A review of recent neurochemical data on inert gas narcosis

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ABSTRACT

Nitrogen narcosis occurs in humans at around 0.4 MPa (4 ATA). Hydrogen narcosis occurs between 2.6 and 3.0 MPa. In rats, nitrogen disturbances occur from 1 MPa and a loss of righting reflex around 4 MPa. Neurochemical studies in striatum of rats with nitrogen at 3 MPa (75% of anesthesia threshold) with differential pulse voltammetry have demonstrated a decrease in dopamine (DA) release by neurons originated from the substantia nigra pars compacta (SNc). Such a decrease is found also with compressed argon, which is more narcotic than nitrogen and with the anesthetic gas nitrous oxide. Inversely, compressed helium with its very low narcotic potency induces DA increase. Microdialysis studies in the striatum have indicated that nitrogen also induces a decrease of glutamate concentration. Nitrogen pressure did not modify NMDA glutamate receptor activities in SNc or striatum but enhanced $GABA_A$ receptors activities in SNc.

Repetitive exposures to nitrogen narcosis suppressed the DA decrease and induced an increase. This fact and the lack of improvement of motor disturbances did not support the hypothesis of a physiological adaptation. The desensitization of the $GABA_A$ receptors on DA cells during recurrent exposures and the parallel long-lasting decrease of glutamate coupled to the increase in NMDA receptor sensitivity suggest a nitrogen neurotoxicity or addiction induced by recurrent exposures.

The differential changes produced by inert gases in different neurotransmitter receptors would support the binding protein theory. ■

Inert gas narcosis

Compressed air or a compressed nitrogen-oxygen breathing mixture at absolute pressures above 0.4 MPa (4 ATA) in humans produces disturbances at the level of the central nervous system (CNS). These disturbances are called nitrogen narcosis, since the work of Behnke *et al*. [1] has related the phenomenon to the narcotic potency of nitrogen that composes 79% of the air and has suggested a correlation between its lipid solubility and its narcotic potency. Indeed, this work established that the symptoms observed with compressed air were a particular manifestation of a general phenomena induced by the inert gases with a partial pressure specific to each gas, depending on their narcotic potency correlated to their lipid solubility [for review see 2].

According to their lipid solubility, three gases are expected to be more narcotic than nitrogen: Xenon is the most narcotic, as it is anesthetic at atmospheric pressure [3,4,5,6,7]; krypton will have a narcotic potency five to six times higher than nitrogen [3,5]; and argon will be twice as narcotic as nitrogen [8]. Three other gases are less narcotic than nitrogen: hydrogen, which will be between two to three times less narcotic than nitrogen [9]; neon, ≠which will be at least three times less narcotic than nitrogen; and helium, which is the least narcotic.

Three inert gases have been extensively studied in man: nitrogen, helium and hydrogen.

Nitrogen narcosis

Nitrogen narcosis occurs in man at around 0.4 MPa and includes spatial and temporal disorientation, euphoria, hallucinations, disruption in motor and locomotor coordination, mood changes and cognitive impairments. A loss of consciousness is obtained for pressures higher than 1.1 MPa. Nitrogen narcosis is reported in all mammals exposed to increased partial pressures

of nitrogen but for higher pressure. In rats, nitrogen induces disturbances from 1 MPa and a loss of righting reflex around 4 MPa [see 2 for review].

Helium narcosis

Helium has a low narcotic potency and is commonly considered as not narcotic. Theoretically, on the basis of lipid solubility, the narcotic effect of helium would occur around 4 MPa [2]. However, the pressure reversal effect [10] counteracts this weak narcotic potency, and the nervous disturbances that occur from 10 bars are different from those observed in narcosis; they are called high pressure nervous syndrome (HPNS) [11,12,13]. Mood changes or sensory hallucinations reported in some cases in helium-oxygen dives during compression or stay for pressure greater than 4 MPa bars could be a narcotic effect of helium rather than a pressure effect [16,17]. Indeed, during dives with narcotic gases added to helium to reduce the HPNS symptoms, narcotic symptoms have been reported from 3 MPa either in nitrogen-helium-oxygen mixtures with nitrogen partial pressures higher than 0.3 MPa, or in hydrogen-helium-oxygen mixtures with hydrogen partial pressures higher than 2.5 MPa [14,15]. Some of them were analogous to those described with helium above 4 MPa and were more intense due to the presence of gas with narcotic potency higher than helium. Moreover, hallucinatory behaviors have been reported in monkeys in helium-oxygen mixtures for pressures of 8 MPa bars and above [18,19,20], which could be due to a narcotic effect of helium at high pressure [20]. Consequently, such symptoms could be the expression of the narcotic potency of gas in addition to the pressure effect that occurred when the partial pressure of gas is too high to be counterbalanced by the pressure effect.

