

Behavior and cytogenesis following irradiation or isoflurane exposure to the developing brain

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Abstract

In this thesis, the effects of an anesthetic agent, isoflurane, on the young brain and resulting behavioral effects were investigated. Anesthesia is commonly used in young children during surgery or other procedures associated with pain or discomfort. Animal studies have demonstrated serious effects on the brain from exposure to anesthesia and recent human studies have found indications of learning impairments following exposure to anesthesia. It is known from animal studies that anesthetic agents can affect proliferation as well as differentiation and can lead to learning impairments. In addition, the effects of irradiation on the young brain were investigated. Cancer is one of the most common causes of death in children and radiotherapy is commonly used to treat cancer (together with surgery and/or chemotherapy). During the last decades, improvements in treatment protocols have led to more and more children surviving their cancers. This has however also resulted in more children experiencing long-term side effects, particularly resulting from radiotherapy. These side effects include impaired intelligence and memory as well as attention deficits. From animal models, it is known that irradiation causes cell death and a long-term reduction in cell proliferation in the young brain that can result in impairment on some memory tasks.

In these experiments, we have used one model of repeated isoflurane exposure and one model for radiotherapy. The animals' behavior was investigated using the IntelliCage system, as well as other behavioral tests, followed by immunohistochemical analysis of the hippocampus. Isoflurane was found to cause a reduction in cell proliferation, accompanied by a reduction in neural stem cells. No evidence of cell death was seen, and the reason behind the reduction is therefore unknown. In addition, less neuronal differentiation was seen following isoflurane exposure, accompanied by an increase in astrocyte differentiation. These effects were especially clear when the young brain was exposed. Animals that were exposed to isoflurane at a young age later developed severe and progressive memory impairments. Following irradiation, a decrease in cell proliferation in the dentate gyrus of the hippocampus was seen. The irradiated animals displayed learning and relearning deficits judged by the IntelliCage analysis, but neither open field nor trace fear conditioning tests could detect impairments.

In summary, we found irradiation-induced changes in the hippocampus and saw changes in behavior, using the IntelliCage system, that were not detectable using other methods like open field and fear conditioning. We also found isoflurane-induced changes that suggest that the young brain is particularly sensitive to anesthetic agents like isoflurane and that isoflurane-anesthesia should be used with caution, especially in pediatric patients.

Keywords: Radiotherapy, isoflurane, anesthesia, dentate gyrus, neurogenesis, memory, learning, IntelliCage, trace fear conditioning, open field, object recognition.

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- I. Barlind A, Karlsson N, Björk-Eriksson T, Isgaard J, Blomgren K. **Decreased cytogenesis in the granule cell layer of the hippocampus and impaired place learning after irradiation of the young mouse brain evaluated using the IntelliCage platform.** *Experimental Brain Research*, (2010) 201, 781-787
- II. Zhu C, Gao J, Karlsson N, Li Q, Zhang Y, Huang Z, Li H, Kuhn HG, Blomgren K. **Isoflurane anesthesia induced persistent, progressive memory impairment, caused a loss of neural stem cells, and reduced neurogenesis in young, but not adult, rodents.** *Journal of Cerebral Blood Flow and Metabolism*, (2010) 30, 1017-1030
- III. Karlsson N, Kalm M, Nilsson MKL, Mallard C, Björk-Eriksson T, Blomgren K. **Learning and activity after irradiation of the young mouse brain analyzed in adulthood using unbiased monitoring in a home cage environment.** (*manuscript*)

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