Insulin signaling in the central nervous system, a possible pathophysiological mechanism of anesthesia-induced delayed neurocognitive recovery/postoperative neurocognitive disorder: a narrative review

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\textbf{ABSTRACT}

\textbf{Introduction:} Impairment in neurocognitive functions ranges between delayed neurocognitive recovery (DNR) and postoperative neurocognitive disorders (pNCD). Incidence varies from 11\% after non-cardiac surgery to 60\% after cardiac surgery.

\textbf{Areas covered:} Insulin receptors (IRs) signaling pathway in the central nervous system (CNS) could be a possible pathophysiological mechanism of anesthesia-induced DNR/pNCD and perioperative intranasal insulin administration could be a preventive approach. This hypothesis is supported by the following evidence: effects of IRs-CNS signaling pathway on neuromodulation; higher incidence of DNR/pNCD in patients with insulin resistance; neurotoxicity of IRs signaling pathways after anesthetic exposure; improvement of neurocognitive impairment after insulin exposure. This narrative review was conducted after a literature search of PubMed, EMBASE and SCOPUS online medical data performed in May 2022.

\textbf{Expert opinion:} Perioperative intranasal insulin is shown to be protective and future studies should address: the role of insulin as a neuromodulator; its integration into neuroprotection approaches; patient populations that might benefit from this approach; a well-defined protocol of intranasal insulin administration in a perioperative background and other disciplines; and possible collateral effects.

1. Introduction

Postoperative course can be complicated by an impairment in neurocognitive functions that ranges between delayed neurocognitive recovery (DNR) and postoperative neurocognitive disorders (pNCD) [1]. Various pathophysiological mechanisms have been hypothesized and available clinical studies used a huge variety of methodological approaches to evaluate these relevant postoperative complications [2,3]. These terms have been proposed to replace the former postoperative cognitive dysfunction (POCD), in order to characterize the specific timeline of these two complications [4,5]. The pooled incidence of these complications is 11\% after noncardiac surgery and 60\% after cardiac surgery [2]. Occurrence of DNR/pNCD imply the impairment of one or more cognitive domains and has relevant impact on functional recovery, hospital and social costs and mortality rate [2,6]. Proven risk factors for DNR/pNCD include: advanced age, education level, history of diabetes mellitus, malnutrition, blood pressure fluctuation during surgery, perioperative hyperglycemia, etc [6,7]. Preclinical and clinical evidence suggests a causal association between anesthesia and DNR/pNCD, and various pathophysiological mechanisms have been proposed: accumulation of amyloid-\(\beta\) (A\(\beta\)) protein, increase in tau proteins phosphorylation, mitochondrial dysfunction, calcium dysregulation, systemic and central nervous system (CNS) inflammatory response, mechanical ventilation, etc [3,8].

In the CNS, the interaction between insulin and insulin receptors (IRs) is part of a signaling system that interferes with cognitive functions through a neuromodulator-like action [9–11]. The relevance of IRs-CNS signaling in cognitive functions is proven by the higher risk of Alzheimer’s disease (AD) in patients with diabetes mellitus (DM) presented with a downregulation of insulin transport through blood brain barrier (BBB) and dysregulation on IRs intracellular cascade [12–14]. Recent evidence also suggests an interaction between anesthetics and IRs in the CNS, and this might contribute to anesthesia-induced DNR/pNCD [15].

This narrative review summarizes: effects of IRs stimulation in peripheral tissues and in CNS; the relationship between insulin resistance and DNR/pNCD; anesthetics effects on IRs and DNR/pNCD; evidence on perioperative role of insulin in preventing DNR/pNCD. The main point of this manuscript is to report the relationship between anesthesia exposure and incidence of DNR/pNCD, as a result of the impact on IRs signaling in the CNS and the perioperative role of intranasal insulin as a preventive approach.

