NeuroToxicology 56 (2016) 159–169

Contents lists available at ScienceDirect

NeuroToxicology

Full Length Article

Single and repeated exposures to the volatile anesthetic isoflurane do not impair operant performance in aged rats

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ARTICLE INFO

Article history:
Received 25 May 2016
Received in revised form 27 July 2016
Accepted 29 July 2016
Available online 3 August 2016

Keywords:
Anesthesia
Isoflurane
Operant behavior
Fixed consecutive number
Incremental repeated acquisition

ABSTRACT

Postoperative Cognitive Dysfunction (POCD) is a complication that can occur in the elderly after anesthesia and surgery and is characterized by impairments in information processing, memory, and executive function. Currently, it is unclear whether POCD is due to the effects of surgery, anesthesia, or perhaps some interaction between these or other perioperative variables. Studies in rodents suggest that the development of POCD may be related directly to anesthesia-induced neuroactivity. Volatile anesthetics have been shown to increase cellular inflammation and apoptosis within the hippocampus of aged rodents, while producing corresponding impairments in hippocampal-dependent brain functions. However, it is unclear whether volatile anesthetics can affect additional aspects of cognition that do not primarily depend upon the hippocampus. The purpose of this study was to use established operant tests to examine the effects of isoflurane on aspects of behavioral inhibition, learning, and motivation in aged rats. Twenty-one adult Sprague-Dawley rats (11 male, 10 female) were trained to perform fixed consecutive number (FCN), incremental repeated acquisition (IRA), and progressive ratio (PR) tasks for a minimum of 15 months prior to receiving anesthesia. At 23 months of age, rats were exposed to 1.3% isoflurane or medical grade air for 2 h. Initial results revealed that a 2 h exposure to isoflurane had no effect on IRA, FCN, or PR performance. Thus, rats received 3 additional exposures to 1.3% isoflurane or medical grade air: 2, 4 and 6 h exposures with 2 weeks elapsing before exposure two, 3 weeks elapsing between exposures two and three, and 2 weeks elapsing between exposures three and four. These additional exposures had no observable effects on performance of any operant task. These results suggest that single and repeated exposures to isoflurane do not impair the performance of aged rats in tasks designed to measure behavioral inhibition, learning, and motivation. This lack of significant effect suggests that the impairments associated with isoflurane exposure may not generalize to all aspects of cognition, but may be selective to tasks that primarily measure spatial memory processes.

1. Introduction

Many studies indicate that a portion of elderly patients experience a marked decline in cognitive performance after surgical procedures conducted under general anesthesia (Bekker et al., 2010; Caza et al., 2008; Krenk et al., 2010; Moller et al., 1998; Orser 2007). This complication is referred to as Postoperative Cognitive Dysfunction (POCD) and is characterized by impairments in information processing, memory, and executive function (Wang et al., 2014). The incidence of POCD in the elderly has been reported to be 26–41% at one week and 10% at 3 months after non-cardiac surgery (Moller et al., 1998; Monk et al., 2008). POCD in older adults can impact quality of life and has been associated with risk of leaving the job market early (Steinmetz et al., 2009). At present, the factors leading to cognitive decline after surgery under anesthesia remain unclear. It is unknown whether POCD is due to the effects of surgery, anesthesia, or perhaps some interaction between these two variables or other perioperative events. Furthermore, it is unclear what the preoperative risk factors are for developing POCD, with some studies suggesting preexisting Alzheimer's disease (AD) pathology and cognitive decline to be potential risk factors (Avidan and Evers, 2011; Evered et al., 2016; Xie et al., 2013).

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http://dx.doi.org/10.1016/j.neuro.2016.07.012
0161-813X/

Given the complexity of POCD and the difficulty in systematically studying this phenomenon in human subjects, research in this field would be significantly enhanced by the development of animal models that could facilitate exploration into the causes and risk factors associated with POCD. In fact, a significant amount of research has been conducted that examined the effects of exposure to anesthesia in aged rodents. Results from these studies suggest that the development of POCD may be directly related to anesthesia-induced neurotoxicity. In particular, volatile anesthetics have been shown to increase cellular inflammation and apoptosis in the hippocampus of aged rodents (Cao et al., 2012; Chen et al., 2013; Gong et al., 2012; Kong et al., 2013; Li et al., 2013a; Tian et al., 2015; Xiong et al., 2013), while producing corresponding impairments in hippocampal dependent brain functions (Cao et al., 2012, 2015; Culley et al., 2003a, 2004; Kong et al., 2013; Li et al., 2013b; Su et al., 2011; Wang et al., 2012; Xiong et al., 2013; Yu and Liu, 2013). These studies primarily used maze paradigms to assess the effects of volatile anesthetics on spatial learning and memory, aspects of cognition that are highly dependent upon the hippocampus. Thus, it is unclear whether volatile anesthetics affect additional aspects of cognitive function that are not primarily dependent upon the hippocampus. For example, it is unclear whether the volatile anesthetics can affect aspects of cognition that rely heavily upon the prefrontal cortex and striatum, such as sequence learning, motivation, and behavioral inhibition.

