the CNS that was

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experienced by humans exposed to hyperbaric conditions. Some literature refer to it as the 'high pressure nervous syndrome' [11]. HPNS is used here for both designations. HPNS entails clinical symptoms and signs, which involve psychological and neuropsychiatric disturbances, neurological signs [12], and changes in clinical neurophysiology recordings [13,14]. Though HPNS has been characterized in humans, it has also been observed in experimental animals exposed to hyperbaric conditions [15-17]. From a neurological point of view, HPNS entails motor, sensory, and vegetative components (Table I). The earliest signs of HPNS begin to occur at pressure of 1.3 MPa (120 m), displaying mild manifestations such as dizziness, nausea, tremor at distal extremities, and moderate alteration of cognitive function [18]. Tremors are of frequent presentation, and are characteristic of HPNS. They involve postural and activity tremors (frequencies of 3-7 Hz and 8-12 Hz) that begin at distal extremities. From them, they propagate to more proximal areas, as HPNS intensifies [19] tremor affects successively the trunk, the neck, and the face in the most serious forms. From a motor point of view, divers suffer from fatigue, muscular weakness [20], cramps, and altered coordination indicating dysmetry [21]. Patent pathological neuromuscular signs, such as fasciculations and myoclonus are rare, occurring only in the most severe cases. Like in tremors, these symptoms occur first at muscles of distal extremities, and then propagate proximally, as the syndrome aggravates, involving muscles of the neck, the face, and the trunk.

Table I. Frequent signs and symptoms of HPNS.

	Clinical sign/symptom	Mild	Severe
Motor	Tremor	Activity tremor in distal extremities	Activity tremor in truck, neck and face
		Muscular weakness amd mild dysmetria	Muscular weakness and severe dysmetria
Sensory, sensory-motor	Hypersensitivity	Increased spinal reflexes, cramps	Fasciculation and myoclonus
	Changes in evoked potentials of various sensory modalities	See changes in evoked potentials	
Behaviour	Reduced performance in cognitive tests	Up to 10 %	Up to 20 %
		Reduced memory span	Hallucinations
		Confusion	Sleepiness
			Impossibility to work at depth
Sleep disorders		Increase of early stages, decrease of deep sleep stages	See EEG
		Fatigue (probably generated by sleep deprivation)	Sleepiness (microsleep)
Autonomic		Nausea	Vomit
		Dizziness	Vertigo and other disorders of balance
		Headache	
		Abdominal pain	
		Reduced appetite	
		Diarrhoea	

Various kinds of alterations of cognitive function occur during HPNS. They may be displayed as subjective sensations or during psychometric tests. Divers frequently report problems with efficiency at work and diminished mental accuracy. For instance, finding difficult to follow a sequence (i.e.: while counting) after a trivial interruption, or suffering from concentration problems. It has been observed that professional divers experience important changes in short-term memory during immersions at 300-350 m [20]. Another study found disturbance of long-term memory [18]. Test of cognitive function revealed progressive reduction of dexterity, and especially in the velocity for solving tests, during acute exposure to high pressure. These alterations occur at depths of less than 180 m and aggravate notoriously at higher pressure. Rostain et al have reported amelioration of intellectual performance during prolonged stay (> 1 day) at a constant depth [22]. The alterations in the resolution of intellectual tests and of sensory and motor performance have been associated with the occurrence of other symptoms such as sleepiness, distress, and psychomotor excitation. More rare psychological and neuropsychological symptoms in the HPNS include euphoria, and occasionally visual or auditory hallucinations [23]. Abraini et al described extreme cases in which the excitation observed in the divers resembled psychotic attacks [6,24], but these cases seem to be exceptional due to individual predisposition of the subjects in study, or a combination of this and the gases used for compression [23]. Bennett et al promoted the use of trimix for improving the effects of HPNS. The prevention of tremor by the use of trimix (vs. heliox) was correlated with diminished visuomotor coordination, manual dexterity, rational capacity, and long-term memory [18]. French and American laboratories use and promote the utilization of trimix, while Norwegian groups still prefer heliox for their oil wells work [2], due to serious cognitive effects observed during their experience with trimix.