2. Material and methods

This narrative review was conducted after a literature search accomplished according to a protocol that defined inclusion and exclusion criteria (preclinical and clinical studies, articles in
DNR/pNCD; anesthesia voltage-dependent (reduction)

Article highlights
- Incidence of postoperative neurocognitive impairment such as DNR and/or pNCD varies from 11% to 60%.
- A causal association between anesthesia exposure and DNR/pNCD onset has been reported by preclinical and clinical studies.
- Insulin receptors signaling pathway has a non-metabolic activity in the CNS and interferes with cognitive functions through a neuromodulator-like action.
- Recent evidence suggests an interaction between anesthetics and insulin receptors signaling in the CNS and shows that perioperative intranasal insulin administration improves the outcome.
- IRs signaling pathway might contribute to anesthesia-induced DNR/pNCD.
- Future studies should address the role of intranasal insulin in neuroprotection, patient population that might benefit of this approach and a well-defined administration protocol.

English, no limit of publication date, no abstract included. Selected studies assessed the effects of IRs stimulation in the whole body, the relationship between insulin resistance, anesthesia exposure and DNR/pNCD and the role of insulin in preventing postoperative neurocognitive impairment. A literature search of PubMed, EMBASE and SCOPUS online medical data was performed in May 2022. The following search terms were used: insulin receptors in peripheral tissues, insulin receptors and brain, postoperative neurocognitive impairment, insulin resistance and cognitive impairment, insulin receptors and anesthesia exposure, intranasal insulin and postoperative cognitive impairment. All authors independently screened and assessed titles, abstract and full-text of the retrieved articles. Selected studies were categorized into 5 chapters: (1) effects of IRs stimulation in peripheral tissues; (2) effects of IRs stimulation in the CNS; (3) insulin resistance and DNR/pNCD; (4) anesthetics effects on IRs and DNR/pNCD; (5) perioperative use of insulin in preventing DNR/pNCD.

3. Main body

3.1. Effects of IRs stimulation in peripheral tissues

Insulin extraction was first reported in 1921 [16]. Early after the initial clinical use, it became evident that insulin administration induces metabolic (reduction in blood sugar concentration and abolishment of glycosuria) and neurological effects (reduction in opioid abstinence symptoms, disappearance of hallucinations and antipsychotic effects) [16–19]. Insulin is a peptide hormone formed by 51 amino acids, structured in 2 chains (α and β) linked together by disulfide bridges [20]. It is produced by β cells of the pancreas islets in response to increase of blood glucose concentration (BGC) and insulin-independent transport of glucose through glucose transporter (GLUT) 2 [21]. The increase of glucose concentration in pancreas β cells leads to membrane depolarization, activation of voltage-dependent Ca²⁺ channels, increase of intracellular [Ca²⁺] and exocytosis of insulin granules [21].

Insulin exerts its action binding transmembrane IRs that are formed by 2 heterodimers (extracellular α subunits and transmembrane β subunits) and expressed with different concentrations and functions in all mammalian tissues (Table 1) [22]. Insulin binding to IRs results into the activation of intracellular tyrosine-kinase activity and induces 2 signaling pathways (Figure 1) [23]:

1. Phosphoinositide 3-kinases (PI3K) induces the intracellular activation of protein kinase B (PKB/Akt) which turns in multiple substrate signaling: -Tre-2/Bub2/Cdc16 (TBC1D1 and TBC1D4) protein domains that induce synthesis and translocation of GLUT4 to cellular surface; -sterol regulatory element binding protein 1 (SREBP1) that promotes glycogen synthesis; -B-cell lymphoma 2 against of cell death (BAD) and caspase-9 (Casp9) that contribute to cell survival; p21 and p27 that regulate cell cycle; -glycogen synthase kinase 3 (GSK3) that stimulate synthesis of glycogen; -S6 kinase beta-1 (S6K1) and eukaryotic translocation initiation factor 4E binding protein 1 (4EBP1) stimulate protein synthesis; -sterol regulatory element-binding transcription factor 1 (SREBF1) that induces lipid synthesis; and forkhead box containing protein O subfamily (FoxO) that contributes to gluconegenesis, gene transcription and lipid synthesis.

2. Proto-oncogene protein p21 (RAS) induces activation of microtubule associated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK), leading to cell proliferation and gene transcription.