Hydrogen narcosis

Hydrogen is another inert gas that has been considered and used for deep diving [21,22,23,24,25,26,27,28]. Hydrogen has a lower density than helium and thus would be better for breathing mechanisms. Its narcotic potency is greater than helium, which may, in accordance with the critical volume hypothesis, reduce some of the symptoms of HPNS. It is, however, explosive in mixtures of more than 4% oxygen, and works carried out by Brauer and Way [29] have established that its narcotic potency would be in agreement with its lipid solubility.

Significant narcotic sensations (different from those reported with nitrogen) of the psychotropic type have been reported in man for pressures between 2.6 and 3 MPa when breathing a hydrogen-oxygen mixture. The hydrogen narcosis was characterized by sensory and somesthetic hallucinations, mood changes, agitation, delirium and paranoid thoughts [15,26,30,31].

Neurochemical studies of inert gas narcosis

To explain the narcotic potency of inert gases, the lipid theory was suggested from the works of Benhke *et al*. [1], based on the Meyer-Overton hypothesis [32,33]. The nitrogen and inert gas theory suggests that there is a parallel between the solubility of a narcotic or anesthetic gas for lipid and its narcotic potency. Consequently the traditional view was that anesthetics dissolve in the lipid bilayer of the cellular membrane and expand its volume. Anesthesia occurs when the volume of a hydrophobic site is expanded 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 anesthesia will be removed. The observation of the pressure reversal effect on general anesthesia [10] that has been reported for different anesthetics including inert gases, has for a long time supported the lipid theory.

However, Franks and Leib [34] and Simon *et al.* [35] report that at anesthetic concentrations there is no significant increase in membrane thickness. Moreover, the critical volume hypothesis suggest that the anesthetics act on the same molecular site, but the works of Halsey *et al.* [36] have suggested a multisite expansion theory.

Some experiments have suggested a "binding mechanism" in which inert gases are bound to specific sites within protein molecules [37,38,39,40,41,42]. Recently, the protein theory has gained increasing support since results obtained from experiments with inhalational anesthetics have been interpreted as evidence for a direct anesthetic-protein interaction [43,44,45,46].

The question is whether inert gases at raised pressures interact by binding processes with proteins. Data obtained by Abraini *et al*. [47], with two inert gases (nitrogen and argon) and one anesthetic gas (nitrous oxide) seem to indicate that inert gases bind directly to a modulatory site of protein receptors and act as allosteric modulators. The results clearly shown that whatever the inert gas used, the pressure of narcotic required to produce 100% loss of righting reflex was elevated significantly as compression rate increased. The rate at which compression was applied influenced the anesthetic potencies of these inert gases and anesthetic gas in a sigmoidal fashion rather than a linear fashion. These findings indicate that inert gas could bind to a modulatory site of protein receptors, producing conformational changes that may impede

