CNS manifestations of HPNS: revisited.

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Talpalar A.E., Grossman Y. CNS manifestations of HPNS: revisited. Undersea Hyperb Med 2006; 33(3): 205-210. Exposure to high pressures (HP) has been associated with the development of the high pressure neurological syndrome (HPNS) in deep-divers and experimental animals. In contrast, many diving mammals are naturally able to withstand very high pressures. Although at a certain pressure range humans are also able to perform to some extent, the severe signs of HPNS at higher pressures motivated the research on the pathophysiology underlying this syndrome rather than on possible adaptive mechanisms. Thermodynamically, high pressure resembles cooling. Both conditions usually involve reduction in the entropy and slowing down of kinetic rates. We have observed in rat corticohippocampal brain slices that high pressure slows and reduces excitatory synaptic activity. However, this was associated with increased gain of the system, allowing the depressed inputs to elicit regular firing in their target cells. This increased gain was partially mediated by elevated excitability of their dendrites and reduction in the background inhibition. This compensation is efficient at low-medium frequencies. However, it induces abnormal spike reverberation at the high frequency band (>50 Hz). Synaptic depression that requires less vesicles/transmitter turn over may serve as an energy-saving mechanism when enzymes and membrane pumps activity are slowed down at pressure. It is even more efficient if a similar reduction is induced in inhibitory synaptic activity. Unfortunately, the frequency response characteristics at this mode of operation may make the system vulnerable to external signals (noise, auditory, visual, etc) at frequencies that elicit 'resonance' responses. Therefore, it is expected that humans exposed to pressures above 1.5 MPa display lethargy and fatigue, certain reduction in cognitive and memory functions when the system is working in an 'economic' mode. The more serious signs of HPNS such as nausea, vomiting, severe tremor, disturbance of motor coordination, and seizures, may be the consequence of an interaction between the 'economic' mode of operation and resonance-inducing environmental disturbances.

INTRODUCTION

Exposure to high pressure (HP) has been associated with the development of the high pressure neurological syndrome (HPNS) in deep-divers and experimental animals (1, 2). By definition, HPNS is induced by the direct effect of HP on the nervous system, and is differentiated from other phenomena that may occur simultaneously such as gas narcosis, compression effects, temperature transients and others. Classic descriptions of HPNS (3) entail motor (4), sensory (5), and autonomic disorders (6) together with cognitive impairments involving psychological disturbances and even psychotic behavior (7). Among the most frequent motor disorders of HPNS are tremors (4), and impaired coordination (8). Autonomic responses related to HPNS often begin with nausea and lightheadedness, which may be followed by dizziness, vomiting and altered respiratory rhythm (6). Abnormal EEG waves (slow activity), drowsiness and sleep disorders are neurological manifestations frequently associated with HPNS (9,10). Slowed conduction velocity of peripheral nerves (11) and of central axons (12), is combined in HPNS with severe hyperexcitability of the CNS (13,14) which eventually produces life threatening epileptiform seizures (15). Additional, though less frequent, neurological manifestations, also attributed to HPNS, are so vast that it involves many of the multiple signs of clinical neurology.

In contrast with all the previous

pathological views, high pressure is not as handicapping as these descriptions of HPNS may predict. Human divers carry out deep undersea activities relatively efficiently at moderate depth (300-500m) while diving mammals (such as many cetaceans and elephant seals) are naturally able to withstand very high pressures (about 2000m) without too serious consequences. Yet, these animals may possess various adaptation mechanisms that are still unknown.

At the organic and cellular levels HP exposure is almost invariably followed by slowing of nerve conduction velocity, depression of synaptic transmission and reduced action potential amplitude. But still there is hyperexcitability of the CNS! As can be seen, HPNS is incomplete as a concept and some of its supposed manifestations have apparent contradictory effects.

Ralph Brauer and collaborators showed that progressive exposure to HP significantly increased the pressure threshold for seizures in mice (16,17). This 'acclimatization' observed *in vivo,* together with observations at a cellular level in our experiments, raise the question whether all CNS phenomena occurring at HP are part of the HPNS or may represent adaptive signs. But, development of adaptive changes may take time (four days in previous experiments). During this period signs of adaptation may be confused with the pathological signs of HPNS. This paper will try to clarify this dilemma.