Among the most frequent vegetative symptoms of HPNS we can mention headache (mostly cephalea), dizziness, nausea and vomit that occur in more serious situations. Diarrhoea, appetite loss, and serious disturbances of balance that impede certain divers to carry out their work are associated to chronic cerebral lesions that do not produce signs at normal pressure, but may produce them at hyperbaric conditions [25,26]. The normal pattern of sleep is altered at high pressure. Polysomnographic studies have shown changes characterized by increase of superficial stages (I and II), and reduction in the occurrence and dura-

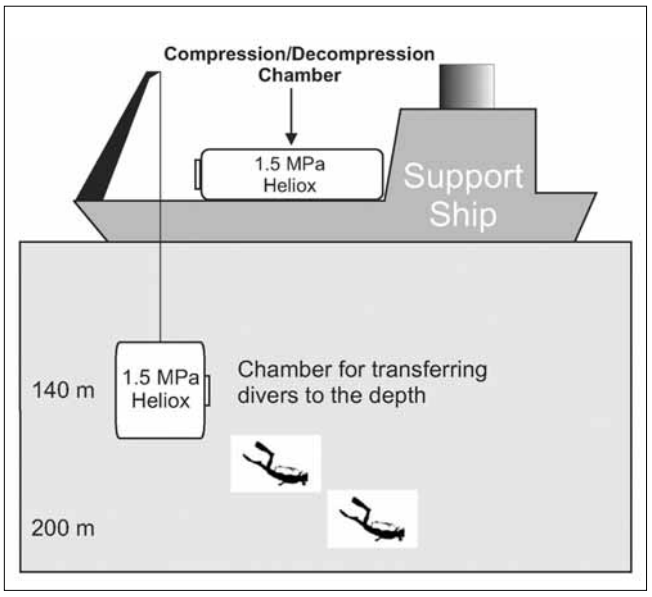

Figure 1. Typical technological environment of deep diving. The support ship provides logistics: gases and material necessary for undersea work. The pressure chamber containing the divers is partially compressed at surface and then submerged to a medium depth. The divers leave the chamber to descent to greater depths for carrying out underwater work.

tion of deep stages (III and IV) [27]. The changes in sleep pattern may be associated with the extreme fatigue experienced by deep divers since altered sleep may produce lack of rest, and diminished memory consolidation. However, the coexistence of factors generating fatigue in high pressure environments makes difficult to establish an etiologic cause. For instance, sleep disorders may add to additional factors like difficult breathing due to the increased density of inspired gases at high pressure.

CLINICAL NEUROPHYSIOLOGY IN HPNS

Clinical neurophysiology of the HPNS entails a variety of changes in electrophysiological studies. These involve alterations of the electroencephalogram (EEG) [1] and of evoked potentials. Typically, the EEG changes are characterized by a marked reduction of alpha waves in the posterior region and by an increase in the slow waves, theta and delta, in the anterior derivatives [25]. Signs like EEG of awakening resembling microsleep may also occur. These findings appear at 170-180 m depth and intensify at higher depths. Most of the studies showed notorious increase in the power spectral density of theta waves in anterior derivatives. This phenomenon is particularly remarkable just after compression (or during the close hours). There is improvement in the EEG recorded under similar conditions days after compression [23]. Sleep EEG also displays specific alterations at high pressure. These are characterized by increase in stages I and II, decrease in the duration of stages III and IV, and instability and reduction of REM periods [27,28].

Hyperbaric conditions are associated with notorious changes in potentials evoked by various sensory modalities (Table II). For instance, auditory evoked potentials seem to be very sensitive to the effect of pressure, often displaying increase in the inter-wave intervals. These effects are observed in early auditory potentials, such as the brainstem auditory evoked potentials [16,29], in later potentials like the middle latency auditory response [29]. Somatosensory evoked potentials (SSEP) show also increase in the latency among the different waves [29], while similar results are reported during recording of visual evoked potentials [30,31]. A study has reported no significant changes in the P300 component amplitude at 1.9 MPa [32], whereas Vaernes et al showed that at 3.6 MPa these component disappeared completely in four up of six divers [31]. Both studies agree that high pressure led to prolongation in the latency of P300, which can be interpreted as an electrophysiological sign of alteration of cognitive function [31,32].