In different mammalian tissues, cellular glucose uptake is mediated by different GLUTs types [24]. Glucose uptake mediated by GLUT1–GLUT3, is an insulin-independent mechanism, while insulin-mediated glucose uptake takes place in muscles (skeletal and cardiac) and adipose cells through insulin-induced GLUT4 synthesis and translocation [24].

In conclusion, in peripheral tissues IRs modulate metabolic (glucose uptake and glycogen, protein and lipid synthesis) and non-metabolic (cell cycle, survival/proliferation/apoptosis and gene transcription) cellular activities.

3.2. Effects of IRs stimulation in the CNS

In the CNS, the IRs have peculiar distribution with highest concentration in the hippocampal, amygdala and para-hippocampal gyrus and intermediate to low concentration in cerebellum, cerebral cortex, caudate nucleus, substantia nigra and white matter [11,25]. The role of IRs in the CNS resides in non-metabolic activities of the intracellular signaling pathways: balancing neuronal proliferation and apoptosis and regulating gene transcription thus acting as neuromodulator-like factor, while neuronal glucose transport is warrant by non-insulin dependent transporters (GLUT1-3) [25,26]. Plasmatic insulin reaches CNS through a 3-component model: from plasma – through BBB – to the CNS interstitial fluid (ISF) and from the ISF – through ependymal cells (EC) – to cerebrospinal fluid (CSF) (Figure 2) [27,28]. After binding IRs on the endothelial BBB cells, plasmatic insulin is transported to ISF by a dedicated process called transcytosis [27]. Transcytosis is a saturable process inversely related with plasma insulin concentration: higher insulin plasma concentration associates with lower transcytosis [28]. Insulin transport from ISF to CSF occurs according to a passive transport through ependymal cells [27]. This process ensures the presence of ‘systemically produced’ insulin into the
CNS with a CSF insulin concentration (≈ 5–10 μU/ml) that is about 5–10% of plasmatic insulin concentration [27]. Insulin in the CNS, to a smaller extent, relies also on neuronal production as proven by the presence of C-peptide (polypeptide in the proinsulin molecule which is removed, leaving the active form of insulin molecule) and insulin distribution in some areas - such as hypothalamus, hippocampus and brain stem where it reaches 10 to 100 fold higher concentration than in the plasma [29].

Several preclinical and clinical studies prove that insulin possesses trophic functions in the CNS through activation of cytosolic enzymes in neuronal and astroglial cells [29–31]. It also acts as a neuromodulator-like neuropeptide through gene expression and regulation of excitatory/inhibitory receptors – as glutamate and gamma-aminobutyric acid (GABA) receptors – thus affecting synaptic plasticity and influencing learning and memory processing [32]. In this setting, insulin exerts a neuroprotective role through increase of glutamate and GABA reuptake [32]. Furthermore, insulin signaling contributes to neurotransmission through inhibition of norepinephrine reuptake and induction of higher expression of N-methyl-D-aspartate (NMDA) receptors [33,34]. The dysfunction of IRs-CNS pathway, induced in preclinical experimental conditions, associates with neuronal mitochondrial dysfunction, increased levels of reactive O2-species and monoamine oxidase (with higher rate of dopamine turnover), defective in hippocampal neurogenesis and synaptic plasticity and

| Tissue/organ | Distribution | Function |
|--------------|--------------|----------|
| Skeletal muscle | Skeletal muscle cells | Stimulation of GLUT4-mediated glucose uptake; regulation of cell growth, differentiation and survival |
| Adipose tissue | Adipocytes | Stimulation of GLUT4-mediated glucose uptake, lipogenesis and suppression of lipolysis; regulation of cell proliferation |
| Heart | Cardiomyocytes | Stimulation of GLUT4-mediated glucose uptake and long-chain fatty acid uptake; regulation of protein synthesis, cell growth, and vascular toxicity |
| Liver | Hepatocytes | Stimulation of glycogen synthesis, lipogenesis and lipoprotein synthesis; suppression of gluconeogenesis/glycogenolysis; VLDL secretion; regulation of hepatic growth, and proliferation/regeneration |
| Pancreas | β cells | Stimulation of β cell insulin secretion; regulation of proliferation and survival |
| Intestine | Epithelial cells | Stimulation of glucose metabolism; regulation of intestinal growth |
| Kidney | Podocytes; distal renal tubules | Stimulation of podocyte function, sodium excretion, and blood pressure control |
| Lung | Epithelial cells | Stimulation of lung development during organogenesis |
| Bone | Osteoblasts | Regulation of proliferation, growth, differentiation, and survival |
| Eye | Neurons of retina | Regulation of proliferation, growth, differentiation, and survival |
| Skin | Keratinocytes | Regulation of proliferation, growth, differentiation, and survival |

