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Propofol reduces infarct size and striatal dopamine accumulation following transient middle cerebral artery occlusion: a microdialysis study

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Abstract

Acute cerebral ischemia is associated with an increased extracellular dopamine accumulation. Attenuation or prevention of excessive dopamine accumulation alleviates the cerebral ischemic damage. Propofol, an intravenous anesthetic, has been suggested to have neuroprotective properties. The effect of propofol on dopaminergic neurotransmitters is unclear. The in vivo microdialysis technique was used in this study to examine the effect of propofol on infarct size and striatal dopamine accumulation in rat model of temporary middle cerebral artery occlusion. Sixteen rats were fitted with a right striatal microdialysis probe. Ischemia was induced by inserting a 4-0 monofilament nylon suture into the middle cerebral artery. Propofol was intravenously infused in eight rats during ischemia (60 min) and reperfusion (60 min) at an average dose of 36 mg/kg/h. Control rats ($n = 8$) received vehicle infusion. The infarct size was determined at the end of the experiment. Propofol significantly reduced infarct size, the median (interquatile range) value was 6.84% (7.68%), significantly lower than that in the control group, which was 28.04% (32.28%) ($p < 0.01$). The middle cerebral artery occlusion significantly increased dopamine accumulation in the striatum. Propofol infusion significantly attenuated this middle cerebral artery occlusion-induced dopamine accumulation. The data demonstrate that propofol, when administered during ischemia and reperfusion, provides neuroprotection in our middle cerebral artery occlusion in rat model. The data also suggest that attenuated dopamine accumulation may be one of the factors contributing to the neuroprotective property of propofol.

Keywords: Cerebral ischemia; Dopamine; Propofol; Infarct size; (Rat)

1. Introduction

Propofol (2,6-diisopropylphenol) is an intravenous anesthetic characterized by its rapid induction of and awakening from anesthesia. In addition, propofol is also widely used as sedative for intensive care patients because of its easy titration. Propofol is lipophilic and easily crosses the blood–brain barrier. Previous observations that propofol depressed electroencephalographic activity (Kochs et al., 1992), decreased the cerebral metabolic rate for oxygen (Dam et al., 1990) and reduced cerebral blood flow (Ergun et al., 2002) suggest that propofol may have a neuroprotective effect against brain ischemia. Various studies have been carried out to examine this suggestion, but the usefulness of propofol in the treatment of acute cerebral ischemia remains to be defined.

Acute cerebral ischemia induces a neurotoxic cascade resulting in various biochemical and metabolic disturbances. One such event is the accumulation of extracellular dopamine. An earlier microdialysis study provided direct evidence that striatal ischemia is associated with excessive dopamine accumulation (Wood et al., 1992). Some mechanisms underlying the detrimental effect of excessive dopamine on neurons have been suggested. Oxidation of large amounts of dopamine promotes the generation of free radicals, in particular, in regions of the brain such as the striatum (Lei et al., 1997). The generated free radicals can further oxidize dopamine. The oxidized dopamine can form covalent bonds, which may lead to modification of protein structure and function, thus tissue damage (Graham, 1984).

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Dopamine can also react with hydroxyl radicals to form the dopaminergic neurotoxin 6-hydroxydopamine (Slivka and Cohen, 1985). Dopamine may directly inhibit mitochondrial respiration (Globus et al., 1987). These facts suggest that attenuation or prevention of dopamine accumulation may reduce cerebral ischemic damage. This was supported by studies which showed that depletion of dopamine alleviated cerebral damage (Lei et al., 1997; Globus et al., 1987). Our previous study also showed that hyperbaric oxygen attenuated ischemia–reperfusion focal cerebral injury accompanied by significantly decreased dopamine accumulation in the striatum (Yang et al., 2002). In the present study, the microdialysis technique was used to evaluate the effect of propofol infusion on infarct size and striatal dopamine level following temporary middle cerebral artery occlusion in rats.

2. Materials and methods

This study was approved by the State University of New York, Upstate Medical University, Syracuse Committee for the Humane Use of Animals, and followed the guidelines established by the National Institutes of Health. Male Sprague–Daley rats weighing 350–400 g (Taconic Farm, Germantown, NY, USA) were used. The rats were randomized into study and control groups ($n = 8$ for each group).

2.1. Anesthesia

The rats were anesthetized by intramuscular injection of a mixture of ketamine and xylazine (150:30 mg/ml) at a dose of 0.6 ml/kg. Anesthesia was maintained with an additional dose as needed in control rats. In study rats, when the propofol infusion started, ketamine and xylazine were no longer used.