FIGURE 1

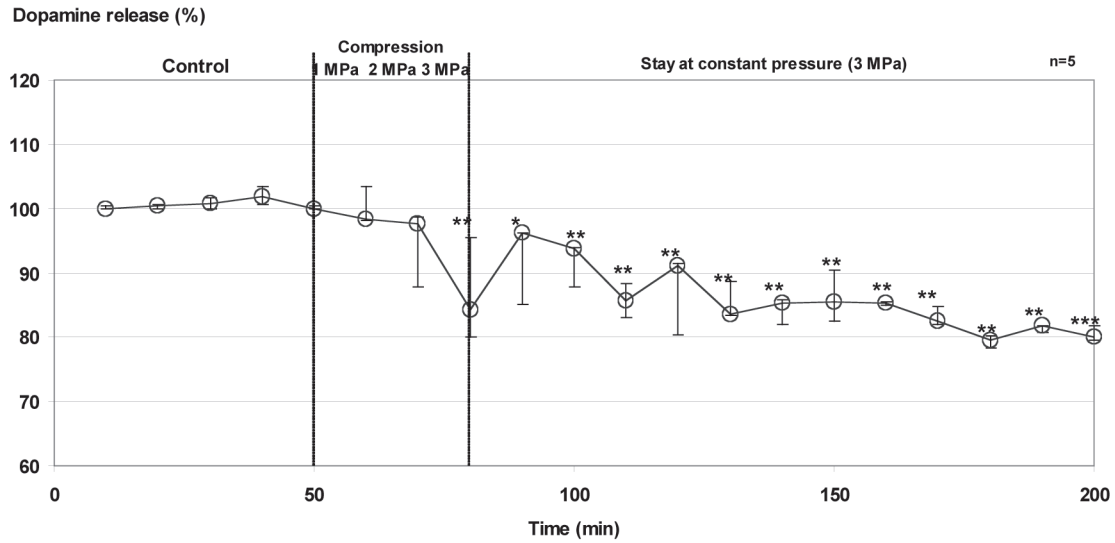

FIGURE 1 – Development of striatal dopamine level recorded by differential pulse voltammetry during exposure of rats to 3 MPa of nitrogen-oxygen pressure (Pp O2 = 40 kPa). Data are presented as median and 25-75 percentiles. (U Mann Whitney test * P<0.5, ** P< 0.2, *** P<0.001).

binding or channel opening. Since lipid theory predicts a linear antagonism as a result of a physical imbalance between the high compressibility of the cellular membrane and the solubility of the inert gas in the lipid, these findings indicate a gas-protein interaction rather than a gas-lipid interaction.

Neurochemical studies of striatal dopamine level

Neurochemical studies have been carried out with differential pulse voltammetry or microdialysis technique on the effects of inert gas narcosis at the basal ganglia structures and, particularly, the nigro-striatal pathway, both of which are implicated in the regulation of motor, locomotor and cognitive processes. These functions are disrupted by inert gas narcosis. The striatum and the substantia nigra are regulated by glutamate excitatory neurotransmission and gamma amino butyric acid (GABA) inhibitory neurotransmission. Thus, the nigro-striatal pathway, which is responsible for the dopamine levels in the striatum, is under a well-balanced control of excitatory and inhibitory neurotransmission.

The interest was to measure the dopamine level in the striatum as an index of the changes induced by pressure and gas mixtures. For this purpose, differential pulse voltammetry that allows measuring the dopamine level in a central nervous structure by oxidation has been used; the current given by this reaction is proportional to the quantity of molecules oxidized, and therefore the amplitude of the peak is related to the dopamine level [48,49].

When rats are exposed to 3 MPa of nitrogen, a decrease in dopamine concentration is recorded in the striatum *(Figure 1, above)*. Similar decreases in dopamine concentration are also recorded with 2 MPa of argon, or with 0.08 MPa of nitrous oxide an anaesthetic gas at atmospheric pressure [50,51,52] *(Figure 2, Page 52)*. A similar decrease in dopamine at the extracellular level has been also reported with nitrogen-oxygen mixtures or nitrous oxide using the microdialysis technique [53]. Behavioral studies showed an associated decrease in motor and locomotor activity [54] and vigilance tasks using a special Skinner box [55,56]. Moreover, microdialysis studies have also indicated that exposure to nitrogen pressure induced a decrease in glutamate and a transient increase in serotonin in addition to the striatal dopamine decrease. No change was recorded for aspartic acid *(Figure 3, Page 53)* [57].

In contrast, with increasing pressure of helium, differential pulse voltammetry indicated that striatal dopamine level is increased *(Figure 2)* [49, 58, 59]. Besides the dopamine increase, microdialysis studies have shown an increase in serotonin and glutamate [60,61]. These studies

