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Research Report

Sevoflurane and Isoflurane induce structural changes in brain vascular endothelial cells and increase blood–brain barrier permeability: Possible link to postoperative delirium and cognitive decline

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ABSTRACT

A large percentage of patients subjected to general anesthesia at 65 years and older exhibit postoperative delirium (POD). Here, we test the hypothesis that inhaled anesthetics (IAs), such as Sevoflurane and Isoflurane, act directly on brain vascular endothelial cells (BVECs) to increase blood–brain barrier (BBB) permeability, thereby contributing to POD. Rats of young (3–5 months), middle (10–12 months) and old (17–19 months) ages were anesthetized with Sevoflurane or Isoflurane for 3 h. After exposure, some were euthanized immediately; others were allowed to recover for 24 h before sacrifice. Immunohistochemistry was employed to monitor the extent of BBB breach, and scanning electron microscopy (SEM) was used to examine changes in the luminal surfaces of BVECs. Quantitative immunohistochemistry revealed increased BBB permeability in older animals treated with Sevoflurane, but not Isoflurane. Extravasated immunoglobulin G showed selective affinity for pyramidal neurons. SEM demonstrated marked flattening of the luminal surfaces of BVECs in anesthetic-treated rats. Results suggest an aging-linked BBB compromise resulting from exposure to Sevoflurane. Changes in the luminal surface topology of BVECs indicate a direct effect on the plasma

Abbreviations: BBB, blood–brain barrier; POD, postoperative delirium; POCD, postoperative cognitive decline; IgG, immunoglobulin G

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membrane, which may weaken or disrupt their BBB-associated tight junctions. Disruption of brain homeostasis due to plasma influx into the brain parenchyma and binding of plasma components (e.g., immunoglobulins) to neurons may contribute to POD. We propose that, in the elderly, exposure to some IAs can cause BBB compromise that disrupts brain homeostasis, perturbs neuronal function and thereby contributes to POD. If unresolved, this may progress to postoperative cognitive decline and later dementia.

1. Introduction

Nearly 60,000 patients undergo general anesthesia every day with the hope of alleviating chronic diseases and improving their quality of life (Brown et al., 2010; Nadelson et al., 2014). Unfortunately, after exposure to anesthetics, a large percentage of elderly patients at age 65 and older exhibit postoperative delirium (POD), and many subsequently develop postoperative cognitive decline (POCD) which may be linked to later dementia (Ansaloni et al., 2010; Inouye et al., 2014; Neufeld et al., 2013; Rudolph and Marcantonio, 2011). In the US, the number of affected individuals continues to rise because the elderly are the fastest growing segment of our population (Howden and Meyer, 2011; Brown and Purdon, 2013; Leslie et al., 2008; Neufeld and Thomas, 2013). POD is characterized by an acute, fluctuating onset of attention disturbance and cognitive change in patients who may otherwise lack a history of neurocognitive manifestations (Bedford, 1955; Burns et al., 2004; Strom et al., 2014). As multifactorial disorders, POD and POCD have been associated with a variety of somatic factors as well as medication intoxication or withdrawal (Strom et al., 2014; van Munster and de Rooij, 2014). Advanced age and exposure to inhaled anesthetics have been widely implicated as risk factors (Bedford, 1955; Brown and Purdon, 2013; Neufeld and Thomas, 2013; Strom et al., 2014).

Although the underlying mechanisms of POD and POCD are unknown (Maldonado, 2013), emerging evidence suggests a common mechanistic link. Aging is a known predisposing factor in a number of vascular pathologies, including chronic vascular inflammation, atherosclerosis, amyloid angiopathy, hyalinosis and hypertension (Clifford et al., 2008; Kalaria, 2010; Rouhl et al., 2012; Vasilevko et al., 2010). The blood vessels in the brain are not spared from these anomalies. Brain vascular endothelial cells (BVECs) line the luminal surfaces of these vessels and contribute both structurally and functionally to the blood–brain barrier (BBB). These cells are held together at their margins by extensive tight junctions associated with prominent tight junctional folds or ridges. The BBB is thought to be further supported by the basement membrane of BVECs, pericytes and the end-feet of astrocytes (Abbott et al., 2010; Zlokovic, 2008). It regulates the movement of various biomolecules into and out of the brain, which is crucial for establishing and maintaining brain homeostasis and enabling the normal functioning of the neurons and glia within their microenvironment in the brain. Factors or conditions that disrupt BBB function can trigger a transient or chronic leakage of plasma components into the brain tissue, thereby disrupting brain homeostasis and triggering disease states (Abbott et al., 2010; Zlokovic, 2008). Several neurodegenerative diseases, most notably Alzheimer's disease (AD), exhibit BBB breakdown as a consistent pathological feature that likely contributes to both disease initiation and progression (Nagele et al., 2011).

In the present study, we tested the hypothesis that exposure to commonly used inhalation anesthetics disrupts BBB integrity, causing an influx of plasma components into the brain that locally disrupts brain homeostasis. To investigate this, young (3–5 months), middle-aged (10–12 months) and old (17–19 months) rats were subjected to either Sevoflurane or Isoflurane anesthesia for 3 h and then were sacrificed immediately or first allowed to recover for 24 h. Using immunohistochemistry (IHC) and immunoglobulin G (IgG) as a tissue biomarker of BBB leak, we compared the functional integrity of BBB between control animals and those exposed to anesthesia with or without 24 h of recovery. Results showed an increased BBB permeability and influx of plasma components into the brain tissue in Sevoflurane-treated animals, but not in those exposed to Isoflurane, compared to controls. Extravasated IgG showed selective affinity for the surfaces of pyramidal neurons. Scanning electron microscopy revealed an increased incidence of BVEC degeneration and death within the walls of brain blood vessels along with a marked flattening of their luminal surfaces and stretching of tight junctional ridges at their margins. The BBB of older and anesthetic-treated older rats appeared to be most sensitive to disruption, and Sevoflurane was more effective than Isoflurane in promoting BBB compromise and luminal surface changes in BVECs. These data link aging-associated decline in BBB functional integrity to the increased vulnerability of brain blood vessels in older animals to the effects of anesthesia. Extrapolation of this data to humans leads us to suggest that, particularly in the elderly, exposure to certain types of anesthetics causes a rapid, transient breakdown of the BBB which results in a critical loss of brain homeostasis and disruption of neuronal function that could, at least in part, account for the expression of symptoms that characterize delirium. Furthermore, if BBB function is not completely restored in elderly patients suffering from POD, we suggest that they are at increased risk for subsequently developing POCD and perhaps even dementia.

2. Results

2.1. *Inhalation anesthetics increase BBB permeability in the rat*

To assess the effects of anesthetics on the functional integrity of the BBB, IHC was used to detect the leak of plasma components from blood vessels into the cerebral cortex of anesthetic-treated