Can the dopaminergic-related effects of general anesthetics be linked to mechanisms involved in drug abuse and addiction?

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General anesthetics (GA) are well known for the ability to induce a state of reversible loss of consciousness and unresponsiveness to painful stimuli. However, evidence from animal models and clinical studies show that GA exposure may induce behavioral changes beyond acute effects. Most research and concerns are focused on changes in cognition and memory. We will look at effects of GA on behavior that is mediated by the dopaminergic system. Pharmacological resemblance of GA with drugs of abuse, and the complexity and importance of dopaminergic systems in both reward seeking and addictive illnesses make us believe that it deserves an overview about what is already known and what matters to us as healthcare workers and specifically as anesthesiologists. A review of available evidence strongly suggests that there may be a link between the effects of GA on the brain and substance abuse, partly explained by their influence on the dopaminergic system.

Editorial comment: what this article tells us
This review article points out that general anesthesia may induce behavioral changes mediated via the dopaminergic system, and that some of the same mechanisms may be involved in substance abuse and reward seeking behavior.

Development of new drugs and technics in anesthesia was of paramount importance to the revolution of modern medicine. The pursuit of the ultimate perioperative homeostatic balance and increased awareness of safety issues allowed us to achieve lower levels of morbidity and mortality as standard of care.[1]

We have used GA regularly since 1846, but we have not been able to build a complete theory that unifies both the molecular effects and the behavioral response of loss and gain of consciousness. The first theory (Meyer–Overton correlation) stated that lipid solubility of GA was responsible for their anesthetic effects.[2] When

such a generalistic statement failed to explain how GA work, then the paradigm moved looking for specific molecular targets. The discovery that GA could interact with the firefly luciferase enzyme directed research toward proteic targets.[3] Today, we know that GA target neurotransmitter receptors in the whole brain, inducing fast modulation of membrane potentials and neuronal cell firing, as well as slower modulation of second messenger cascades and protein synthesis compounds that are responsible for fast behavioral changes involving arousal, memory, nociception and fear. Additionally, research has shown us that exposure to GA can also be responsible for changes that are not so short-lived.

Reports of temporary cognitive impairment and long-term neurodevelopmental impairment in animal models of anesthetic exposure[4–6] as well as clinical reports of decline in cognitive performance after surgery/anesthesia in humans[7,8] brought an old question to the spotlight: can GA exposure change the way we subsequently behave? Now we know that factors such as surgical procedure together with individual factors influence patient cognitive outcome[9,10] and that exposure to GA alone has not been proven to be responsible for cognitive impairment in humans, even in groups thought to be particularly susceptible such as children.[11] Most research is focused on cognitive processes, but one particular clinical study, the ISPOCD, reported both higher risk of prematurely leaving labor market and of dependence on social transfer payments in patients who developed postoperative cognitive dysfunction,[12] suggesting that impairment may extend beyond cognition. Do GA exert a more subtle influence on us, not necessarily through a decline in cognition? To answer this particular questions, we will focus our discussion on other dimensions of behavior. The molecular resemblance of GA with drugs of abuse and the misuse of GA for recreational purposes[13] raise concerns about the possible role of GA as agents that induce changes in motivational behavior. From all the neurotransmitters that are targeted by GA, dopamine (DA) is the most important in motivational and reward circuitries, with a strong role in conditioning behaviors. In this review, we will focus on the possible link between the effects of GA and drug abuse and how these mechanisms may help explain some of the potential effects of GA on the brain.

Understanding the role of dopamine

DA is a catecholaminergic neurotransmitter present both in the central nervous system and in several other tissues such as the cardiovascular and digestive systems. DA is synthesized by the hydroxylation of the amino acid L-tyrosine to L-DOPA by tyrosine hydroxylase (TH) which is further converted to DA by DOPA decarboxylase (or aromatic L-amino acid decarboxylase). DA is stored in vesicles in the presynaptic terminal by the action of vesicular monoamine transporter. DA release from dopaminergic neurons into the synaptic cleft is achieved either through a calcium-dependent exocytic process similar to other neurotransmitters or through membrane DA transporter (DAT). Once in the synaptic cleft, DA binds to and activates DA receptors (DAR). According to their biochemical and pharmacological properties, the receptors can be divided into two subtype families: D1-like receptor subfamily that includes the D1 and D5 receptors, and the D2-like receptor subfamily comprising the D2, D3, and D4 receptors.[14] The turnover of extracellular DA involves both degradation by two main enzymes: monoamine oxidase and catechol-O-methyltransferase and reuptake by DAT, all critical elements in DA homeostasis.[15,16]

Dopaminergic neurotransmission plays a critical role in processes such as learning, memory, motivation, reward, risk assessment and locomotion.[17–19] Conditions that challenge DA balance may impair these functions. In the brain, we can find higher content in production areas like *pars compacta* of the *substantia nigra* (SN) and the ventral tegmental area (VTA). From these, dopaminergic pathways project to the nucleus accumbens (NAc), the frontal cortex (FC), and the striatum (Str).