EVOLUTION OF HPNS

HPNS is mostly described as an acute phenomenon that in general tends to ameliorate during prolonged stay at constant pressure. For instance, the changes induced initially in the sleep pattern are observed during the first week under pressure and display improvement afterwards. However, only decompression to normal pressure succeeds in restoring the regular sleep pattern [28]. Brauer et al described these as processes of adaptation to high pressure, which occurring after prolonged stay at constant pressure [5] may explain the improvement of HPNS signs observed days after compression [22]. In general, the effects of high pressure, including those described in HPNS and those attributed to rapid compression, are transient and reversible upon decompression [33]. This suggests that HPNS is a benign condition limited to the permanence in hyperbaric environments. However, a single publication suggests that deep diving may lead to sub-acute or even chronic conditions. For instance, that an impairment of short-term memory during diving may persist even at sea level [21]. Moreover, Todnem et al examined neurologically deep divers at normal pressure and found that they suffered chronic problems (like tremor, long-term memory impairment and reduced concentration span) more often than a control group [34]. Sets of neurological tests combined with complementary diagnosis means showed undoubtedly that saturation divers suffer from chronic lesions associated with their work. However, it is difficult to establish the cause of the observed lesions because it is difficult to discriminate lesions derived from previous HPNS from those produced as consequence of micro embolism generated by subclinical decompression sickness [34].

HPNS IN EXPERIMENTAL MODELS

HPNS has been studied in vivo in experimental models using rodents, non-human primates, and human subjects, and in vitro utilizing cells or tissue from animals or human. The former are mostly simulated dives that used helium as compression medium [2]. Tremor in deep divers found then their experimental equivalent in the 'radicular activity associated to tremor' seen in isolated spinal cord preparations [35]. Changes in SSEP observed in humans were simulated by delay in the P4 (250 ms) in dogs [36]. Similarly, the lower performance in solving psychometric tests and the impairment in retrograde memory [6] are associated to altered evoked potentials, depression of synaptic activity, and other electrical disturbances occurring in neocortical regions [36-38], in the cortico-hippocampal connection [4, 40], and in the hippocampus itself [16,17,41]. The most dramatic signs of HPNS have been described in experimental animals exposed to pressures not yet

directly explored by humans (> 800 m). These animals displayed hypertonus, muscular spasms, paroxistic convulsive seizures, and also blunt myoclonic epileptic seizures. In these cases, high pressure is seen as an acute model of epilepsy [40].

Pressure increases the startle response: at high pressure, a stimulus of 50 % less intensity may produce a response that resembles that of control, while the response induced by a constant stimulus may increase by 250 % [42]. Such a phenomenon has lead to speculate that naval sonars might produce an exaggerated startle response in whales that are actively diving [10]. This might made them ascend rapidly, causing decompression sickness, stranding and death [43].

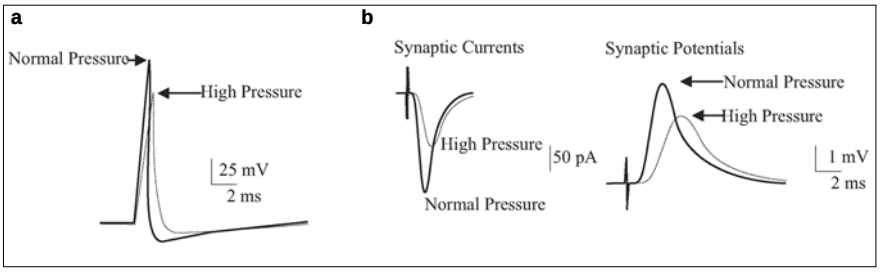

Figure 2. Electrophysiological recordings displaying the effects of pressure on action potentials and synaptic transmission: a) High pressure (10.1 MPa) slows the kinetics of initiation and decay of action potentials, decreases their amplitude and prolongs their time-course; b) Effects of pressure on synaptic currents and potentials necessary for integration of neuronal information. High pressure reduces the initial slope, increases the decay time, reduces amplitude and increases the duration of synaptic currents and potentials. These changes may produce delay in the transfer and processing of neuronal information.