FIGURE 2

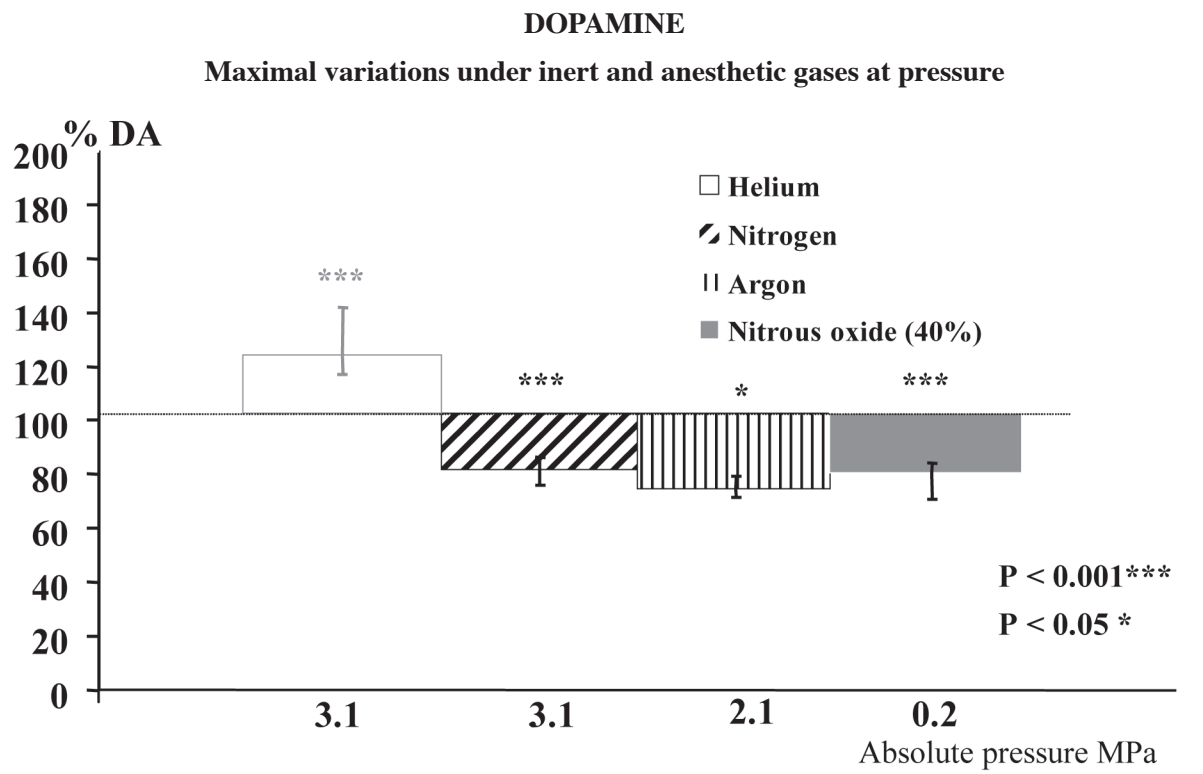

FIGURE 2 – Median values and 25-75 percentile of dopamine level in the striatum of rat exposed to 3.1 MPa (31 ATA) of helium-oxygen mixture, or nitrogen-oxygen mixture, 2.1 MPa (21 ATA) of argon-oxygen mixture (PpO_2 = 40 kPa) and to nitrous oxide at 0.2 MPa (2 ATA) (80 kPa of N_2O).

demonstrated, at least at the level of dopamine and glutamate release in the striatum, the opposite effect of pressure (probably HPNS) and narcotic gases. Thus, the nitrogen-induced decrease of dopamine and glutamate levels is attributed to a narcotic effect rather than to an effect of pressure *per se*.

The GABA neurotransmission could be implicated in these changes. We know that general anesthetics, including inhalational agents, have been shown to enhance $GABA_A$ receptor activities [45,62,63]. Moreover, the administration of $GABA_A$ antagonist resulted in an increase of the onset pressure of argon required to produce 100% loss of righting reflex in rats [64]. Consequently, the narcotic gas could affect GABA and, reciprocally, glutamate neurotransmission.

The nigro-striatal pathway is under the control of excitatory glutamatergic afferents from the prefrontal cortex or thalamus to the striatum [65] and subthalamic nucleus to the substantia nigra, acting on NMDA receptors located on dopaminergic (DA) neurons [66,67]. This was demonstrated by the increased activity of dopaminergic neurons [68] and by the enhanced striatal DA release [69,70] when NMDA is administered in the substantia nigra pars compacta (SNc) or in the striatum [71,72]. In addition, most afferents in SNc are GABAergic [73] and mediate an inhibitory control on the nigro-striatal pathway preferentially through $GABA_A$ receptors [74] localized on DA neurons [75].

