

Recent neurochemical basis of inert gas narcosis and pressure effects.

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Rostain J.C., Balon N. Recent neurochemical basis of inert gas narcosis and pressure effects. *Undersea Hyperb Med* 2006; 33(3):197-204. Compressed air or a nitrogen-oxygen mixture produces from 0.3MPa nitrogen narcosis. The traditional view was that anaesthesia or narcosis occurs when the volume of a hydrophobic site is caused to expand beyond a critical amount by the absorption of molecules of a narcotic gas. The observation of the pressure reversal effect on general anaesthesia has for a long time supported the lipid theory. However, recently, protein theories are in increasing consideration since results have been interpreted as evidence for a direct anaesthetic-protein interaction. The question is to know whether inert gases act by binding processes on proteins of neurotransmitter receptors. Compression with breathing mixtures where nitrogen is replaced by helium which has a low narcotic potency induces from 1MPa, the high pressure nervous syndrome which is related to neurochemical disturbances including changes of the amino-acid and monoamine neurotransmissions. The use of narcotic gas (nitrogen or hydrogen) added to a helium-oxygen mixture, reduced some symptoms of the HPNS but also had some effects due to an additional effect of the narcotic potency of the gas. The researches performed at the level of basal ganglia of the rat brain and particularly the nigro-striatal pathway involved in the control of the motor, locomotor and cognitive functions, disrupted by narcosis or pressure, have indicated that GABAergic neurotransmission is implicated via GABA_A receptors.

INTRODUCTION

All mammals including man exposed to increasing pressure of breathing gas mixtures show disturbances at the level of the central nervous system, which differ according to which gas is used. In Man, compressed air or compressed nitrogen-oxygen mixtures produce from 0.3 MPa, nitrogen narcosis (1). When nitrogen is replaced by a gas less narcotic than nitrogen such as helium, the breathing mixture induces from 1 MPa the High Pressure Nervous Syndrome (HPNS) (2).

INERT GAS NARCOSIS

1 - Nitrogen narcosis

When men are exposed to pressures of

air higher than 0.3 MPa, they exhibit the signs and symptoms shown in Table I.

NITROGEN NARCOSIS IN MAN
Temporo - spatial disorientation
Memory troubles
Euphoria
Hallucinations
Mood changes
Impaired neuromuscular coordination
Psychomotor and intellectual decrements

Table 1. Signs and symptoms of nitrogen narcosis in man from 0.3MPa (3 bars, 4 ATA).

When laboratory animals are exposed to compressed air or to increased pressures of nitrogen-oxygen, they also present signs and

symptoms of a narcotic type for pressure higher than 0.8 to 1 MPa. Behnke et al. (3) have related the phenomenon to the narcotic potency of nitrogen that is 79% of air. Similar signs and symptoms have been observed by inert gases other than nitrogen but they vary according to the narcotic potency of the gas. From the numerous attempts that have been made to correlate the narcotic potency of helium, neon, argon, krypton and xenon to physical properties it seems that the most satisfactory correlation, is afforded by lipid solubility (Table 2).

Gas	Molecular weight	Solubility in lipid	Rank (narcotic potency)
			Least narcotic
He	4	0.015	1
Ne	20	0.019	2
H ₂	2	0.036	3
N ₂	28	0.067	4
A	40	0.14	5
Kr	83.7	0.43	6
Xe	131.3	1.7	7
			Most narcotic

Table 2. Molecular weight and lipid solubility of inert gases and their rank from the least narcotic to the most narcotic.

According to the lipid solubility hypothesis, three gases are more narcotic than nitrogen: xenon is anaesthetic at atmospheric pressure (4, 5, 6, 7, 8), krypton causes dizziness (4, 6) and argon will be narcotic about twice the pressure of nitrogen (1, 9). Three other gases are less narcotic than nitrogen. These are hydrogen which would be between two to three times less narcotic than nitrogen (10), neon which would be at least three times less narcotic than nitrogen (11, 12) and last, helium which is the least narcotic.

2 - Pressure effects and helium narcosis

Based on the lipid solubility hypothesis, the narcotic effect of helium would occur around 400 m (1). However, pressure counteracts this weak narcotic potency according to the pressure reversal effect and the critical volume hypothesis

(13). The symptoms that occur are different from those observed in narcosis and they are called the High Pressure Nervous Syndrome (HPNS). The HPNS includes behavioural symptoms and electrophysiological changes which are described in Table 3. It is generally considered that helium is not narcotic.