The halogenated volatile anesthetics (isoflurane, sevoflurane, and desflurane) are commonly used for the induction and maintenance of general anesthesia and they have been associated with the development of POCD (Bilotta et al., 2016; Qiao et al., 2015). These agents are positive modulators of $GABA_A$ receptors (Forman and Chin, 2008; Orser et al., 2002), and theyalso antagonize glutamate receptors and inhibit glutamate release (Forman and Chin, 2008; Son, 2010). In the hippocampus, volatile anesthetics are believed to produce memory impairments by over-activating $\alpha5GABA_A$ receptors, thereby disrupting normal memory-regulating physiological functions (Martin et al., 2009; Wang and Orser, 2011). Given that $GABA_A$ receptors are widely distributed throughout the brain (Bowery et al., 1987), it is feasible that volatile anesthetics, through positive modulation of $GABA_A$ receptors, could disrupt additional areas of cognitive function.

In order to test this assumption, the present study employed specific tasks from the National Center for Toxicological Research (NCTR) Operant Test Battery (OTB) to examine the effects of isoflurane on various aspects of complex brain function in aged rats. Specifically, the incremental acquisition (IRA) and progressive ratio (PR) tasks were used to assess learning and motivation. The IRA task requires the subject to perform a predetermined sequence of lever responses each session, and, thus, provides a measure of sequence learning (Cohn and Paule, 1995), an aspect of cognition thought to be subserved by the prefrontal cortex (Kesner and Churchwell, 2011), hippocampus, (Ketchum et al., 2015) and striatum (Yin, 2010). The PR task requires that the subject perform an increasing number of lever presses for each subsequent reinforcer and has widely been used as a classic method for evaluating motivation in rodents (Hodos and Kalman, 1963; Hutsell and Newland, 2013; Jones et al., 1995; Oleson et al., 2011; Reichelt et al., 2016). Research has demonstrated the PR and IRA tasks to be sensitive to various psychoactive compounds in rats (Ferguson and Paule, 1996; Mayorga et al., 2000; Popke et al., 2000a,b) and monkeys (Buffalo et al., 1994; Ferguson and Paule, 1993; Frederick and Paule, 1997; Paule, 1990), including the anesthetic, ketamine (Paule et al., 2011), and specific behavioral

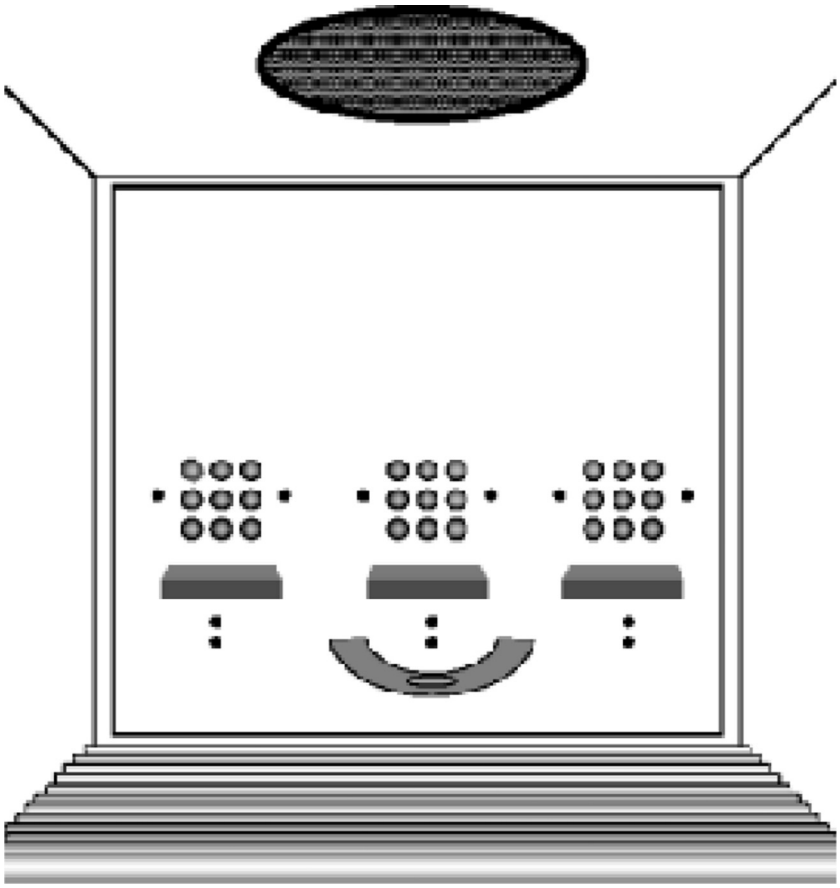

Fig. 1. Operant test chamber response panel.