Studies performed with microdialysis in the rat striatum have shown, at atmospheric pressure (0.1 MPa), that NMDA infusion by retrodialysis in the striatum increased extracellular glutamate levels by up to 720% compared to baseline from the beginning to the end of the experiment *(Figure 4, Page 54)*. Similar NMDA infusion also increased extracellular dopamine levels by up to 990% compared to baseline, from the beginning to the end of the experiment *(Figure 5, Page 55)*. Nitrogen at 3 MPa with NMDA retrodialysis infusion induced no changes of extracellular glutamate levels compared to baseline from the compression stage to the end of the 3 MPa

FIGURE 3

Effects of nitrogen on extracellular level of dopamine, serotonin, glutamate and aspartate in rat

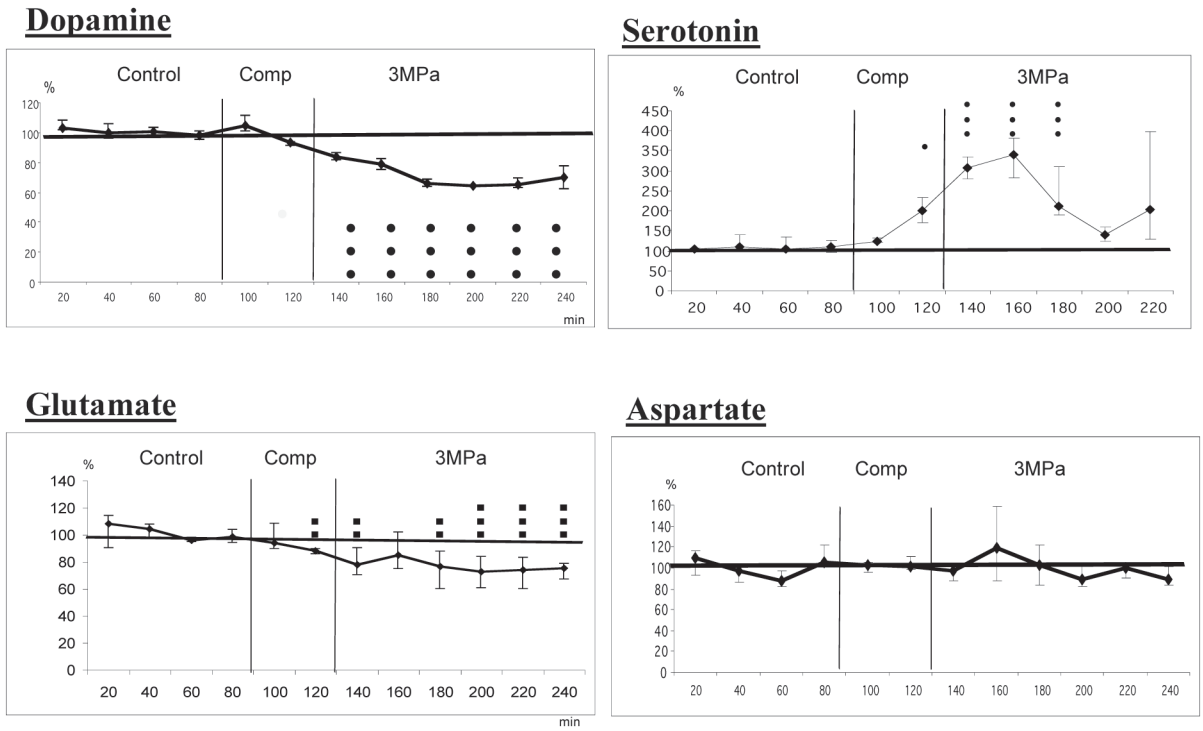

FIGURE 3 – Development of dopamine, glutamate, serotonin and aspartate levels recorded by microdialysis in the striatum of rats exposed to 3 MPa of nitrogen-oxygen pressure.
(U-Mann Whitney test • $P<0.05$; •• $P<0.2$; ••• $P<0.001$).

period *(Figure 4)*. No significant difference was found between the nitrogen exposure group and the nitrogen plus NMDA group. In contrast, with nitrogen at 3 MPa and NMDA retrodialysis infusion, extracellular dopamine levels increased compared to baseline up to 850% during the maximal pressure period *(Figure 5)*. No significant difference has been revealed in the developments of dopamine ratio between groups submitted to striatal NMDA retrodialysis infusion under nitrogen pressure or at atmospheric conditions.