Table II. Effects of high pressure in clinical eletrophysiological studies.

Study	Depth	Electrophyisiological findings	Publication	*n*
EEG	500 m 610 m	Increased low frequency activity, decreased high frequency activity occurring deeper than 300 m	Rostain et al [12]	4
AEP (BAEP)	450 m	Shortening wave I latency, prolongation intervals I-III and III-V	Lorenz et al [14]	4
BAEP	615 m	Prolongation of complex IV-V	Lorenz et al [15]	5
BAEP	110 m	Shortening of wave I latency, prolongation intervals I-III and III-V	Weibing et al [13]	4
AEP (MLR)	180 m	Disappearance of component Pa, increase of component P0	Wada et al [29]	6
VEP	360 m	Prolongation of P100	Vaernes et al [31]	6
–	360 m	Prolongation of N75, no change in P100 or N145	Todnem et al [30]	14
P300	250-350 m	Prolongation of P300	Vaernes et al [31]	6
–	350-360 m	Disappearance of P300, prolongation of earlier waves	Vaernes et al [31]	4/6
–	180 m	Prolongation of P300	Wada et al [32]	2
SSEP	–	No change latency in N9-N14, increased latency in N9-N20	Wada et al [29]	6

EEG: electroencephalogram; AEP: auditory evoked potentials; BAEP: brainstem auditory evoked potentials; SSEP: somatosensory evoked potentials; VEP: visual evoked potentials; MLR: middle latency responses,

CELLULAR AND MOLECULAR EFFECTS OF HIGH PRESSURE

Pressure opposes to molecular processes that involve volume expansion. This effect has been used for the study of membranes, pumps [44] and ionic channels like sodium [45], potassium [46], and calcium channels [47], and even for the study of gating currents in some of them [48]. Pressure reduced the kinetics of opening and close of the channels while inducing minimal effect on the channels' maximal conductance [48]. Similar effects were described for channels gated by ligands, like receptors for acetylcholine [49], glycine [50], GABA [51], and glutamate [52], transmembrane transporters such as the Na-K ATPase pump [44] or a Na^+/Ca^{2+} exchanger [53]. These changes may lead to the reduction in the amplitude and the slowing down of the kinetics of action potentials, and to the reduction of axonal conduction velocity [54,55] (Fig. 2a). Synaptic depression, depression of synaptic currents and potentials [56], and increased synaptic latencies [4,57] seem to be most relevant effect of high pressure (within the range 0.1 to 10.1 MPa) in the nervous system (Fig. 2b). These effects are mostly due to depression in the presynaptic release of neurotransmitter rather than on changes on post synaptic receptors, which are minor [49-52]. High pressure also affects dynamic synaptic processes increasing facilitation, post-tetanic potentiation, and short-term synaptic depression [4,58]. These effects that are associated with hyperexcitability at a neuronal [17] and systemic [40] levels, suggest that in sum they lead to a relative decrease in inhibition with respect to excitation [40]. Pressure reversal of anaesthesia may act in a similar way, in which a relative increase in excitability or reduction of inhibition may counteract the CNS depression induced by anaesthetic agents [40].

CONCLUSIONS

HPNS is a syndrome of hyperexcitability of the CNS that is correlated at the neuronal level with general depression of synaptic activity, and in particular with relative reduction of inhibitory influences. If high pressure depresses both, excitatory and inhibitory synaptic activity how hyperexcitability arises? Excitatory circuits in the CNS, that are mostly monosynaptic, are depressed but they are less depressed that inhibitory circuits, which are bi or polysynaptic. Provided the two types of synapses are equally depressed by high pressure, this may lead to a proportional reduction of inhibition that depends on more synapses [40]. Moreover, the increase in the synaptic latencies and axonal conduction may cause that inhibition is exerted later than normal reducing the regular filtering of excitatory inputs. This is particularly relevant for at high frequency transfer of signals [40]. The occur-