Figure 1. IR intracellular signaling pathway; insulin receptors (IRs), proto-oncogene protein p21 (RAS), phosphoinositide 3-kinases (PI3K), microtubule associated protein kinase (MAPK), protein kinase B (Akt), glucose transporter type 4 (GLUT4), B-cell lymphoma 2 against of cell death and caspase-9 (BAD/Casp9), sterol regulatory element binding protein 1 (SREBP1), glycogen synthase kinase 3 (GSK3), S6 kinase beta-1/eukaryotic translocation initiation factor 4E binding protein 1 (S6K1/4EBP1), sterol regulatory element-binding transcription factor 1 (SREBF1), forkhead box-containing protein O subfamily (FoxO).
impairment of normal response to stress by hypothalamic-pituitary-adrenal axis [35,36].

In conclusion, insulin transport through the BBB and IRs-CNS signaling pathway generate complex and relevant modulatory system with direct and indirect effects on neuronal survival, neuroprotection and neuropeptide provoking neurobehavioral disorders as: anxiety, mood, feeding and cognitive disorders in case of intracellular signaling pathway dysfunction.

### 3.3. Insulin resistance and DNR/pNCD

Persistent hyperinsulinemia induced by insulin resistance (as in type 2 DM), associates with downregulation of insulin transport through BBB, inhibition of Aβ protein processing, acceleration of neuronal tau protein phosphorylation and neuroinflammation, leading to frontal cortex dysfunction and AD-type neurodegeneration, while intracellular hoarding of misfolded Aβ proteins reduces IRs expression in the CNS and stimulates CNS innate immune system [13,37–43]. For these reasons, AD is considered a brain-specific form of DM (so called ‘type 3 diabetes’) in animal and human models [39]. Neuronal changes associated with AD are characterized by impaired energy metabolism, mitochondrial dysfunction, chronic oxidative stress, DNA damage and cell loss, leading to abnormalities in the expression of genes encoding CNS insulin and insulin receptors, a lower CSF/plasma insulin concentration ratio and a reduced IRs tyrosine-kinase activity [38,44].

Several clinical evidence, derived by studies in cardiac and noncardiac surgical patients, demonstrates that insulin resistance and type 2 DM, especially when hemoglobin A1c (HbA1c) values are suboptimal, associate with increased risk of DNR/pNCD [45–51]. Patients undergoing coronary artery bypass graft surgery with type 2 DM, diabetic retinopathy, insulin therapy and high serum levels of HbA1c, have an increased risk for DNR/pNCD at 7th postoperative day and 6th month follow-up [46]. In this setting, patients with type 2 DM show a pronounced systemic and neuronal inflammatory response that predicts DNR/pNCD [47]. The relationship between insulin resistance, the production of systemic inflammatory factors – interleukin 6 (IL-6) and tumor necrosis factors α (TNF-α) – and the increase in DNR/pNCD at the 7th day after surgery, was clinically proven in an observational study that enrolled 131 patients undergone cardiac surgery [48]. This evidence has been confirmed also in noncardiac surgery where ‘preoperative metabolic syndrome’ (i.e. insulin resistance, obesity, arterial hypertension) and insulin resistance have been independently proven to predict of DNR/ pNCD at 7th postoperative day [49,50].

In conclusion, preclinical and clinical studies suggest that insulin resistance, DM-induced cerebral dysfunction and AD-type neurodegeneration, are interrelated events that associate with DNR/pNCD in both cardiac and noncardiac surgical patients.