**HIGH PRESSURE NERVOUS SYNDROME IN MAN
HELIUM - OXYGEN
up to 6.1MPa**

BEHAVIORAL SYMPTOMS	ELECTROPHYSIOLOGICAL CHANGES
TREMOR FASCICULATIONS, MYOCLONIA DYSMETRIA SOMNOLENCE COGNITIVE IMPAIREMENTS up to -20%	EEG: INCREASE IN SLOW WAVES, DECREASE IN FAST ACTIVITIES CHANGES IN EVOKED POTENTIALS, IN CORTICAL EXCITABILITY CYCLE SLEEP: INCREASE IN STAGES 1 and 2 DECREASE IN STAGES 3 and 4, REM HYPER-REFLEXIA

Table 3. Signs and symptoms of HPNS up to 6.1 Mpa (610 msw) with helium-oxygen-mixture.

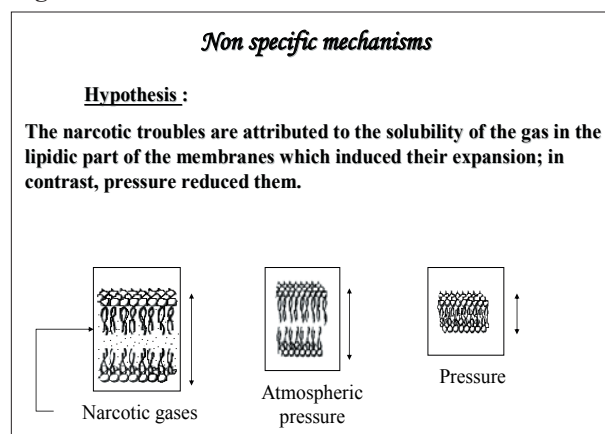
However, from recent data obtained during experimental dives with narcotic gases added to helium at great pressure (14, 15), there were mood changes or sensory hallucinations reported in some cases in helium-oxygen dives to pressure greater than 4 MPa (400m), which could be due to a narcotic effect of helium rather than a pressure effect (16, 17). Moreover, hallucinatory behaviour has been also reported in monkeys breathing a helium-oxygen mixture at pressures of 8 MPa and above (18, 19, 20), which could be due to the narcotic effect of helium at high pressure (20).

Origins and Mechanisms of Inert Gas Narcosis

Comparatively little is known about the cause and mechanisms of the signs and symptoms produce by inert gas breathing at pressure. Although the carbon dioxide theory has been eliminated as the cause, the lipid theory has provided several hypotheses as to the possible mechanisms of inert gas narcosis. From the works of Behnke et al. (3),

the nitrogen and inert gas theory suggested that there is a parallel between the affinity of a narcotic or anaesthetic gas for lipid and its narcotic potency. Consequently the traditional view was that anaesthetics dissolve in the lipid bilayer of the cellular membrane and expand its volume. Anaesthesia then occurs when the volume of a hydrophobic site is caused to expand beyond a critical amount by the absorption of molecules of a narcotic gas; if the volume of this site is restored by increasing pressure, then the anaesthesia will be removed (Fig. 1). The observation of this pressure reversal effect on general anaesthesia (13) that has been reported for different anaesthetics including inert gases has supported the lipid theory.

Fig.1



This is the reason of the use of narcotic gases in a helium-oxygen mixture for deep diving such as nitrogen or hydrogen, to decrease the clinical symptoms of HPNS such as the tremor. With the helium-nitrogen-oxygen mixture, depths of 650 and 686 msw were reached (21, 22) and several dives were performed between 450 and 600 msw with a reduction of many HPNS symptoms (Table 4) (2, 23, 24, 25).

Hydrogen is another inert gas which has been considered and used for deep diving (26, 27, 28, 29, 30, 31, 32, 33), for several reasons. Hydrogen has a greater narcotic potency than

helium, which may in accordance with the critical volume hypothesis reduce some of the symptoms of HPNS. It has also a lower density than helium and thus could be better for breathing. Brauer and Way (33) have established that its narcotic potency is in agreement with its lipid solubility. It is, however, explosive in mixtures of more than 4% oxygen.

**HIGH PRESSURE NERVOUS SYNDROME
 HELIUM – NITROGEN - OXYGEN
 up to 4.5 MPa**

BEHAVIORAL SYMPTOMS	ELECTROPHYSIOLOGICAL CHANGES
SOMNOLENCE COGNITIVE IMPAIRMENTS around – 10%	EEG: INCREASE IN SLOW WAVES, DECREASE IN FAST ACTIVITIES CHANGES IN EVOKED POTENTIALS, IN CORTICAL EXCITABILITY CYCLE SLEEP: INCREASE IN STAGES 1 and 2 DECREASE IN STAGES 3 and 4, REM HYPER-REFLEXIA

Table 4. Effects of addition of nitrogen (5%) in the helium-oxygen-mixture on signs and symptoms of HPNS.

