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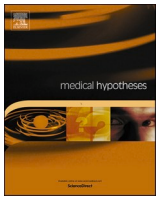

Is adiponectin deficiency a critical factor for sevoflurane induced neurocognitive dysfunction?

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ABSTRACT

The global rise in obesity has resulted in an increase in the number of surgical procedures under general anaesthesia in this patient population. Sevoflurane is one of the most widely used volatile aesthetic agent in developed countries. Clinical evidence suggests obesity is a risk factor for cognitive dysfunction after surgery. Experimentally animals with pre-existing cerebral insults are more susceptible to the neurotoxic effects of sevoflurane compared with their normal counterparts. Nevertheless, the mechanism underlying this vulnerability in obese subjects is not fully elucidated.

Obesity is associated with a significant reduction of adiponectin, an adipocyte-derived molecule with neurotrophic and anti-inflammatory properties. Adiponectin receptors are abundantly expressed in hippocampus and cortex. Moreover, adiponectin deficiency is associated with exacerbation of neuroinflammation, neuronal dysfunction and cognitive impairment in animal models of obesity and Alzheimer's disease. Based on these observations, we hypothesize that adiponectin deficiency plays a critical role in sevoflurane induced cognitive dysfunction in obese subjects accounting for its higher incidence in this patient population. With diminished protective effects from adiponectin, sevoflurane may further exacerbate neuroinflammation by activating the proinflammatory pathways and increase the synthesis of inflammatory cytokines in the brain, leading to significant neuronal dysfunction and cognitive impairment. On the other hand, treatment with adiponectin or adiponectin receptor agonists may have therapeutic potential in minimizing the risk of postoperative cognitive impairment in obese patients undergoing surgery. As an oral adiponectin agonist is available, it can be expeditiously evaluated in clinical trials if our hypothesis is validated.

Introduction

Obesity is a major public health concern worldwide, and its prevalence is increasing in developed countries. Patients with obesity often develop metabolic syndrome with hyperglycaemia, hyperinsulinemia, dyslipidaemia, as well as conditions that require surgical treatments such as osteoarthritis and certain cancers [1]. They are also more prone to postoperative complications, including wound infections, respiratory compromise, and perioperative neurocognitive disorders (PNDs) [2]. PNDs can occur commonly in the postoperative period, with approximately half of certain patient groups experiencing cognitive dysfunction during the first month of hospitalization following surgery [3]. With both obesity and the demand for surgery in this patient group rising, PNDs are becoming more concerning for perioperative health providers. General anaesthesia is frequently required for the types of surgery in this patient population, and sevoflurane is one of the most commonly used agent in developed countries due to its fast onset, elimination, and recovery [4].

While general anaesthesia is necessary for surgery, it can also pose potential risks to cognitive function, and the neurotoxicity of

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sevoflurane has been a subject of long-standing evaluation. In previous reports, it has been shown to have minimal impact or even neuroprotective effects in some models [5–7]. However, recent data have revealed that subjects with certain underlying medical conditions such as diabetes or pre-existing cognitive impairment are more susceptible to develop neuroinflammation and cognitive dysfunction after sevoflurane exposure [2,8,9]. Therefore, it is worthwhile when considering the effect of sevoflurane on the brain to qualify the specific context of exposure. For example, during pregnancy maternal exposure of sevoflurane disrupts oligodendrocyte myelination in the postnatal hippocampus and induce neurological disorders in offspring in mice [10], impairs the learning and memory function via NLRP3 related inflammasome activation [11] and induces neurotoxicity in via CDK5 induced tau phosphorylation [12] in offspring of rats. On the other end of the spectrum where PNDs occurs more commonly sevoflurane inhibits histone acetylation and induce cognitive dysfunction/synaptic deficit through CEBP/ANP32A overexpression [13] and inhibits adult hippocampal neurogenesis and trigger cognitive impairment through BDNF and Neurotrophin-3 (NT-3) pathway [14] in aged mice. In experimental Alzheimer's disease (AD) models (3xTg mice) mimicking subjects with pre-existing cognitive impairment, sevoflurane induces neuroinflammation, glutamate excitotoxicity and apoptosis in AD but not in wild type mice [9] and activates the pyroptotic cell death program via NLRP3 activation and exacerbate the progression of AD [15].