rence of the described phenomena is associated to exposure to high pressure environments: they intensify when increasing pressure, and ameliorate upon decompression. Nevertheless, deep diving environments display more variables than high pressure, whose effects may be exerted concomitantly with it. High concentration of gases (helium) that are often assumed as 'inert' (but whose effects are not well known), change in the properties of matter (increased density), or alteration of their regular properties (increased conduction of heat, sound, and others), which may eventually produce neurological signs without being properly HPNS. For instance, the increased conduction velocity of sound in helium may cause disorientation because it may not allow the normal perception of interauricular phase-delay [10]. Moreover, HPNS (the neurological signs dependent on high stable pressure) has been differentiated from the effects of compression (progressive increase of pressure). This last is particularly relevant during rapid compression [59]. Some experimental studies using fluorocarbon as a compression mean have shown parallel effects between hydrostatic pressure and helium suggesting that HPNS is caused by the direct effect of pressure [36]. Therapeutic attempt trying to alleviate HPNS consequences have used antiepileptic drugs (enhancing inhibition) or gases with known narcotic effect (N_2 or H_2 in trimix). The results of these attempts are ambiguous producing improvement of certain signs but exacerbation of others. This relative inefficacy is thought to happen because the same substances that antagonize hyperexcitability at high pressure may prevent the development of natural adaptive mechanisms that according to certain studies may occur in terrestrial mammals and even in humans [5]. The stranding of whales, natural deep divers, which is broadly associated to the use of naval sonar in their proximity, suggest that they may suffer an exaggerated startle response, or even an audiogenic seizure when intense noise at frequency produced by the sonar reaches them while diving in the depth [10]. A similar effect suggest that natural adaptation allows survival at high pressure, but not a regular functioning of neurological and cognitive faculties (which may turn their CNS more labile to additional environmental disturbances). If human divers experience similar changes, these may turn them more sensitive to factors that are innocuous at normal pressure like noise at frequency, fluorescent lights and flashes, or computer screens. There is need for additional studies to elucidate the validity of these hypotheses.