In the past, several groups have studied the effects of hydrogen at pressure in man and in animals (27, 33; 35, 36, 37). The results have been contradictory. However, Edel et al. (38) and Fife (39) suggested that the use of hydrogen in diving could be beneficial (2). In the last twenty years, COMEX has carried out several experiments with hydrogen in mice, rats, monkeys and men (40, 41). In human divers, significant narcotic sensations which were different from those reported with nitrogen, were reported from 240 metres, when breathing hydrogen oxygen mixtures.

Experiments performed in hydrogen-oxygen mixtures (HYDRA VII, IX) or in hydrogen-helium-oxygen mixtures (HYDRA V, VI, X) have shown narcotic effects of a psychotropic type which occur when the partial pressure of hydrogen is higher than 2.5 MPa. Indeed, psychotic like disorders have been observed in some subjects, which consisted of hallucinations, mood disturbances, agitation,

delirium and paranoid thoughts (42, 43). These results indicated that pressures of hydrogen higher than 2.4-2.5 MPa may induce narcosis and are consistent with the work of Brauer et al. (10) and Brauer and Way (33) which predicted hydrogen narcosis around 2.5 and 3.0 MPa. However, the use of helium-hydrogen-oxygen mixtures with a partial pressure of hydrogen which did not exceed 2.5 Mpa reduces the clinical symptoms of HPNS (Table 5) and a depth of 701 m has been reached using this mixture (17, 20).

**HIGH PRESSURE NERVOUS SYNDROME
HELIUM – HYDROGEN - OXYGEN
up to 4.5 MPa**

BEHAVIORAL SYMPTOMS	ELECTROPHYSIOLOGICAL CHANGES
COGNITIVE IMPAIREMENTS less than 5%	EKG: INCREASE IN SLOW WAVES, DECREASE IN FAST ACTIVITIES SLEEP: INCREASE IN STAGES 1 and 2 DECREASE IN STAGES 3 and 4, REM

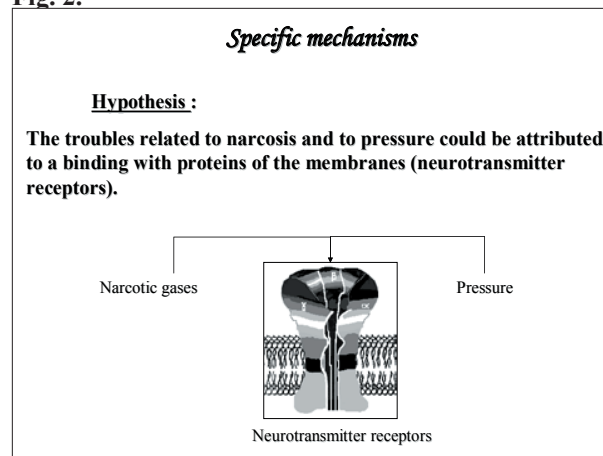
Table 5. Effects of addition of hydrogen (up to 2.5 MPa) in the helium-oxygen mixture on the signs and symptoms of HPNS.

The reduction or even the suppression of some clinical symptoms obtained by narcotic gases added to a helium-oxygen mixture supports the lipid theories. However there were also other effects recorded with some symptoms of HPNS which indicate that the lipid theory is insufficient to explain alone the effects of pressure and inert gases at pressure.

Recently, protein theories have been proposed due to results obtained from some experiments with inhalational anaesthetics which have been interpreted as evidence for a direct anaesthetic-protein interaction (44, 45, 46, 47). The question is whether inert gases do exert binding processes on proteins at raised pressure. Data obtained by Abraini et al. (48) with two inert gases (nitrogen and argon) and an anaesthetic gas (N₂O) seem to indicate that

inert gases bind directly to a modulatory site of a protein receptor and act as allosteric modulators. The results clearly showed whatever the inert gas used, the pressure required to produce a 100% loss of righting reflex increased significantly as the compression rate increased. The rate at which compression was applied influenced the anaesthetic potencies of these inert gases in a sigmoidal fashion rather than a linear fashion as the lipid theory would suggest. The sigmoidal curve indicates a gas-protein interaction. The gas could bind to modulatory sites of protein receptors, producing conformational changes and thereby make channel opening more or less favourable (Fig 2).

Fig. 2.



Recently, neurochemical studies have been carried out on the effect of inert gas narcosis at the level of the basal ganglia, and particularly at the level of the nigro-striatal pathway. These structures are implicated in the regulation of motor, locomotor and cognitive processes which are disrupted by inert gas narcosis and HPNS.

The studies performed by differential pulse voltametry at the level of the striatum with carbon multifiber electrodes have shown (49, 50, 51, 52):

1 - A decrease of dopamine when rats are exposed to increased pressures of nitrogen, argon, or to an anaesthetic gas such as the

nitrous oxide.

2 - An increase of dopamine when rats were exposed to helium pressure.

These results demonstrated, at least at the level of the striatal DA, an opposing effect of pressure and narcotic gases.