SIGNS OF HPNS OR SIGNS OF ADAPTATION?

HP is simultaneously inducing pathological and adaptive processes, the manifestations of which may easily be mistaken for one another. Therefore, we first attempted to differentiate between the phenomena with obvious pathology from the less severe signs.

In Table 1 we classified common signs present at HP into two categories: a) clear pathological signs that are associated with hyperexcitability and b) neurophysiological signs that suggest reduced excitability of the CNS. While signs in the first group are certainly part of HPNS, signs in the second group might be either relatively 'innocuous' signs of HPNS or be 'adaptive' changes of the CNS in response to HP. All these signs have been reported to be 'direct' consequence of HP. However, a deficiency in temperature control may inflict some of the signs attributed to HPNS.

Table 1 - CNS alterations at high pressure

Pathological Signs (HPNS)	Neurophysiological Changes at HP
Tremor (8-12 Hz)	Changes in EEG recordings
Myoclonus	Altered Evoked Potentials
Muscular Spasms	Modified Physical Performance
Convulsions	Reduced Cognitive Performance
Psychotic Behavior	Modified Sleep Pattern

It is worth noticing that from a thermodynamic point of view, HP closely resembles cooling; under both conditions entropy in the system is reduced. Therefore, most biological processes may be slowed down. This is in accord with cellular and molecular processes being depressed and decelerated at HP (see below). In addition, pressure reduces normal metabolism at a systemic (18) and cellular level (19-20,21). Thus, impaired physical performance and disturbed cognitive capabilities at HP are predictable not only because of the direct effects of pressure but also indirectly by a reduction of metabolism and rate of energy supply. Consequently, it is conceivable to expect some pressure – dependent depression of performance rather than pure hyperexcitability.

NEURONAL HYPEREXCITABILITY SEEMS TO ARISE AS A COMPENSATORY MECHANISM TO HP

The HPNS most serious consequences are characterized by hyperexcitability. This is not what is 'logically' expected by the direct effect of HP. How and why does hyperexcitability occur? In cellular preparations HP slows the kinetics of most ionic currents (22). Consequently axonal conduction velocity and action potential amplitude are reduced. These have been observed in many preparations from single axons in invertebrates (23) to mammalian brain slices (13, 14). HP depressed fast synaptic transmission in a similar range of preparations. Single synapses of invertebrates (24-25,26) and synaptic potentials in the cerebellum (27), hippocampus (13), and dentate gyrus (12) showed this effect. Figure 1 schematically illustrates the behavior of a neuron of the corticohippocampal region receiving excitatory synaptic inputs under normal and HP conditions. (Fig. 1).

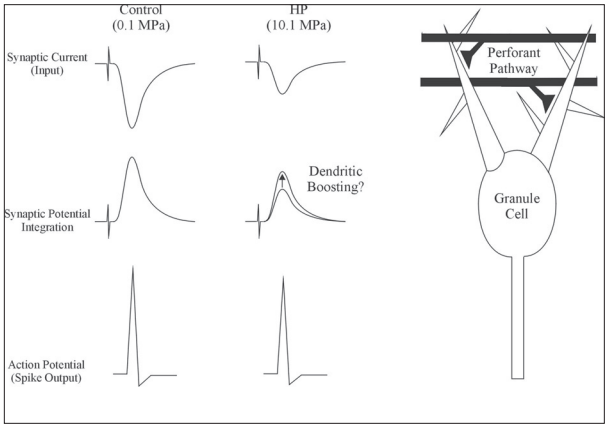

Fig. 1. High pressure effects on excitatory synaptic transmission, neuronal integration and antidromically induced action potentials. Note that in contrast with reduction of excitatory synaptic inputs and antidromic action potentials neuronal ability to fire an action potential in response to a reduced excitatory synaptic input is enhanced at HP.