These results indicated that the increase of dopamine induced by infusion of NMDA in the striatum is not suppressed by nitrogen pressure. Thus, these data indicated that NMDA receptors in the striatum are not disturbed by nitrogen narcosis. However, the increase of glutamate release induced by infusion of NMDA in the striatum is suppressed by nitrogen pressure [75]. This result suggests that nitrogen narcosis induces some disturbances at the level of the glutamatergic thalamo-striatal pathway and that the release of glutamate could be reduced by activation of GABA neurotransmission by nitrogen narcosis.

The substantia nigra is under the control of GABA neurotransmission and also of glutamate neurotransmission. To determine the role of these two neurotransmissions in the nitrogen increase striatal DA level, studies have been performed in rat bioinstrumented with guide cannula in the SNc for drug injections and multi-fiber carbon electrodes in the striatum to recorded dopamine release.

The injection of NMDA in the SNc suppressed the decrease of dopamine in the striatum induced by

FIGURE 4

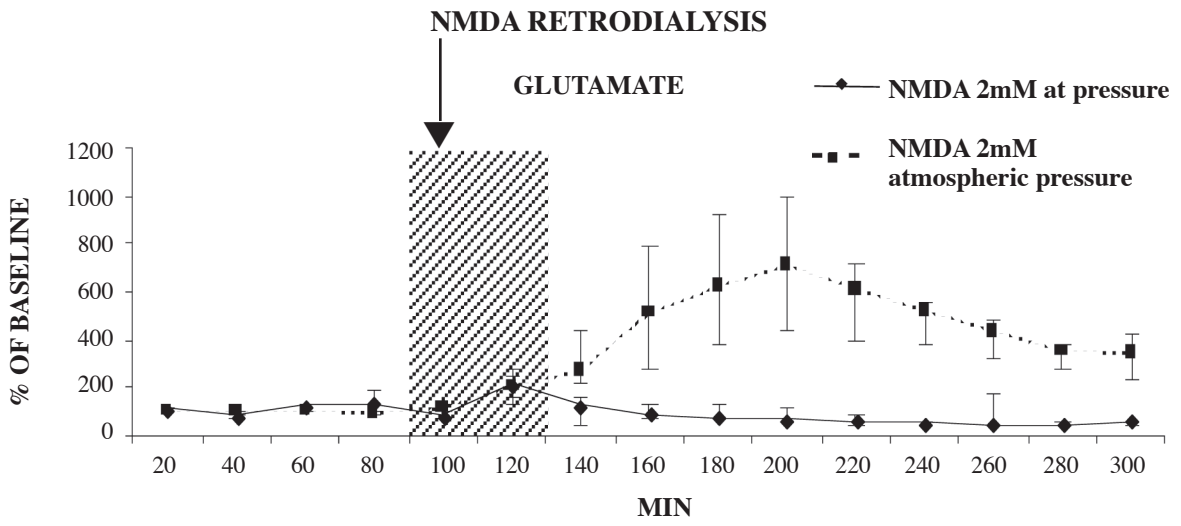

FIGURE 4 – Increase of striatal glutamate levels during retrodialysis of NMDA at atmospheric pressure and during nitrogen – oxygen exposure at 3 MPa. Mann Whitney U test: increase of glutamate at 0.1 MPa (n=4) P<0,001; increase of glutamate at 3 MPa (n=5) P<0.018. P<0.001 between the two expositions.

nitrogen pressure. Moreover, the injection of NMDA in the SNc never suppressed the decrease of dopamine levels induced by nitrous oxide.

These two results demonstrated that the mechanisms involved in the decrease of DA are different according to the gas used: Nitrous oxide is an antagonist of NMDA receptors and nitrogen has no action on this receptor. As at the level of the striatum, GABA receptors in the SNc could be involved in the decrease of striatal DA. The effects of an antagonist of $GABA_A$ receptor on DA cells (Gabazine) and of an agonist of $GABA_A$ receptors on GABAergic interneurons (Muscimol) have been studied at the level of the SNc.