2.2. Cannulation jugular vein and femoral artery

The right jugular vein was cannulated with a silastic catheter (0.025 in. ID, 0.047 in. OD). The right femoral artery cannulation was performed with a 20-gauge i.v. catheter (Insyte-WTM; Becton-Dickinson, Sandy, UT, USA). This cannula served for monitoring systemic blood pressure.

2.3. Brain ischemia–reperfusion injury model

The right common carotid artery, internal carotid artery and external carotid artery were exposed and isolated. The distal portion of the external carotid artery was ligated with 4-0 silk sutures. The common carotid artery and internal carotid artery were temporarily clamped with Schwarz-microvascular clips. The middle cerebral artery was occluded by inserting a 4-0 monofilament nylon suture via a small puncture. The skin was closed with 3-0 silk running sutures. After 1 h of ischemia, reperfusion was achieved by pulling the 4-0 monofilament nylon suture to the origin of the external carotid artery.

2.4. Intracerebral probe placement

An intracerebral cannula guide was implanted into the right striatum. The stereotaxic coordinates from the bregma were: mediallateral, 4 mm from the middle line and dorsal–ventral, 4 mm ventral from the surface of the dura (Paxinos and Watson, 1998). The cannula guider was fixed to the skull with acrylic dental cement. After operation, rats were allowed to recover for 7 days.

2.5. Microdialysis procedure

A microdialysis probe (CMA/12, 14/02 PC, CMA/Microdialysis, Stockholm, Sweden) was inserted through the cannula guide into the striatum. Artificial cerebrospinal fluid (CSF, CMA/Microdialysis) was perfused at 2 μl/min. Body temperature was monitored with a rectal probe and controlled at approximately 37.0–37.5 °C with a heating pad and light. The microdialysis samples were continuously collected into an ice-cold vial at 15-min intervals and measured immediately.

2.6. Propofol infusion

In study rats, propofol infusion (DIPRIVAN, Zeneca Pharmaceuticals; Wilmington, DE, USA) was started immediately following the occlusion of the middle cerebral artery via the right jugular vein catheter with a CMA/12 Microdialysis pump (CMA/Microdialysis). The initial infusion rate was 150 mg/kg/h and was titrated to maintain the blood pressure within 20% of the baseline value. The average infusion rate was 36 mg/kg/h. In the control group, a vehicle (Intralipid) was given.

2.7. Dopamine measurement

Dopamine and metabolites were measured by using reverse-phase liquid chromatography with an ESA Model 5014 high sensitivity analytical cell and ESA Hypersil ODS column (15 cm × 4.6 mm ID). The mobile phase consisted of 75 mM $NaH_2PO_4H_2O$), 1.4 mM OSA, 10 mM EDTA and 10% acetonitrile. The concentration of dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC) was determined by comparison with peak areas of standards run with each experiment.

2.8. Determination of infarct size

At the end of 2 h of reperfusion, anesthetized rats were perfused via cardiac puncture with normal saline followed by 20 ml of 2% 2,3,7-triphenyltetrazolium chloride solution. The brains were removed, and then fixed in 10%

formaldehyde. Twenty-four hours later, the brains were sectioned into eight coronal sections and optically scanned. The size of the infarct area and hemispheric area of each section were traced using computer-assisted color image selection by Adobe PhotoShop 6.0. The area was measured and analyzed using Scion Image 4.0.2b (NIH image software for PC). The percentage of infarction was calculated by dividing the sum of the total infarct area by the sum of the total area of the ipsilateral hemisphere in one brain to produce a cubic measurement.

2.9. Data analysis

The average percent infarct volume was calculated for each rat in both groups. The median and interquartile range of the measurements for each group was compared. The Mann–Whitney nonparametric test was used to examine the hypothesis that there is no difference in the median percent infarct volume between the two groups. The baseline values of dopamine, DOPAC were determined by using a mean value of three consecutive samples prior to middle cerebral artery occlusion. The changes in dopamine and DOPAC are expressed as percent variations from the mean baseline and are expressed as means ± S.E. One-way repeated measures analysis of variance was used to analyze the time-course data within the group while Student's paired *t*-test was used (Statview 4.0, Abacus Concepts, CA, USA) for the comparison of two groups.

3. Results

3.1. Systemic blood pressure

The baseline blood pressure was similar in both groups of rats (118 ± 10 vs. 120 ± 12 mm Hg in control and study groups, respectively). No significant changes in blood pressure were observed in the control group during the entire experiment. Systemic blood pressure in the propofol-treated group was slightly decreased when the propofol infusion was initiated (105 ± 8 and 98 ± 12 mm Hg at the end of the ischemia and the end of reperfusion, respectively).

3.2. The effects of propofol on infarct size

The median (interquatile range) percent infarct volume in the study group was 6.84% (7.68%), which was significantly lower than the 28.04% (32.28%) in the control group ($p < 0.01$).