Adipose tissue is no longer considered merely as a storage organ for triglycerides as evidence has been accumulating over the past decades regarding its biological and biochemical activities. More recently adipose tissue has been deemed as an important endocrine organ regulating metabolic activities in other organs via the release of adipokines, ie., cytokines from adipose tissues [16]. Adipokines have major roles in metabolic regulation, especially on the regulating insulin sensitivity in different organs [17]. Examples of adipokines include TNF-alpha, leptin, resistin, interleukin-6 and adiponectin and dysregulation of these substances lead to severe metabolic diseases [17].

Obesity is characterized by excessive accumulation of adipose tissues that in turn may become dysfunctional thus affecting their communication with the brain, muscles, and liver [18–20]. It is also associated with the reduction of circulating adiponectin [17], one of the most abundant adipokines, accounting for about 0.01 % of total serum proteins in humans and 0.05 % in rodents [21]. Adiponectin is a key element of central and peripheral signalling for lipid metabolism, energy regulation, insulin sensitivity, immune function, and inflammatory responses. Apart from being a metabolic regulator, adiponectin possesses neurotrophic and anti-inflammatory properties [22]. From previous population-based studies in regions such as the United Arab Emirates and China, a positive correlation was observed between increased visceral fat and decreased circulating plasma adiponectin levels in obese subjects [23,24]. It has been suggested that the low-grade systemic inflammation that often accompanies obesity may be linked to adiponectin deficiency [25]. Chronic reduction in adiponectin is frequently observed in obese patients, contributing to the pathogenesis of different obesity-related diseases.

A reduction in adiponectin also has an impact on the central nervous system (CNS) and can lead to brain aging and cognitive impairment. Animals with reduced adiponectin demonstrate exaggerated mitochondrial dysfunction and immunosenescence [26]. Circulating adiponectin can pass through the blood–brain barrier and bind to adiponectin receptors in the brain [27]. Adiponectin can bind to adipoR1 in the ventral tegmental area, regulating anxiety-related behaviour [28] and to adipoR2 in the hippocampus to facilitate contextual fear extinction [29]. Upon adiponectin binding, the adaptor protein APPL1 is stimulated and activates AMP-activated protein kinase (AMPK), which is a mediator for the anti-inflammatory effect of adiponectin [30]. Adiponectin can also enhance glucose metabolism in hippocampal neurons [31], in which a reduction of adiponectin receptor sensitivity [32] and glucose utilization are seen in subjects with cognitive impairment. Interestingly adiponectin/adiponectin receptor signalling prevents mitochondrial dysfunction and oxidative injury in the animal model of traumatic brain injury [33].

In addition, there is strong evidence for the neuroprotective effect of adiponectin in both *in vitro* and *in vivo* models. Adiponectin participates in neurogenesis and neural stem cell proliferation [34]. It improves CNS function by enhancing insulin sensitivity [35], regulating glucose utilization [31], and reducing neuronal apoptosis [36]. Moreover, a previous report demonstrated that 18-month-old mice with adiponectin deficiency showed Alzheimer's disease-like neuropathology, significant cognitive impairment, and neuroinflammation in the brain [35]. Adiponectin deficiency also exaggerates sepsis-induced microvascular dysfunction in murine brains [37]. Another report further revealed that adiponectin suppresses β-amyloid-induced neuroinflammation in microglia, which is dependent on the adiponectin-AMPK pathway [38]. These data support adiponectin as a promising target for improving cognitive impairment. Although there is still no clinical evidence linking adiponectin and sevoflurane-induced cognitive dysfunction, clinical reports revealed that decreased adiponectin levels are seen in the patients after hip replacement surgery [39]. A preliminary report further indicated that adiponectin treatment may also attenuate isoflurane neurotoxicity in rats [40]. In general, the role of adiponectin in sevoflurane or surgery-related cognitive dysfunction is still unknown, and little data evaluating the potential role of adiponectin involved in this cognitive dysfunction are available.