At atmospheric pressure, activation of $GABA_A$ receptors induces a large increase of DA concentration. Blockade of $GABA_A$ receptors induce a low-level increase of DA. These results demonstrated a direct and an indirect GABAergic control in SNc on the striatal DA level through $GABA_A$ receptors located both on dopaminergic neurons and on GABAergic interneurons [51,52].

With nitrogen pressure, the agonist of the $GABA_A$ receptor (Muscimol) suppressed the decrease of DA levels, and the antagonist of the $GABA_A$ receptor increased the level of DA considerably .

Based on these results, we conclude that the nitrogen-induced decrease of DA (-20%) is due to a facilitation of GABAergic input to dopaminergic pathway via sensitization of $GABA_A$ receptors [52,76].

These neuropharmacological studies carried out at the level of the nigro-striatal pathway indicate that 3 MPa of nitrogen did not change the activity of $GABA_A$ receptors on interneurons and of NMDA receptors on DA neurons but induce a potentiation of $GABA_A$ receptors on DA cells in the SNc *(Table 1, facing page)*

Another aspect of nitrogen narcosis is the repetitive exposures to nitrogen at pressure. Adaptation to nitrogen narcosis was subjectively reported by humans. However, some studies in humans failed to detect an improvement of motor disturbances, following five successive exposures to a relative pressure of 0.55 MPa [77].

Recently, Lavoute *et al*. [51] have shown that repetitive exposures to pressure inducing nitrogen narcosis changed the release of striatal dopamine in rats. The first nitrogen exposure at 3 MPa led to a significant decrease of the striatal extracellular level of dopamine by up to -20%, as previously observed in voltammetric or microdialysis studies *(Figure 2)* [50,78]. Successive exposures at 1 MPa of nitrogen modified the dopaminergic neurotransmission in the striatum. The DA level

FIGURE 5

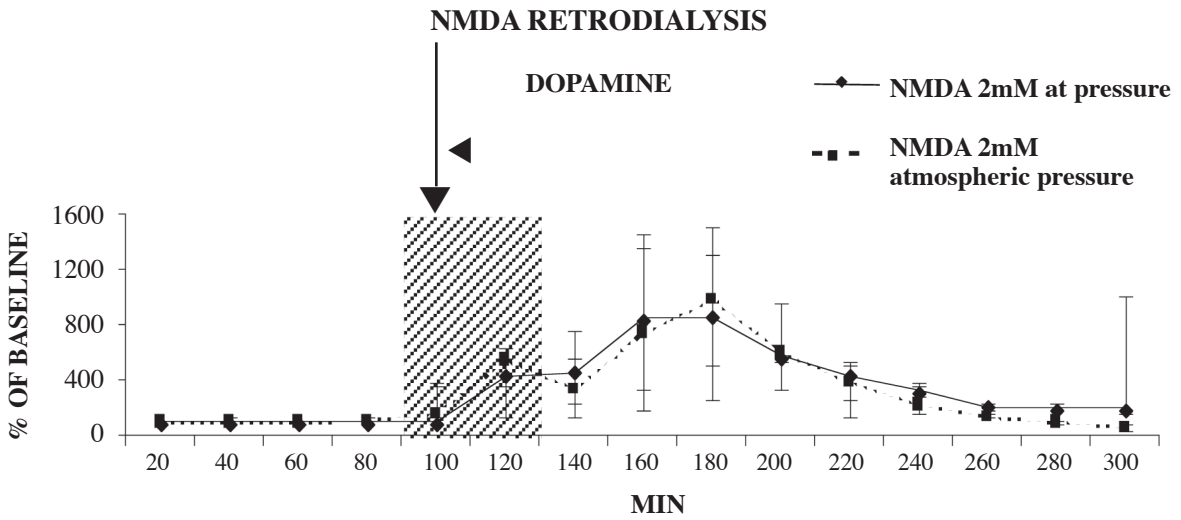

FIGURE 5 – Increase of striatal dopamine levels during retrodialysis of NMDA at atmospheric pressure and during nitrogen – oxygen exposure at 3 MPa. Mann Whitney U test: increase of dopamine at 0.1 MPa (n=6) P<0.001; increase of dopamine at 3 MPa (n=5) P<0.001. P<0.415 between the two expositions.