REFERENCES

1. Brauer RW, Dimov S, Fructus X, Gosset A, Naquet R. Syndrome neurologique et electrographique des hautes pressions. Rev Neurol (Paris) 1969; 121: 264-5.
2. Bennett PB, Rostain JC. The high pressure nervous syndrome. In Brubakk AO, Neumann TS, eds. Bennett's and Elliott's Physiology and Medicine of Diving. 5 ed. Philadelphia: Elsevier-Saunders; 2003. p. 330-9.
3. Talpalar AE, Grossman Y. CNS manifestations of HPNS: revisited. Undersea Hyperb Med 2006; 33: 205-11.
4. Talpalar AE, Grossman Y. Modulation of rat corticohippocampal synaptic activity by high pressure and extracellular calcium: single and frequency responses. J Neurophysiol 2003; 90: 2106-14.
5. Brauer RW, Dutcher JA, Hinson W, Vorus WS. Prolonged exposure of mice to He-O2 at high pressure: effects on seizure and anesthesia liability. J Appl Physiol 1986; 61: 2005-11.
6. Abraini JH. Evidence for inert gas narcosis mechanisms in the occurrence of psychotic-like episodes at pressure environment. Neuroreport 1995; 6: 2435-9.
7. Wlodarczyk A, McMillan PF, Greenfield SA. High pressure effects in anaesthesia and narcosis. Chem Soc Rev 2006; 35: 890-8.
8. Somero GN. Physiological and biochemical adaptations of deep sea fishes: adaptative responses to the physical and biological characteristics of the abyss. In Ernst WG, Morin JG, eds. The environment of the deep sea. Englewood Cliffs, NJ: Prentice-Hall; 1982. p. 275-8.
9. Baird RW, Webster DL, McSweeney DJ, Lingon AD, Schorr GS, Barlow J, et al. Diving behaviour of Cuvier's (*Ziphius cavirostris*) and Blainville's (*Mesoplodon densirostris*) beaked whales in Hawaii. Can J Zool 2006; 84: 1120-8.
10. Talpalar AE, Grossman Y. Sonar versus whales: noise may disrupt neural activity in deep-diving cetaceans. Undersea Hyperb Med 2005; 32: 135-9.
11. Bennett PB, Towse EJ. The high pressure nervous syndrome during a simulated oxygen-helium dive to 1500 ft. Electroencephalogr Clin Neurophysiol 1971; 31: 383-93.
12. Rostain JC. The high pressure nervous syndrome at the central nervous system level. In Jannasch HW, Marquis RE, Zimmermann AM, eds. Current perspectives in high pressure biology. London: Academic Press; 1987. p. 137-48.
13. Weibing X, Qingling Z, Lingsong P, Ruqing T. Changes in human brainstem auditory evoked potentials during a 1,100 kPa He-O_2 simulated saturation dive. Undersea Hyperb Med 1998; 25: 111-4.
14. Lorenz J, Brooke ST, Petersen R, Torok Z, Wenzel, J. Brainstem auditory evoked potentials during a helium-oxygen saturation dive to 450 meters of seawater. Undersea Hyperb Med 1995; 22: 229-40.
15. Lorenz J, Athanassenas G, Hampe P, Plath G, Wenzel J. Human brainstem auditory-evoked potentials in deep experimental diving to pressures up to 62.5 bar. Undersea Biomed Res 1992; 19: 317-30.
16. Fagni L, Soumireu-Mourat B, Carlier E, Hugon M. A study of spontaneous and evoked activity in the rat hippocampus under helium-oxygen high pressure. Electroencephalogr Clin Neurophysiol 1985; 60: 267-75.
17. Fagni L, Zinebi F, Hugon M. Evoked potential changes in rat hippocampal slices under helium pressure. Exp Brain Res 1987; 65: 513-9.
18. Vaernes R, Hammerborg D, Ellertsen B, Peterson R, Tonjum S. Central nervous system reactions during heliox and trimix dives to 51 ATA, DEEP EX 81. Undersea Biomed Res 1983; 10: 169-92.
19. Spencer J, Findling A, Bachrach AJ, Gelfand R, Lambertsen CJ, Karreman G. Tremor and somatosensory studies during chamber He-O_2 compressions to 13.1, 25.2, 37.3, and 49.4 ATA. J Appl Physiol 1979; 47: 804-12.
20. Aarli JA, Vaernes R, Brubakk AO, Nyland H, Skeidsvoll H, Tonjum S. Central nervous dysfunction associated with deep-sea diving. Acta Neurol Scand 1985; 71: 2-10.
21. Rostain JC, Gardette-Chauffour MC, Lemaire C, Naquet R. Effects of a H_2-He-O_2 mixture on the HPNS up to 450 msw. Undersea Biomed Res 1988; 15: 257-70.
22. Rostain JC, Lemaire C, Gardette-Chauffour MC, Doucet J, Naquet R. Estimation of human susceptibility to the high-pressure nervous syndrome. J Appl Physiol 1983; 54: 1063-70.
23. Vaernes R, Hammerborg D, Ellertsen B, Peterson R, Tonjum S. CNS reactions at 51 ATA on trimix and heliox and during decompression. Undersea Biomed Res 1985; 12: 25-39.
24. Abraini JH, Ansseau M, Fechtali T. Pressure-induced disorders in neurotransmission and spontaneous behavior in rats: an animal model of psychosis. Biol Psychiatry 1993; 34: 622-9.
25. Vaernes R, Bennett PB, Hammerborg D, Ellertsen B, Peterson RE, Toonjum S. Central nervous system reactions during heliox and trimix dives to 31 ATA. Undersea Biomed Res 1982; 9: 1-14.
26. Todnem K, Nyland H, Riise T, Kambestad BK, Vaernes R, Hjelle JO, et al. Analysis of neurologic symptoms in deep diving: implications for selection of divers. Undersea Biomed Res 1990; 17: 95-107.
27. Seo Y, Matsumoto K, Park YM, Mohri M, Matsuoka S, Park KP. Changes in sleep patterns during He-O2 saturation dives. Psychiatry Clin Neurosci 1998; 52: 141-2.
28. Rostain JC, Gardette-Chauffour MC, Naquet R. EEG and sleep disturbances during dives at 450 msw in helium-nitrogen-oxygen mixture. J Appl Physiol 1997; 83: 575-82.
29. Wada S, Yokota A, Matsuoka S, Kadoya C, Mohri M. Effects of hyperbaric environment on human auditory middle latency response (MLR) and short latency somatosensory evoked potential (SSEP). J UOEH 1989; 11: 441-7.
30. Todnem K, Vaernes R, Kambestad BK. Visual evoked and brain stem auditory evoked potentials in divers. Aviat Space Environ Med 1991; 62: 982-5.
31. Vaernes RJ, Hammerborg D. Evoked potential and other CNS reactions during a heliox dive to 360 msw. Aviat Space Environ Med 1989; 60: 550-7.
32. Wada S, Urasaki E, Kadoya C, Matsuoka S, Mohri M. Effects of hyperbaric environment on the P300 component of event-related potentials. J UOEH 1991; 13: 143-8.