As can be seen, the amplitude and kinetics of a single action potential, and in particular the kinetics and amplitude of synaptic currents and potentials, are depressed at HP. Nevertheless, the ability to elicit an action potential in response to a synaptic input was enhanced in the granule cells (GC) of the dentate gyrus (14) and at pyramidal neurons of the hippocampal CA1 area (13). However, this apparent increased neuronal excitability does not necessarily imply hyperexcitability at the system level. The output of these neurons at HP was actually maintained during orthodromic synaptic activation, or even reduced by approximately 30 % in somatic action potentials evoked by antidromic stimulation of the axons (14). Thus, this increase in gain should not be mistaken for absolute hyperexcitability and may well be an adaptive mechanism compensating for HP induced synaptic depression.

Increased gain seems to occur at the dendrites or soma of the postsynaptic neuron. It is presumably the consequence of a relative reduction in the efficacy of synaptic inhibition (14) and suggests increased activity (28) or slowing of the kinetics of the NMDA receptors at glutamatergic synapses (29). However, such increased postsynaptic gain may induce at the system level true hyperexcitability (true HPNS) under certain conditions of frequency activation.

In corticohippocampal areas this increased gain compensates relatively well for the reduction of synaptic inputs, for single and short trains of stimuli at low frequency (< 25 Hz), But, at higher frequencies it seems to be over-compensating , inducing additional spike firing. The mechanism for this frequency dependence seems to derive from the characteristic circuit hardwiring of inhibitory inputs and by the reduction of axonal conduction velocity. Central circuits, like the corticohippocampal connection use narrow temporal windows for

information transfer. Contiguous areas like the entorhinal and the dentate gyrus are connected by excitatory inputs. The dentate gyrus modulates cortical inputs that may cross to the CA3 and CA1 areas of the hippocampus. This gate normally functions as a low pass filter. Incoming suprathreshold inputs elicit spikes at the GCs, and these action potentials activate recurrent inhibition in parallel with the transfer of signals to the CA3 area (Fig. 2).

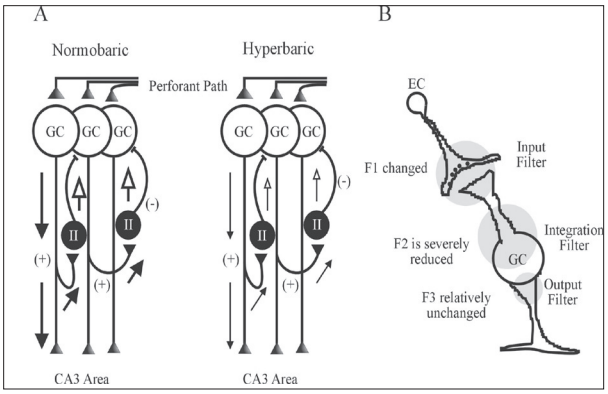

Fig. 2. HP modulation of the temporal window for firing coupling at the corticohippocampal circuitry. A: Schematic presentation of the corticohippocampal connection: GC, granule cells of the dentate gyrus; II, recurrent inhibitory interneurons. Thinner arrows (at HP) represents relatively slower conduction velocity and reduced synaptic release at excitatory (black) and inhibitory (hollow) pathway. B: Relative HP changes at different critical areas of the circuit (filters); EC, spiny stellate neuron of the entorhinal cortex generating the perforant path.

Thus recurrent inhibition prolongs the 'refractory period' of the GC determining the duration of the time window for repetitive firing. This interval is quite long in low-pass filtering. If inhibitory synaptic input is reduced (14,30) and conduction velocity of axons of the GC and of the inhibitory interneuron is diminished, activation of inhibition is weaker and delayed and therefore allows the GC to fire at higher frequencies. This alters the low pass filter properties of the DG at HP. For this area (and presumably at the CA1) hyperexcitability, at a cellular level, seems to serve as an adaptive response. However, as stated above, the system also is too responsive to high frequency stimulation. This may induce systemic hyperexcitability, as reported in HPNS.