Hypothesis

Adiponectin deficiency is not only a common hallmark of metabolic disorders, but also an antecedent to the development of neuroinflammation and neuronal dysfunction [34], and the level of adiponectin is inversely correlated with the degree of obesity [22]. In view of this and the above observations we hypothesized that adiponectin dysregulation may contribute to the increased susceptibility of obese patients to sevoflurane induced cognitive dysfunction. Sevoflurane triggers the activation of proinflammatory pathways such as JNK or NF-kB pathways and increase the synthesis of inflammatory cytokines in the brain which may lead to synaptic and neuronal dysfunction and finally to cognitive dysfunction. In normal subjects, this phenomenon can be attenuated by the actions of adiponectin. However, in obese subjects with adiponectin deficiency, the neuroprotective effect of adiponectin is diminished and thus increase the susceptibility of the brain to neuroinflammation, neuronal dysfunction and subsequent cognitive impairment. The summary figure of proposed hypothesis is illustrated in Fig. 1.

Evaluation of the hypothesis

Accumulating data suggest adiponectin and adiponectin receptor play prominent roles in the evolution of CNS conditions in obese subjects. It has been shown extensively that sevoflurane induces neurotoxic effects and lead to cognitive deterioration in various animal models including aged rats [41], pre-existing cognitive impairment [9] and metabolic disorders [8]. Obesity is a metabolic disorder characterized by the reduction of adiponectin. Given that obese subjects are more vulnerable to postoperative complications [2] and the neuroprotective characteristics of adiponectin, it is reasonable to speculate that adiponectin deficiency plays an important role in sevoflurane induced cognitive dysfunction in obese subjects.

To assess the validity of this hypothesis, an experimental design of animal work is required. We have established an obese animal model in which C57 mice are fed with high fat diet for 2–3 months according to the previous reports [42]. We will first fully characterize the effect of sevoflurane exposure in these obese animals including the neuroinflammatory response, synaptic function, and cognitive changes. To confirm the role of adiponectin deficiency in the susceptibility of sevoflurane induced cognitive dysfunction, we have established a strain of