Parkinson's disease (PD) is a DA-related pathology in which there is a state of low DA levels in SN, characterized by several motor coordination and involuntary movement disorders. PD treatment is based on the use of DA precursors such as Levodopa (L-DA) and DA

agonists. Importantly, several reports show that the prolonged use of these drugs in PD patients is related to an increase in compulsive gambling/shopping/eating behavior, hypersexuality, and hyperphagia disorders.[20]

Changes in brain DA content induce behavioral modifications, but how does this knowledge correlate with the anesthesia field?

Occupational addiction in anesthesia

Substance abuse in health professionals[21] is a known problem. The literature about this subject shows that occupational hazards do not translate in an increase in mortality of anesthesiologists compared either with other specialties or general population[22,23]; however, there seem to be an increased risk of substance abuse and suicide.[24,25]

The pharmacokinetic of short-acting drugs such as propofol, remifentanil, and volatile anesthetics make them virtually impossible to trace in routine testing, and unless the health worker is caught consuming or stealing, only testing all health workers for drugs of abuse would give us the real picture.

The anesthesiologist faces professional challenges such as exposure to stressful situations and work overload that can lead to isolation, burnout,[26] and depression.[27] Physicians under these conditions may, therefore, develop maladaptative strategies that lead to substance abuse.[28] Stress is a known trigger of changes in brain reward circuits[29] that may enhance the reinforcing properties of drugs. GA have pharmacological similarities to drugs of abuse: reports show characteristics of high psychological dependence such as relapse, strong cravings, and continuous auto-administration irrespective of negative consequences.[30] On the top of the most misused drugs, we can find opioids and intravenous anesthetics, benzodiazepines, and lastly volatile anesthetics. There is also speculation that environmental exposure to GA can induce changes that in a certain way could lead to the development of addictive traits.[31] The fact that healthcare professionals exposed to stressful environments also have easy access to drugs with abuse and misuse potential turn this issue not an institutional problem but a public health one.

May general anesthetics be involved in development of addiction?

Several drugs used during anesthetic procedures have a direct effect on the dopaminergic system. The most well-known and studied substances that induce DA changes and addiction are opioids, but we will focus specifically on GA. Acute exposure to most GA produces a mixture of sensations described as feeling drunk, confusion, sedation, and loss of concentration capacity. It can also induce psychadelic-like effects such as dissociation, hallucinations, and distortions in perception of reality. Volatile anesthetics are chemically similar to solvent agents often used as recreational drugs and produce similar behavioral effects.[32,33] It is impossible to talk about anesthetics and DA without recalling the origins of anesthesia: the first two substances used as anesthetics, nitrous oxide and ether, were used recreationally even before being introduced in medical practice as stated in historical reports describing "laughing gas parties".[34] In human studies,[35–38] subanesthetic doses of sevoflurane, nitrous oxide, propofol, and ketamine all correlated with liking and were rated as something the subject "will try again"; they also produced dose-related reinforcement and abuse-related subjective effects. Ketamine is a well-known club drug, and users display riskier behavior.[39] The effects of GA exposure in behavior of animal models have also been studied and correlates with behavioral changes similar to drugs of abuse such as anxiety and craving. Nitrous oxide is known to induce anxiolysis in animal models, and the effect is reversed by the benzodiazepine antagonist flumazenil.[40] These reports suggest that exposure to GA can induce addictive behaviors both in animal models and in humans.

The impact of general anesthetics on brain dopamine

As above mentioned, GA act in the whole brain: they modify neuronal system, the release and reuptake of neurotransmitters, and the way neurons respond to them. The sum of all these effects represents the behavioral endpoint of GA action: loss of consciousness, immobility, and amnesia. DA is believed to contribute to GA

effects as the amount of dopaminergic activity influences the amount of GA needed to induce anesthesia.[41] On the other end, the depletion of brain DA can induce a state of immobility.[42]

We will now make considerations on the modulation of DA in brain by different anesthetic agents. Most of the data are based in microdialysis studies where samples of brain intersticial fluid are sampled during exposure to GA alone or with DA modulators in translational research using rodent and primates.

Halotane

Exposure to halothane in high doses increases extracellular DA levels in Str[43–45] and potentiate the dopaminergic action of other drugs.[46,47] The level of dopaminergic metabolites is also increased indicating a higher turnover. The use of lower anesthetic doses fail to increase DA levels; however, DA metabolites still increase. So, there seems to be a complex dose-related response, but there is always some effect. In the NAc, there is also an increase in DA.[48] So evidence show that halothane seems to induce DA availability in areas that play an important role in DA driven behavior.

Isoflurane

Isoflurane anesthesia also induces a dose-dependent increase in Str DA[49–51] with lower doses failing to show changes in brain DA but producing changes in metabolites.