### 3.4. Anesthetics effects on IRs and DNR/pNCD

Several preclinical and clinical evidence suggests that general and local anesthetics interfere with IRs signaling pathways in peripheral tissues and in CNS, thus possibly inducing DNR/ pNCD [52–79].

General anesthetics interfere with IRs in peripheral tissues with various mechanisms: halogenated anesthetics (sevoflurane and isoflurane) inhibit the intracellular IRs-MAPK/ERK signaling pathway, inducing insulin resistance, hyperglycemia and hyperinsulinemia; propofol interferes with IRs signaling, stimulating tyrosine-kinase activity of skeletal muscle IRs resulting in pronounced BGC changes; α-2 adrenoceptor agonist (as dexmedetomidine) reduces insulin secretion and leads to increased BGC after injection in dogs models, because of its action on α receptors expressed by pancreatic β cells [52–55]. Also local anesthetics affect the intracellular IRs cascade, through PI3K/AKT and MAPK/ERK signaling pathways and it can lead to pro-apoptotic and anti-proliferative events [56–59].

Preclinical evidence on CNS toxicity induced by general anesthetics suggests an association between IRs-mediated intracellular pathways and cognitive dysfunction [60–69]. Multiple exposures of mice models to either sevoflurane or isoflurane, but not desflurane, were found to reduce PI3K/Akt
pathway activity, leading to development of neurotoxicity and worsening of cognitive performance (learning and memory) [61,62]. Sevoflurane and isoflurane can induce neurotoxicity through elevated phosphorylation of MAPK which inhibit ERK signaling, causing neuroapoptosis [63,64]. Propofol inhibits both PI3K/Akt and MAPK/ERK signaling pathway in in-vitro neurons, inducing apoptosis and reducing cell proliferation [65,66]. On the other hand, the use of dexmedetomidine, as anesthetic adjuvant, promotes PI3K/Akt and MAPK/ERK signaling pathways in in-vitro cells [67,68]. Urethane and ketamine-induced anesthesia reduces MAPK/ERK signaling pathway and increase tau protein phosphorylation [69].

Local anesthetics have several potential neurotoxic effects including seizures and CNS depression [56]. Differences in terms of toxicity between local anesthetics are still under scrutiny, especially their neurotoxic effects [70]. Longer-acting local anesthetics have higher CNS toxicity than the shorter-acting [71]. In vitro models have shown that neurotoxicity of local anesthetics is triggered by PI3K and MAPK-pathways of CNS cells, which interfere with neuronal survival and induce neuronal apoptosis respectively [72,73]. Intravenously administered lidocaine, tested to reduce incidence of DNR/pNCD after cardiac surgery, was investigated in a randomized controlled trial enrolling 114 patients receiving lidocaine infusion and 127 patients receiving placebo [74]. Recorded results proved that lidocaine did not reduce DNR/pNCD incidence at 6th week and 1st year postoperatively, while doses of >35 mg/kg were reported to be an independent predictor of DNR/pNCD in diabetic patients, exerting neurotoxic effect.

In conclusion, exposure to both general and local anesthetics interferes with IRS signaling pathways, resulting in neurotoxicity. The main mechanisms that lead to impairment of cognitive performance are: neuroapoptosis, reduction of cell proliferation and increase of tau protein phosphorylation.

3.5. Perioperative use of insulin in preventing DNR/pNCD

Preclinical and clinical evidence suggests that insulin administration associates with reduced neuronal damage and when used in the perioperative period, might exert a protective effect toward DNR/pNCD [15,47,75,76].