33. Overman WH, Brauer RW, Burke ER. Failure to find residual memory deficits in monkeys after repeated HPNS. Undersea Biomed Res 1989; 16: 115-27.
34. Todnem K, Vaernes R. Acute and chronic effects of deep diving on the nervous system. Tidsskr Nor Laegeforen 1993; 113: 36-9.
35. Tarasiuk A, Grossman Y. Pressure-induced tremor-associated activity in ventral roots in isolated spinal cord of newborn rats. Undersea Biomed Res 1990; 17: 287-96.
36. Harris DJ, Coggin RR, Roby J, Turner G, Bennett PB. EEG and evoked potential changes during gas- and liquid-breathing dives to 1000 msw. Undersea Biomed Res 1985; 12: 1-24.
37. Kaufmann PG, Bennett PB, Farmer JC Jr. Cerebellar and cerebral electroencephalogram during the high pressure nervous syndrome (HPNS) in rats. Undersea Biomed Res 1977; 4: 391-402.
38. Gruenau SP, Ackermann MJ. Quantification of high pressure nervous syndrome (HPNS) tremor in the guinea pig. Undersea Biomed Res 1978; 5: 95-104.
39. Okuda S, Matsuoka S, Mohri M. Topographic electroencephalographic studies in a hyperbaric environment –specific reference to high pressure nervous syndrome. J UOEH 1988; 10: 247-61.
40. Talpalar AE, Grossman Y. Enhanced excitability compensates for high-pressure-induced depression of cortical inputs to the hippocampus. J Neurophysiol 2004; 92: 3309-19.
41. Fagni L, Zinebi F, Hugon M. Helium pressure potentiates the N-methyl-D-aspartate and D,L-Homocysteate induced decreases of field potentials in the rat hippocampal slice preparation. Neurosci Lett 1987; 81: 285-90.
42. David JM, Risso JJ, Weiss M, Brue F, Pellet J. Hyperbaric effects on sensorimotor reactivity studied with acoustic startle in the rat. Physiol Behav 1988; 42: 237-44.
43. Jepson PD, Arbelo M, Deaville R, Patterson IA, Castro P, Baker JR, et al. Gas-bubble lesions in stranded cetaceans. Nature 2003; 425: 575-6.
44. Pfeiler, E. Effects of hydrostatic pressure on Na^+-K^+-ATPase and $Mg2^+$-ATPase in gills of marine teleost fish. J Exp Zool 1978; 205: 393-492.
45. Conti F, Fioravanti R, Segal JR, Stuhmer W. Pressure dependence of the sodium currents of squid giant axon. J Membrane Biol 1982; 69: 23-34.
46. Conti F, Fioravanti R, Segal JR, Stuhmer W. Pressure dependence of the potassium currents of squid giant axon. J Membrane Biol 1982; 69: 35-45.
47. Heinemann S, Stuhmer W, Conti F. Single AchR-channel currents recorded at hydrostatic pressure. Proc Natl Acad Sci U S A 1987; 84: 3229-33.
48. Conti, F, Inoue I, Kukita F, Stuhmer W. Pressure dependence of sodium gating currents in the squid giant axon. Eur Biophys J 1984; 11: 137-47.
49. Heinemann S, Conti F, Stuhmer W, Neher E. Effects of hydrostatic pressure on membrane processes: Sodium channels, calcium channels, and exocytosis. J Gen Physiol 1987; 90: 765-77.
50. Shelton CJ, Doyle M, Price G, Daniels S, Smith EB. The effect of high pressure in glycinergic and kainate-sensitive receptor channels expressed in *Xenopus oocytes*. Proc Royal Soc London Biol Sci 1993; 254: 131-7.
51. Shelton CJ, Daniels S, Smith EB. Rat brain $GABA_A$ receptors expressed in *Xenopus oocytes* are insensitive to high pressure. Pharmacol Commun 1996; 7: 215-20.
52. Daniels S, Grossman Y. In Brubakk AO, Neumann TS, eds. Bennett's and Elliot's Physiology and Medicine of Diving. 5 ed. Philadelphia: Elsevier-Saunders; 2003. p. 265-99.
53. Paul ML, Philp RB. Effect of pressure on the release of endogenous dopamine from rat striatum and the role of sodium-calcium exchange. Undersea Biomed Res 1992; 19: 1-12.
54. Grossman Y, Kendig JJ. Pressure and temperature: time-dependent modulation of membrane properties in a bifurcating axon. J Neurophysiol 1984; 52: 693-708.
55. Grossman Y, Kendig JJ. Pressure and temperature modulation of conduction in a bifurcating axon. Undersea Biomed Res 1986; 13: 45-61.
56. Campenot RB. The effects of high hydrostatic pressure on transmission at the crustacean neuromuscular junction. Comp Biochem Physiol 1975; 52: 133-140.
57. Etzion Y, Grossman Y. Pressure-induced depression of synaptic transmission in the cerebellar parallel fibre synapse involves suppression of presynaptic N-type Ca^{2+} channels. Eur J Neurosci 2000; 12: 4007-16.
58. Talpalar AE, Grossman Y. High pressure and increased $[Ca^{2+}]_o$ modulation of frequency-dependent synaptic depression suggest modular function of the vesicular readily-releasable pool [submitted].
59. Bennett PB, Coggin R, McLeod M. Effect of compression rate on use of trimix to ameliorate HPNS in man to 686 m (2250 ft). Undersea Biomed Res 1982; 9: 335-51.