Nitrous oxide

The use of this volatile NMDA antagonist induced a slight DA increase in NAc and a decrease or no effect in Str.[52,53]

Xenon

Use of xenon failed to change DA levels in NAc. There are no works regarding other brain areas.[54]

Ketamine

In animal models, the NMDA antagonist seems to have almost no effect in DA levels when used in low dosages, but higher subanesthetic and anesthetic dosages increase DA in Str, NAc and FC.[55–58] This effect is also seen in human in vivo imaging studies that report an increase in striatal DA release after an acute challenge with ketamine.[59] But when the exposure is repeated, there is a reduction in FC dopaminergic function with impairment in working memory and executive functions.[60]

Pentobarbital

Pentobarbital induces decreases DA in the NAc, producing a state of ataxia in rodents. It also inhibits the effect of L-DOPA in extracellular DA increase.[50] Like other GAs, when given in lower doses does not change DA levels.[58]

Propofol

Propofol at lower subanesthetic dosages decreases DA NAc content while more clinically relevant higher subanesthetic and anesthetic dosages of propofol increase NAc DA levels.[61] Propofol also has the ability to induce expression of DeltaFosB in NAc, a protein whose expression is also increased by drugs of abuse.[62] Additionally, propofol exposure decreases DA levels in Str and in FC.[63]

Measurements of dopaminergic activity either in DA production, degradation, and reuptake can be used to assess dopaminergic pathways. DA is degraded into 3,4-Dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). In rodents, DOPAC is the major metabolite and DOPAC accumulation provides an indicator of dopaminergic neurons activity, while the DOPAC:DA ratio is an indication of DA turnover. In Str, DA metabolite levels are increased by halothane, isoflurane, sevoflurane, and propofol exposure.[44–46,64] In the NAc, they are increased after exposure to isoflurane,[65] sevoflurane, and propofol. In addition, DAT seems to be inhibited by most GAs. In fact, studies show that halothane, isoflurane, propofol, ketamine, ethomidate, and thiopental inhibit specific synaptosomal uptake of DA in a concentration-dependent manner in rat brain.[41,66,67] The overall effect of exposure to GA is a dose-dependent increase in DA and its metabolites during acute exposure.

What are the implications of changed DA levels induced by GA?

We will now focus the effect of GA in brain areas relevant to DA-driven behavior. Striatal influence of GA seems to be "agent" and "dose-specific", but there is no doubt that GA have an impact on Str DA release. The Str serves as the entry point for cortical and thalamic inputs into basal ganglia circuitry. The release of DA in Str during reward learning tasks is known to be an important modulator of acquisition of habit or goal-directed tasks. Disorders that affect DA such as PD, Huntington's disease, and substance abuse produce impairments in these processes. Exposure to GA specifically halothane, isoflurane, and ketamine have the potential to impair those functions through changes in Str DA.[43–47,49–51,55]

The NAc is believed to participate in many functions that have been shown to be important in reward learning tasks.[68] Most drugs of abuse are known to produce an increase in DA levels at the NAc, in a manner similar to propofol, ketamine, and halothane.[48,52,57]

Dopaminergic activity in the prefrontal cortex (PFC) plays an important role in cognitive functions. DA depletion in PFC impairs working memory performance tasks in primates[69,70] and the use of DA agonists improves performance in animals with poor working memory.[71,72] Both human and animal studies suggest that repeated exposure to noncompetitive NMDA antagonists reduces PFC dopaminergic function with impairment in working memory and executive function.[73,74] We can speculate that while acute exposure to GA with NMDA antagonist activity induces increase in PFC DA, continuous exposure is prone to decrease PFC DA and impair working memory and executive function performance which is the pattern found in chronic users. Chronic exposure to GA, such as repeated anesthetic procedures, theoretically can induce the same changes. Such as stated earlier, there are concerns of a similar mechanism responsible for development of addiction in susceptible individuals subjected to environmental exposure.

To summarize, increase in DA metabolites suggests that most GA induce higher DA levels and turnover in several brain regions, especially in the Str and in the NAc. Activation of these particular areas is a hallmark pattern of several drugs that induce addiction and impair DA driven behavior.

Conclusion

Review of the literature suggests that general anesthesia modulates the dopaminergic pathways. Behavioral data both in human and animal models support the possible development of an addictive trait in subjects exposed to GA. Some of the molecular features of drugs of abuse concerning DA are also found in GA such as DA release and availability in areas such as NAc and Str. It is likely that all behavior functions that rely on dopaminergic transmission can be potentially impaired after GA exposure. Changes in reward system and memory formation potentially may impair cognitive abilities such as reasoning, language comprehension, planning, and spatial processing. Several clinical trials show that surgery and anesthesia may cause "postoperative cognitive dysfunction" and changes in dopaminergic brain systems may contribute to this phenomenon. However, we still do not know how much it impacts on our behavior. The potential to play with reward mechanism, decision-making processes and cognitive performance impose a need for judicious use of GA. Further research is needed to answer all these questions and provide both even better standard of care to our patients and less occupational hazards to healthcare workers.

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