did not return to basal value but was increased by +15%. This fact and the lack of improvement of motor disturbances do not support the hypothesis of a physiological adaptation and suggest an eventual neurotoxicity. This possible neurotoxicity has been studied through the activities of excitatory and inhibitory pathways of the central nervous system particularly via NMDA and $GABA_A$ receptors [79,80]. The results obtained with agonist or antagonists of NMDA and $GABA_A$ receptors indicate that repetitive nitrogen exposure induces a decrease in the activity of the dopaminergic pathway, reflecting increased GABAergic neurotransmission linked to alteration of $GABA_A$ receptors. These findings demonstrate a parallel long-lasting decrease of glutamate release coupled to an increase in NMDA receptor sensitivity [79]. Consequently, repetitive exposure to nitrogen narcosis modifies the neurochemical activities compared to a single exposure. These results call for further investigations of repetitive exposure in order to discover the mechanisms implicated in the changes and to determine whether nitrogen neurotoxicity or nitrogen addiction induced by recurrent exposures do exist.

TABLE 1 - Nitrogen at 3 MPa

NMDA Receptors (SNc, striatum)	**normal**
$GABA_A$ (Da cells in SNc)	**potentiated**
$GABA_A$ (interneurons in SNc)	**normal**

from Lavoute C. Ph.D. Thesis 2007

TABLE 1 – Changes in NMDA and $GABA_A$ receptors activities during a first exposition to 3 MPa of nitrogen-oxygen pressure (PpO_2 = 40 kPa).

Protein crystallography under xenon and nitrous oxide

According to the lipid theory, the inert gas expands the lipid bilayer and disrupts the ionic current. In contrast, the protein theory suggests binding between the gas and a protein of the membrane or receptors.

Xenon (Xe) and nitrous oxide (N_2O) act by blocking the NMDA receptor. The binding characteristics of these two gases were examined, using X-ray crystallography, on two soluble proteins as structural models [81]: urate oxidase, which is a prototype of a variety of intracellular globular proteins, and annexin V, which has structural

and functional characteristics that allow it to be considered as a prototype for the NMDA receptor.

One N_2O molecule or one Xe atom binds to the same main site in both proteins. The gas-binding sites are always hydrophobic flexible cavities buried within the monomer. Comparison of the effects of Xe and N_2O on urate oxidase and annexin V reveals an interesting relationship with the *in vivo* pharmacological effects of these gases.

Based on these data, Colloc'h *et al*. [81] hypothesized a step-by-step mechanism of inhaled anesthetic action in which the graded dose-response effect would depend on cavity size and order of filling. Xe and N_2O would first bind to brain intracellular proteins possessing large hydrophobic cavities, which constitute easy targets for inhalational anesthetics, thereby disrupting the activity of these proteins in a manner sufficient to induce moderate neuronal dysfunctions and leading to the early stages of anesthesia (amnesia and hypnosis). If gas concentration rises, the smaller hydrophobic gas-binding cavities within the NMDA receptor would then begin to be filled, thereby disrupting the receptor function and leading to surgical anesthesia (deep sedation and lack of autonomic and motor responses to noxious stimuli).

Similar step-by-step mechanisms of general anesthesia, which assume a causal link between the behavioral effects of anesthesia, from amnesia and hypnosis to ''surgical anesthesia'' and the progressive occupation of the anesthetic binding sites from globular proteins to ion channel receptors, may occur for other types of inhaled anesthetics or narcotic gases and/or ion channel receptors, such as the $GABA_A$ receptor, which is thought to be the molecular target of most volatile anesthetics.

As the binding sites between molecules of the gas and protein are hydrophobic cavities, a link could be made between the membrane theory and the protein theory; and such mechanisms may also explain a number of critical exceptions to the Meyer-Overton rule.

In conclusion, the recent neurochemical studies carried out at the level of the nigro-striatal pathway in the basal ganglia have indicated that compressed nitrogen is a "co-agonist" of the $GABA_A$ receptors. It decreases the glutamate release without change of NMDA receptor activities, in contrast to nitrous oxide, which is an antagonist of NMDA receptors. These results support the protein binding theory. Moreover, repetitive exposures to nitrogen narcosis modify these changes in a way suggesting nitrogen addiction.

More studies are need to determine the mechanisms implicated in the glutamate decrease, the origin of the changes induced by recurrent exposures to nitrogen narcosis and the involvement of similar mechanisms at the level of other central nervous system structures that could be implicated in the development of nitrogen narcosis.

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