3.3. The effect of propofol on striatal dopamine accumulation

Baseline levels (pg/10 μl) of dopamine and DOPAC in the striatum of the two groups were not different. Dopamine was approximately 16 pg/10 μl and DOPAC was 24 pg/10 μl. As shown in Fig. 1, middle cerebral artery occlusion induced an immediate increase in dopamine level, which reached to approximately 1800% of baseline during 15 min of ischemia and remained elevated, thereafter, during the entire reperfusion period. There was no significant change in dopamine levels in the propofol-treated rats during either ischemia or reperfusion. DOPAC levels were not significantly changed during ischemia and reperfusion in both groups, and thus, the data are not presented.

4. Discussion

The main findings in the present study are: (1) middle cerebral artery occlusion-induced focal cerebral infarct was

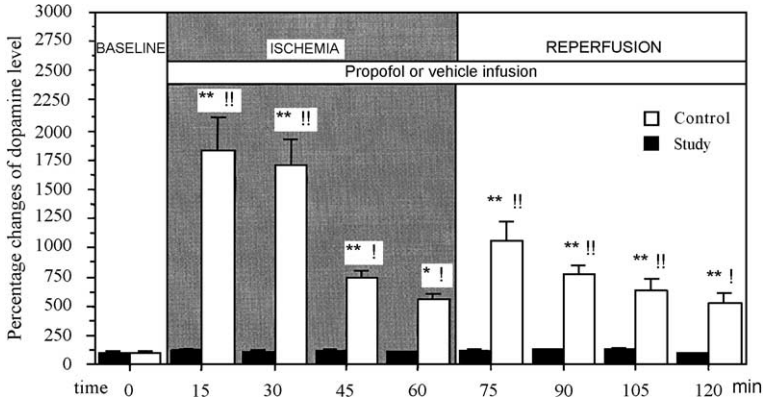

Fig. 1. The changes in striatal dopamine levels before (baseline), during (ischemia) and after (reperfusion) middle cerebral artery occlusion with or without propofol infusion. Middle cerebral artery occlusion induced an immediate increase in dopamine level, which reached approximately 1800% of baseline level during 15 min of ischemia and remained elevated during the entire ischemia–reperfusion period. There was no significant change in dopamine level in propofol-treated rats during either ischemia or reperfusion. Open column: middle cerebral artery occlusion without propofol infusion; dark column: middle cerebral artery occlusion with propofol infusion. $*p < 0.05$; $**p < 0.01$ vs. baseline; $!p < 0.05$; $!!p < 0.01$ between groups. Results are expressed as means ± S.E.

associated with exceedingly high dopamine accumulation in the striatum; (2) propofol infusion during ischemia and reperfusion reduced the cerebral infarct size and significantly decreased dopamine accumulation in the striatum.

The usefulness of propofol in the treatment of cerebral ischemia remains to be defined. Propofol has been reported to decrease infarct size (Lee et al., 2000), to improve behavior in focal ischemia (Kochs et al., 1992), to inhibit neuronal apoptosis after brain ischemia and to reduce neuronal death in the CA-1 pyramidal cell layer of the hippocampus (Kodaka et al., 2000; Yamaguchi et al., 2000). Conversely, propofol has also been reported not to have a protective effect in focal ischemia (Tsai et al., 1994) and in recovery of population spikes of CA-1 pyramidal layer following ischemia (Zhang et al., 2001). There seems no easy way to explain these discrepancies. Species, study models and baseline anesthetics may all be responsible. Ketamine was used in the present study, which has been suggested to have a neuroprotective effect (Reeker et al., 2000). The middle cerebral artery occlusion model of cerebral ischemia is surgically invasive and some anesthetic must be given. These anesthetic agents must be compared to identify relevant differences. To what extent ketamine might have protected the brain from ischemic injury in our study is not known. However, the reduced infarct size and dopamine accumulation in the propofol-treated rats were probably not due to the effect of ketamine, since ketamine was stopped when propofol was given.

Clinically, it is believed that in order to achieve neuroprotection against cerebral ischemia, electroencephalographic (EEG) burst-suppression should be attained. Therefore, a very high dose of propofol is needed. However, with a high dose, the protective effect of propofol may be offset by a major, and sometimes, dangerous decrease in systemic blood pressure secondary to its direct myocardial depressant effect resulting in a decrease in cerebral perfusion (Chen et al., 1997). However, one study demonstrated that maximal EEG suppression was not required for neuroprotection (Warner et al., 1996). Young et al. compared the protective effect of isoflurane and propofol in cerebral ischemia reperfusion injury at dose levels that produced similar affects on brain electrical activity. They found a 21% reduction in mean hemispheric infarct volume in the propofol group when compared with the isoflurane group (Young et al., 1997). Their data suggest that in addition to EEG suppression, other properties of anesthetics may also account for their neuroprotective effect. The dose of propofol used in the present study was titrated for each rat to achieve anesthesia and to maintain hemodynamic stability. The electrical status was not monitored in the present study, as EEG was not available. However, the dose of propofol used in the present study would not cause EEG silence (Lee et al., 2000). The present study suggests that the neuroprotective effect of propofol may be achieved at a dose that does not cause EEG silence. The present study also supports the notion that the neuroprotection provided by propofol might not be solely dependent on its EEG suppressive effect (Sano et al., 1992).