PRESSURE VERSUS COMPRESSION RATE AS DETERMINANTS OF HPNS AND PRESSURE ADAPTATION

Adaptation to HP seems to take time. High compression rates may produce not only temperature perturbations or direct pressure effects but also may influence the development of HP adaptation. Changes in temperature/ pressure conditions obviously change the state of matter. However, if these changes are too fast, matter may not change its state as expected but adopt a metastable phase. For instance, cooling under 273^{o} K (0 ^{o} C) under normal conditions leads to crystallization of water and the formation of regular ice (ice-I). However, if water is cooled rapidly, the rate of cooling may exceed that of crystallization. If cooling continues beyond the temperatures allowing crystallization, water will remain liquid (supercooled) under its regular freezing point and will not solidify again (glass formation; amorphous structure). A similar phenomenon has been described during compression of phospholipid monolayers that keep liquid-glass in a metastable composition under rapid compression-expansion (supercompressed membranes) exerted by pressures relevant for the normal respiratory system (31).

Adaptation to HP may require a specific organization of biological material i.e.membranes. It is difficult to deduce this from the experiments on the respiratory system by Hall et al. (Fig. 3**)** on the actual compression rates that may be involved with HP adaptation. However, if conceptually correct, we postulate that compression rates may determine the state of membranes, which evolves either into

adaptation or HPNS. Further research may reveal the compression rates allowing efficient adaptation.

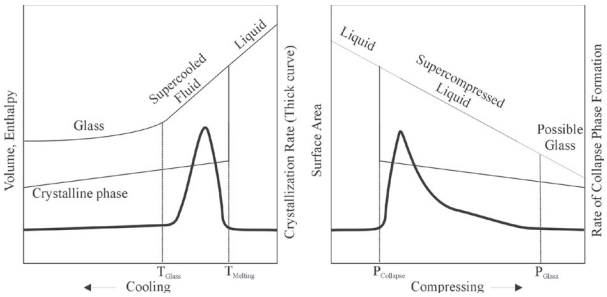

Fig. 3. Comparison between state transitions during supercooling of liquids and supercompression of phospholipids (Modified after HB Hall et al; [i]). A: Change of state during cooling. The thick line and right axis show the rate of crystallization. If cooling is faster than crystallization the substance becomes a glass. B: Postulated changes of state during compression of monolayers. The thick line and right axis represent the rate of collapse phase formation. Depending on compression rate membranes may either adopt the collapse phase, or turn progressively into more viscous liquids and potentially become glasses.

Recent studies on HP adaptation also imply that environmental conditions may influence the performance and comfort of deep divers. Our research suggests that, devices or conditions producing oscillations at the high biological range (>25 Hz) may induce, at high pressure, an aversive resonance response at the CNS. A possible example of this phenomenon is the effect of naval sonar on deep diving cetaceans. Sonar pinging seemly induces an exaggerated startle response and loss of coordination at HP producing rapid ascent, 'decompression sickness', and stranding of these animals (32). Therefore, it is suggested that special attention should be put in preventing sensory inputs at those frequencies produced by devices such as fluorescent tubes, computers or television screens, noise or sonar activity in deep waters or in the pressure chamber. Further research may shed light on compression rates and compression media allowing optimal HP adaptation.

REFERENCES

1. Brauer RW, Dimov S, Fructus X, Fructus P, Gosset A, Naquet R. Neurologic and encephalographic syndrome of hyperbarism. *Rev Neurol* (Paris) 1969; 121:264-5.
2. Bennett PB, Rostain JC. The high pressure nervous syndrome. In: Brubakk AO, Neuman TS, eds. The physiology andedicine of diving (5th Edition) Philadelphia: Saunders Elsevier Science Ltd, 2003: 323-357.
3. Jain KK. High-pressure neurological syndrome (HPNS). *Acta Neurol Scand* 1994; 90:45-50.
4. Berghage TE, Lash LE, Braithwaite WR, Thalmann ED. Intentional tremor on a helium-oxygen chamber dive to 49.5 ATA. *Undersea Biomed Res* 1975; 2: 215-22.
5. 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.
6. Tarasiuk A, Grossman Y. High pressure modifies respiratory activity in isolated rat brain stem-spinal cord. *J Appl Physiol* 1991; 71:537-45.
7. 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.
8. 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.
9. Rostain JC, Gardette-Chauffour MC, Gourret JP, Naquet R. Sleep disturbances in man during different compression profiles up to 62 bars in helium-oxygen mixture. *Electroencephalogr Clin Neurophysiol*. 1988; 69:127-35.
10. 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.
11. Burnet H, Lenoir P, Jammes Y. Changes in respiratory muscle activity in conscious cats during experimental dives at 101 ATA. *J Appl Physiol* 1992; 73:465-72.
2. 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.
3. Fagni L, Zinebi F, Hugon M. Evoked potential changes in rat hippocampal slices under helium pressure. *Exp Brain Res* 1987; 65:513-9.
4. Talpalar AE, Grossman Y. Enhanced excitability