The neurological effects of insulin administration were described shortly after the initial experimental and clinical use [11–14]. The possible protective effect of insulin in cerebral ischemia was studied by Strong et al. in 1985 [77]. In a pre-clinical model of cerebral ischemia, mild hypoglycemia induced by insulin administration protected brain mitochondrial activity in vitro and led to better electrophysiological functions. In 1987, Robertson et al. proved in a model of spinal cord damage, that reduction of blood glucose with insulin resulted in improved recovery of electrophysiological functions when compared to a control group, probably because of a reduced lactic acid production [78]. The effects of insulin administration before experimental CNS ischemia on neurologic functions in rats were investigated by Le May et al. in 1988, showing that insulin-induced normoglycemia or mild-hypoglycemia associated with decreased neurological deficit and increased survival [79]. In 1991, Voll et al. determined that insulin exerted its neuroprotective mechanism through a neuromodulatory role, causing neuronal inhibition in most areas of the CNS, and a growth factor effect, promoting neuronal survival [80]. The role of insulin in preventing apoptosis was first studied by Tanaka et al. in 1995 that proved how cerebellar insulin deprivation induced increased neuronal apoptosis [81]. In 2005, Duarte et al. showed that insulin protected against oxidative stress-induced apoptosis and necrosis in the brain and how extended exposure to reactive oxygen species contributed to the pathophysiology of neurodegenerative diseases [82]. The neuroprotective role of insulin in chronic neurodegenerative diseases was also studied by Rensink et al. in 2004; evidence suggested that it had an important effect in regulating Aβ fibrillation in patients with AD, preventing neuronal degeneration by inhibiting interaction between Aβ fibrils and cell surface [83]. Mice undergoing anesthesia showed a higher level of tau protein phosphorylation compared to controls and this mechanism was proposed that could relate anesthesia and DNR/pNCD [84,85]. Evidence suggested that intranasal insulin administration before anesthesia associated with lower levels of tau protein phosphorylation, hence this treatment can prevent these disorders [86]. Furthermore, general anesthesia was reported to enhance changes or reductions of synaptic proteins, such as post-synaptic density protein 95, and brain-derived neurotrophic factor, while prior administration of intranasal insulin can preserve the physiological asset [86–88].

In humans, intranasal administration of insulin led to rapid distribution to the CNS through olfactory and trigeminal neurons and the passage of cribriform plate and is hypothesized to exert neuroprotective effects [89]. This technique was used in patients suffering from ischemic stroke events, during acute, subacute and chronic phase, and in memory-impaired patients, diagnosed with mild cognitive impairment, AD, Parkinson’s disease and multiple system atrophy diagnosis [89–96]. A recent clinical study proved a reduced incidence of postoperative delirium in anesthetized patients when treated with preoperative intranasal insulin [97].

4. Conclusion

Considering the effects of IRS-CNS signaling pathway on neuronal survival, neuroprotection and neuromodulation, the higher incidence of DNR/pNCD in patients who presented insulin resistance, neurotoxicity induced to IRS signaling pathways after exposure to general and local anesthetics and the improvement of neurocognitive impairment after insulin exposure, we support the hypothesis that IRS-CNS signaling pathway could be a possible pathophysiological mechanism of anesthesia-induced DNR/pNCD and perioperative intranasal insulin administration could be a preventive approach.

The main limitation of this paper is the lack of clinical evidence as it is a very innovative topic. Future trials should appropriately be designed in order to better investigate the proposed hypothesis and address the patient population that might benefit of perioperative intranasal insulin administration.
5. Expert opinion

DNR/pNCD can complicate the postoperative course of the patients exposed to anesthesia, compromising one or more cognitive domains, resulting in a slower functional recovery, higher social costs and mortality rate. Incidence of these complications is higher in patients undergoing cardiac surgery compared to noncardiac one and the pathophysiological mechanisms listed below have been proven: advanced age, education level, history of diabetes mellitus, malnutrition, blood pressure fluctuation intraoperatively, perioperative hyperglycemia. Exposure to anesthesia was proposed to be another risk factor as it is demonstrated to be associated with accumulation of Aβ protein, increase in tau proteins phosphorylation, mitochondrial dysfunction, calcium dysregulation, systemic and CNS inflammatory response, impact of mechanical ventilation, etc. As neuronal glucose transport is ensured by non-insulin dependent transporters (GLUT1 – GLUT3) and insulin in the CNS exerts non-metabolic activities through intracellular signaling pathways such as neuronal proliferation, apoptosis and gene transcription, the hypothesis proposed is the impact of anesthetics on IRs signaling in the CNS, thus increasing DNR/pNCD incidence and determine worse postoperative outcomes.