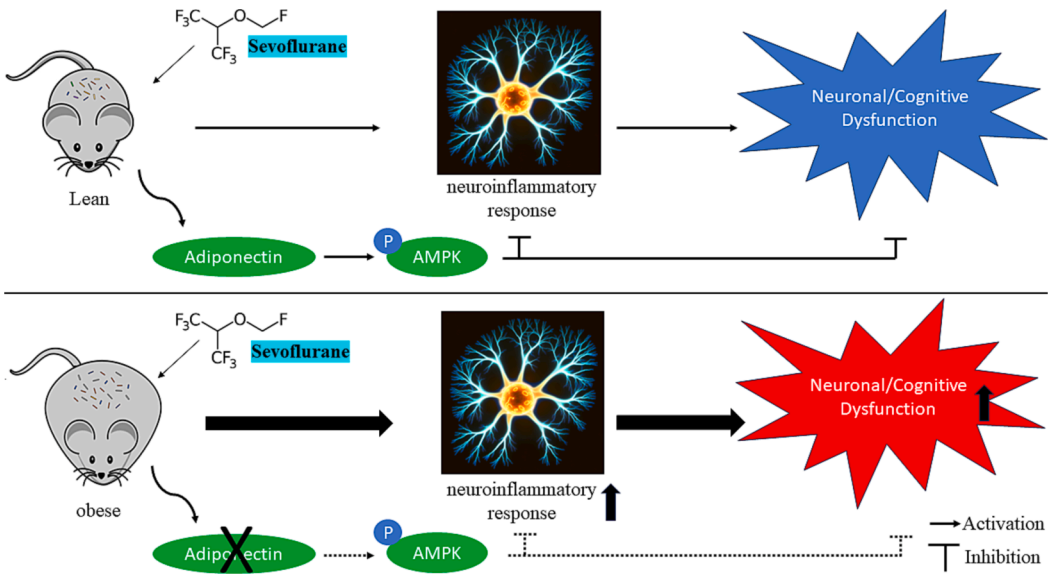

Fig 1. Summarized diagram for the hypothesis. Summarized figure for the hypothesis. In the upper panel, sevoflurane triggers neuroinflammation in lean healthy subjects. At the same time however, adiponectin can activate AMPK pathway which may protect the brain from sevoflurane induced neuroinflammation and cognitive dysfunction. In the lower panel, obese subjects may have hypoadiponectinemia and may lack the protective effects from adiponectin as described above, thus be vulnerable to sevoflurane induced neuroinflammation and subsequent cognitive dysfunction. AMPK: AMP-activated protein kinase.

endogenous adiponectin knockout mice without obesity [43]. Finally, the neuroprotective effects of adiponectin or its agonist supplement, including AdipoRon, ADP355, ADP399 or JT003 [44] will be examined in our obese and adiponectin knockout animal models to further confirm our hypothesis.

Consequence of hypothesis and discussion

Obesity is widespread with worldwide prevalence having doubled since 1980. The onset of obesity is occurring earlier, and such patients are more likely to develop conditions that require surgical treatment under general anaesthesia. These include operative treatment for degenerative joint diseases and complications arising from type 2 diabetes that often coexists with obesity. Obese patients undergoing major surgery are likely to receive less fat-soluble inhalational agents such as sevoflurane or desflurane to facilitate early emergence and reduce residual anaesthetic effects from more lipid soluble agents. Experimental evidence points to an increased susceptibility of brains from obese subjects to cognitive dysfunction and hence to develop PNDs following surgery under general anaesthesia. In such cases, it will prolong hospitalization, delay recovery and rehabilitation that in sum would increase the social and financial burden to the society and the patient's family. Further, subjective cognitive impairment is negatively correlated with quality of life.

Currently there are only limited understanding in the pathogenesis of PNDs and although neuroinflammation is known to be involved in its development of PNDs, there are knowledge gaps in how sevoflurane can induce neuroinflammation more readily in obese patients. Adiponectin is an important adipokine in neuroprotection and anti-inflammation. Without the protection from adiponectin, animals are more prone to develop neuropathology and neuroinflammatory response [45]. If our hypothesis is confirmed, not only it can broaden our understanding on the pathogenesis of PNDs, but it will also facilitate the development of potential therapeutic interventions to minimize the risk of PNDs in obese patients, which will improve the postoperative quality of life and reduces costs to the public health system.

Limitations of the hypothesis

Although the neuroprotective effects of adiponectin have been well reported in previous reports, dose of the adiponectin must be carefully considered as excessively high level of adiponectin may be associated with adverse cardiovascular and cerebrovascular events [46]. Therefore, the dose of adiponectin or its agonist should be carefully selected before carrying out the study to confirm the hypothesis.

Conclusions

In conclusion, we presented our hypothesis that adiponectin deficiency plays a pivotal role in the increased risk of cognitive dysfunction in obese patients after surgery under general anaesthesia. We described the possible mechanisms underpinning this hypothesis including the increased propensity for the anaesthetic agent sevoflurane to exacerbate neuroinflammation, apoptosis and synaptic/neuronal dysfunction in the presence of adiponectin deficiency. The proposal of this hypothesis hopefully encourages both basic and clinical research to evaluate the effects of adiponectin supplementation or adiponectin receptor stimulation in perioperative subjects with obesity to see whether it may reduce the risk of cognitive dysfunction after surgery. From the basic science perspective, experimental animal models with specific knockout of adiponectin or its receptor are needed to confirm the role of adiponectin and its associated signalling pathways in sevoflurane induced cognitive dysfunction. From the clinical perspective, clinical trials designed to evaluate the effects of perioperative adiponectin /agonist supplement in patients with obesity are required.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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