compensates for high-pressure-induced depression of cortical inputs to the hippocampus. *J Neurophysiol* 2004; 92:3309-19.

5. Cromer JA, Hunter WL Jr, Bennett PB. Alteration of high pressure nervous syndrome in rats by alteration of colonic temperature. *Undersea Biomed Res* 1976; 3:139-50.
6. 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.
7. Brauer RW, Dutcher JA, Hinson W, Vorus WS. Effect of habituation to subanesthetic N2 or N2O levels on pressure and anesthesia tolerance. *J Appl Physiol* 1987; 62:421-8.
8. Piantadosi CA, Thalmann ED, Spaur WH. Metabolic response to respiratory heat loss-induced core cooling. *J Appl Physiol* 1981; 50:829-34.
9. Pfeiler E. Effects of Hydrostatic Pressure on Na+-K+-ATPase and Mg++-ATPase in Gills of Marine Teleost Fish. *J Exper Zool* 1978; 205: 393-401.
20. Theron M, Guerrero F, Sebert P. Improvement in the efficiency of oxidative phosphorylation in the freshwater eel acclimated to 10.1 MPa hydrostatic pressure. *J Exp Biol* 2000; 203:3019-23.
2. Vettier A, Sebert P. Pressure resistance of aerobic metabolism in eels from different water environments. *Mitochondrion* 2004; 3:347-54.
22. Heinemann SH, Conti F, Stuhmer W, Neher E. Effects of hydrostatic pressure on membrane processes: Sodium channels, calcium channels, and exocytosis. *J Gen Physiol* 1987; 90:765-78.
23. Grossman Y, Kendig JJ. Pressure and temperature: time-dependent modulation of membrane properties in a bifurcating axon. *J Neurophysiol* 1984; 52:693-708.
24. Parmentier JL, Shrivastav BB, Bennett PB. Hydrostatic pressure reduces synaptic efficiency by inhibiting transmitter release. *Undersea Biomed Res* 1981; 8:175-83.
25. Grossman Y, Kendig JJ. Synaptic integrative properties at hyperbaric pressure. *J Neurophysiol* 1988; 60:1497-512.
26. Golan H, Colton JS, Moore HJ, and Grossman Y. Analysis of evoked and spontaneous quantal release at high pressure in crustacean excitatory synapses. *Pfluegers Arch* 1995; 430:617–625.
27. 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.
28. Zinebi F, Fagni L, Hugon M. Excitatory and inhibitory amino-acidergic determinants of the pressure induced neuronal hyperexcitability in rat hippocampal slices. *Undersea Biomed Res* 1990; 17:487-493.
29. Mor A, Grossman Y. Pressure modulation of isolated glutamate NMDA synaptic response in mammalian central nervous system. *Euro J Underwater Hyperbar Med* 2004; 5:101-103.
30. Zinebi F, Fagni L, Hugon M. Decrease in recurrent and feed-forward inhibitions under high pressure of helium in rat hippocampal slices. *Eur J Pharmacol* 1988; 153:191-199.
31. Smith EC, Crane JM, Laderas TG, Hall SB. Metastability of a supercompressed fluid monolayer. *Biophys J* 2003; 85:3048-57.
32. Talpalar AE, Grossman Y. Sonar versus whales: noise may disrupt neural activity in deep-diving cetaceans. *Undersea Hyperb Med* 2005; 32:135-9.
33. Hall SB et al. http://www.ohsu.edu/research/sbh/results.html