Propofol shares a similar structure with well-known, phenol-based free radical scavengers such as butyrate hydroxytoluene and water-based analogues of vitamin E. Oxygen-derived free radicals play a major role in mediating the tissue destructive effects of ischemia–reperfusion. Studies have suggested that propofol has antioxidant properties, prevents lipid peroxidation and enhances tissue antioxidant capacity (Kvam et al., 1993; Green et al., 1994; Runzer et al., 2002). A recent study showed that propofol attenuated ischemia–reperfusion induced lipid peroxidation in the therapeutic doses used in anesthesia (Kahraman et al., 1997). The generation of oxygen-derived free radicals during ischemia and reperfusion is greatly enhanced by increased dopamine accumulation (Ishii et al., 1994). The present study suggests that the antioxidant effect of propofol may be enhanced by reduced dopamine accumulation in focal cerebral ischemia injury.

The balance between inhibitory neurotransmitter action and the excitatory neurotransmitter effect is essential for maintaining normal neuronal function (Globus et al., 1991). It has been observed that during the acute stage of focal cerebral ischemia, the extracellular space is flooded by both potentially harmful (e.g., aspartate, glutamate, and dopamine) and protective (e.g., taurine, γ-aminobutyric acid (GABA), and adenosine) agents. The relative importance of these events for the development of cell death in the ischemic penumbra continues to be examined (Hillered et al., 1989). Propofol has been reported to directly activate GABA receptors and to potentiate the action of GABA, which attenuates the increase in glycine level (Sano et al., 1995). The present study suggests that the neuroprotective effect of propofol may be partially due to its ability to inhibit dopamine accumulation.

Elevated dopamine accumulation plays an important role in ischemic striatal injury. Several studies observed that (1) free radicals are generated (Lei et al., 1997); (2) these radicals may further oxidize dopamine, and in return, oxidized dopamine can form covalent bonds, which may cause modification of protein structure and function (Graham, 1984); (3) dopamine can also react with hydroxyl radicals to form the dopaminergic neurotoxin 6-hydroxydopamine (Slivka and Cohen, 1985); and (4) dopamine inhibits mitochondrial respiration (Ben-Shachar et al., 1995). One study also showed that depletion of dopamine alleviated brain damage (Lei et al., 1997). Our previous study showed that hyperbaric oxygen diminished middle cerebral artery occlusion-induced infarct size associated with a significantly reduced dopamine accumulation in the striatum (Yang et al., 2002). The present study showed that propofol also reduced middle cerebral artery occlusion-induced infarct size associated with a significantly reduced dopamine accumulation in the striatum. The actual mechanism underlying the inhibition of dopamine release by propofol is unknown. However, the present study supports

the importance of dopamine in the development of cerebral ischemic injury, and suggests that it may be a therapeutic approach to inhibit dopamine release in order to reduce focal cerebral ischemic injury.

The striatum is supplied exclusively by the lenticulostriatal end arteries, and a striatal infarct represents the ischemic core (Badr et al., 2001). In recent years, in vivo microdialysis has been used to directly detect changes in the striatal dopamine content in response to ischemia. Using a transient middle cerebral artery occlusion model, Lei et al. (1997) observed that ischemia induced an immediate increase in striatal dopamine release. The striatal dopamine level returned to baseline 40 min after ischemia started. The immediate increase in striatal dopamine release has also been observed in global ischemia models (Globus et al., 1987). Furukawa et al. (2001) observed that 10 min of ischemia induced by four-vessel occlusion brought about an immediate increase in the striatal dopamine level and reached a peak in 20 min. Our study is in agreement with theirs and supports the notion that the increased dopamine accumulation following middle cerebral artery occlusion reflects acute ischemia in the striatum, and that dopamine is a sensitive marker of ischemia.

In summary, the middle cerebral artery occlusion induced focal cerebral ischemic injury in association with excessive extracellular dopamine accumulation. Propofol administration at an anesthetic dose during ischemia and reperfusion significantly alleviated the ischemic injury in association with reduced dopamine accumulation in the striatum.

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