SÍNDROME NEUROLÓGICO DE ALTA PRESIÓN

Resumen. Introducción. *La presión, como la temperatura, es una variable termodinámica que afecta los estados de la materia. La alta presión es una característica medioambiental de las profundidades del mar, donde las presiones aumentan a razón de 0,1 MPa (1 atm) cada 10 m. Humanos expuestos a alta presión, generalmente buzos profesionales, sufren trastornos neurológicos proporcionales a esa exposición.* Desarrollo. *El sistema nervioso es uno de los tejidos más sensibles a los efectos de la presión. Su alteración, conocida como el síndrome neurológico de alta presión (SNAP), comienza a mostrar signos a unos 1,3 MPa (120 m) y se acentúa a profundidades mayores. El SNAP se manifiesta con temblores en las extremidades distales, náuseas y/o moderados trastornos psicomotores. Consecuencias más graves son temblores proximales, vómitos, hiperreflexia, somnolencia y compromiso cognitivo. Estadios graves del SNAP presentan fasciculaciones, mioclonos y, en casos extremos, psicosis, crisis convulsivas focalizadas o generalizadas. El SNAP muestra un electroencefalograma caracterizado por disminución de ondas de alta frecuencia (alfa y beta) e incremento de ondas lentas, modificaciones en potenciales evocados auditivos, visuales y somatosensoriales, disminución de conducción nerviosa y cambios en latencia de reflejos. Estudios en animales de experimentación demostraron que estos signos son progresivos y directamente dependientes de la presión. A nivel neuronal y de redes, el SNAP muestra depresión de transmisión sináptica y, paradójicamente, hiperexcitabilidad.* Conclusión. *El SNAP se asocia con exposición a alta presión y su medioambiente tecnológico. Estudios experimentales sugieren hipótesis etiológicas y perspectivas terapéuticas y de prevención. [REV NEUROL 2007; 45: 631-6]*
Palabras clave. *Canales de calcio. Epilepsia. Hiperexcitabilidad. Liberación sináptica. Redes neuronales. SNAP.*