Other studies performed by microdialysis at the level of the striatum have shown in addition to an increase of dopamine with increasing pressure of helium, an increase of serotonin, glutamate, and aspartate but with different kinetics (53, 54, 55, 56, 57). The same studies performed with nitrogen have shown a decrease of dopamine and glutamate, an increase of serotonin and no change of the level of aspartate (58, 59, 60). Moreover, microdialysis and differential pulse voltametry studies have indicated that dopamine at the striatal level is also decreased when rats are exposed to increase pressures of argon (51, 52), and nitrous oxide (51, 52, 61, 62).

GABA neurotransmission is one of the processes implicated in these changes from the use of agonists of GABA_A or GABA_B receptors which have demonstrated changes when injected in the substantia nigra reticulata (SNr) or substantia nigra pars compacta (SNc) (63, 64, 65).

The injection of 1nM of muscimol (agonist GABA_A) in the SNr at atmospheric pressure did not induce changes in DA release in the striatum. In contrast, with helium oxygen pressure, the injection of the same dose of muscimol blocked the increase of DA induced by pressure (65, 66). At atmospheric pressure, the injection of 10 nM of baclofen (agonist GABA_B) in the SNr induced a 40% decrease of striatal DA release. With helium pressure, the decrease of DA release produced by baclofen persisted. The motor and locomotor hyperactivity (LMA) one of the HPNS symptoms in the rat, which is correlated to the change of striatal DA release, is reduced by the activation of the GABA_B receptor and increased by the activation of the

GABA_A receptors (65, 66).

Consequently, the activation of GABA_B receptors in the SNr decreased both dopamine and motor and locomotor hyperactivity by the inhibition of the nigro striatal pathway (NSP) and the thalamo cortical pathway and suggests the implication of these receptors in the regulation of the NSP and the development of LMA

The activation of GABA_A receptors inhibits directly the NSP and consequently produces a decrease of striatal dopamine but induces also a disinhibition of the nigro-thalamic pathway which induces an activation of the thalamo-cortical pathway and an activation of LMA. Consequently, helium pressure may act by the stimulation of GABA_A receptors of GABA neurons of the SNr which produces both a disinhibition of dopaminergic neurons of the nigro-striatal pathway and of glutamatergic neurones of the thalamo-cortical pathway which also induces an increase of striatal DA and of LMA.

CONCLUSION

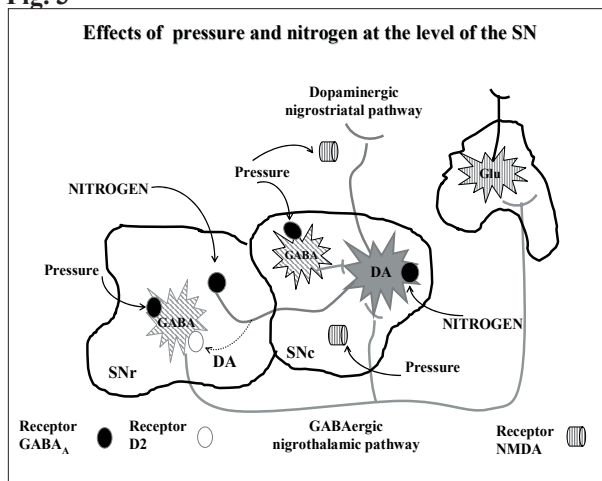
In conclusion at pressure, our results suggest a change in the sensibility of the GABA_A and GABA_B receptors in the SNr, and in the SNc, with a greater response by the GABA_A postsynaptic receptors on the GABAergic nigrothalamic pathway in the SNr and in the GABAergic interneurons of the SNc.

Alternatively, the similarity between the effects obtained with GABA injection (decrease of DA and LMA) and those obtained with nitrogen suggest that nitrogen acts directly on the GABA_A receptors of the dopaminergic neurons of the NSP and produces a decrease of DA and consequently of the motor and locomotor activities.

The results obtained with pressure and narcotic gases would be the consequence of a balance or an imbalance between the effects

of pressure on the GABAergic nigrothalamic pathway and the effects of narcotic gases on GABA_A receptors of the dopaminergic nigro striatal pathway. The opposing effects of pressure and narcotic gases on GABA_A receptors could be due to different receptor subunit compositions (Fig 3).

Fig. 3



These recent results at the neurochemical level give new indications on the development of inert gas narcosis and of the high pressure nervous syndrome. The disruption of GABA neurotransmission is one of the aspects of the mechanisms implicated in these symptoms and serotonin or glutamate neurotransmission with NMDA receptors (Fig 3). Other systems which could play a role in the occurrence of inert gas narcosis from microdialysis studies have indicated changes in their release at the level of striatum and that studies on HPNS have indicated a potentiation of NMDA receptors (55, 56, 57, 67).

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