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学位論文内容の要旨

Dissertation Abstract

博士の専攻分野の名称：博士（歯学） 氏名：Huang Helai

学 位 論 文 題 名

Measurement and analysis of blood glucose levels in rats at 5, 10, and 15 minutes after administration of general anesthetics.

（全身麻酔薬投与後 5, 10, 15 分におけるラットの血糖値の測定と解析）

Keywords: Hyperglycemia, Three-drug combination anesthetic, Propofol, Isoflurane, Sevoflurane

In recent years, from the perspective of animal ethics, appropriate analgesic effects have been required in the use of anesthesia for laboratory animals. Pentobarbital anesthesia (Nembutal®) was commonly used for rat surgeries; however, since this drug does not provide analgesic effects, it has been recommended to avoid using it alone since around 2016 (Dikmen et al, 2016; Okamura, 2016). Then, a new anesthesia method—a mixture of three drugs (MMB, medetomidine hydrochloride 0.375, midazolam 2, and butorphanol tartrate 2.5 in mg/kg) has become widely adopted worldwide. MMB has been demonstrated to provide adequate sedation, analgesia, and muscle relaxation as proper anesthetic effects, and its impact on vital signs and the composition of blood and body fluids has also been examined.

MMB is known to markedly increase blood glucose levels (Okamura, 2016). The inhalation anesthetics isoflurane (ISO) and sevoflurane (SEVO), which are also commonly used in animal experiments, have a blood glucose-elevating effect, although not as much as MMB (Dikmen et al, 2016; Okamura, 2016). On the other hand, propofol and pentobarbital (Nembutal®, Somnopentyl®, now discontinued), which should not be applied alone, have no glycemic elevating effect (Kitamura et al, 2009; Okamura, 2016). These data were measured at 15 minutes or more after anesthesia, so the acute changes in blood glucose levels within the first 15 minutes after anesthesia are unknown.

We conducted blood sampling from the tail vein under MMB anesthesia to use blood glucose levels as an indicator of hunger in rats kept under various fasting and feeding schedules. In fact, when we measured blood glucose levels in blood samples acutely obtained from rats within 10 min after MMB injection, we found that they were significantly higher than normal, but there was no previous study that measured such acute blood glucose elevation occurred within minutes after anesthesia administration. So, there was no knowledge to explain the mechanism of acute blood glucose elevation at all. Therefore, the aim of this study was to investigate the temporal changes in blood glucose levels immediately after the administration of anesthesia and to clarify the mechanism of acute hyperglycemia induced by general anesthetics.

Hyperglycemia induced by MMB is unlikely to occur in a hypoglycemic state following fasting. However, when the blood glucose concentration is higher than the fasting blood glucose level and glucose-induced insulin secretion is ongoing, medetomidine, a component of the triple combination anesthesia, induces hyperglycemia by suppressing insulin secretion via α_2 receptors. In both the propofol i.v. and propofol i.p. groups, there were no significant changes in blood glucose levels at any measurement point—5, 10, or 15 minutes after administration. These results are consistent with previous studies (Myles et al, 1995; Zuurbier et al, 2008; Kitamura et al, 2009; Tanaka et al, 2011; Yasuda et al, 2013; Sato et al, 2013) suggesting less effect of propofol on blood glucose dynamics. This may be associated with propofol's insulin secretion-promoting effect, as indicated by previous studies (Li et al, 2014; Sato et al, 2013; Sato et al, 2020). The inhalation anesthetics SEVO and ISO both showed a significant hyperglycemic effect as early as 5 minutes after administration. The results of this study indicated that the hyperglycemic effect of isoflurane was up to 2.7 times stronger than that of sevoflurane.

As described above, MMB, SEVO, and ISO were found to induce acute hyperglycemia within 5 to 10 minutes after administration. The findings obtained from this study are highly valuable for considering the effects of general anesthetics on glucose dynamics.