The present narrative review provides an overview of the effects of IRs stimulation in peripheral tissues and in CNS; of the relationship between insulin resistance and DNR/pNCD; of anesthetics effects on IRs and DNR/pNCD; of perioperative role of insulin in preventing DNR/pNCD. It can serve as a methodological guide to design dedicated trials that evaluate the role of insulin signaling in the CNS on neurocognitive performance through a neuromodulator-like action in a perioperative setting. Despite the numerous preclinical studies, protective role of preoperative intranasal insulin on reducing DNR/pNCD incidence is actually supported by weak evidence in clinical settings, even if this frame of reference may impact short and long-term prognosis of patients who are at high risk of DNR/pNCD after exposure to anesthesia, length of stay and unit costs of healthcare services.

Currently, there is a particular interest on analyzing the effects of anesthesia and specific drugs on cerebral metabolism, brain circuits, oscillation patterns through cerebral monitoring and on considering the different crosstalk between brain and other organs, systems or procedures/treatment approach such as for example kidney, endocrine system or mechanical ventilation. These findings are useful to avoid burst suppression pattern, intracranial hypertension or hypotension, ischemia, neuroinflammation, etc. Actually, use of intranasal insulin is not part of the daily clinical practice and this fact limits drafting a wide-shared posology protocol and route of administration. Therefore, future clinical studies are crucial for the evolution of this research field. This would be the best approach to obtain the use of intranasal insulin in patients with high risk of DNR/pNCD undergoing surgical procedures and extend the implementation of intranasal insulin out of a perioperative background, such as a neurological, diabetological, geriatric and nutritional context.

Five years from now, we are confident that there will be a clear explanation regarding the role of insulin as a neuromodulator, its integration into neuroprotection approaches, patient population that might benefit of this approach, a well-defined protocol of intranasal insulin administration in a perioperative background and other disciplines and possible collateral effects.

Abbreviations list

| Abbreviation | Description |
|--------------|-------------|
| Aβ           | amyloid-β   |
| AD           | Alzheimer’s disease |
| BAD          | B-cell lymphoma 2 against of cell death |
| BBB          | blood–brain barrier |
| BGC          | blood glucose concentration |
| Casp9        | caspase-9 |
| CNS          | central nervous system |
| CSF          | cerebrospinal fluid |
| DM           | diabetes mellitus |
| DNR          | delayed neurocognitive recovery |
| 4EBP1        | eukaryotic translocation initiation factor 4E binding protein 1 |
| EC           | ependymal cells |
| ERK          | extracellular signal-regulated kinase |
| FoxO         | forkhead box-containing protein O subfamily |
| GABA         | gamma-aminobutyric acid |
| GLUT         | glucose transporter |
| GSK3         | glycogen synthase kinase 3 |
| Hb1Ac        | hemoglobin A1c |
| IL-6         | interleukin 6 |
| IRs          | insulin receptors |
| ISF          | interstitial fluid |
| MAPK         | microtubule-associated protein kinase |
| NMDA         | N-methyl-D-aspartate |
| PI3K         | phosphoinositide 3-kinases |
| PKB          | protein kinase B |
| pNCD         | postoperative neurocognitive disorders |
| PCOD         | postoperative cognitive dysfunction |
| RAS          | proto-oncogene protein p21 |
| S6K1         | S6 kinase beta-1 |
| SREBF1       | sterol regulatory element-binding transcription factor 1 |
| SREBP1       | sterol regulatory element binding protein 1 |
| TNF          | tumor necrosis factor |

Author contributions

EQ: conception and design of the paper, interpretation of the relevant literature, writing and editing the manuscript. CS: conception and design of the paper, interpretation of the relevant literature, writing and editing the manuscript. FB: conception and design of the paper, interpretation of the relevant literature, writing and editing the manuscript.

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**This paper reports a reduced incidence of postoperative delirium in patients treated with preoperative intranasal insulin.**