Effects of Propofol and Nimodipine on the Changes of Polyamine Contents following Kainate-Induced Neurotoxicity in Rat Brain

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INTRODUCTION

Propofol (2,6-diisopropylphenol) is a short acting intra-
venous anesthetic recently introduced into clinical practice for induction and maintenance of anesthesia1. It is now widely used not only as an induction, but also a sole anesthetic and sedative agent2,3 and has barbiturate-like actions and has been shown to improve neurologic outcome and to decrease neurological damage4. Although the anesthetic properties of propofol are well established
and it is gaining increasing popularity in neuroanesthesia practice, its cerebral protective and studies of its influence on seizure activity in experimental animals and its use in epileptic patients have resulted in some controversial findings. Cerebral protection against neuronal injury is an important challenge for researchers in neuroscience field. The mechanisms that could explain propofol's potential cerebral protective effect remain to be determined.

The endogenous excitatory amino acids, glutamate and aspartate, have been implicated in the neuronal damage resulting from cerebral ischemia, and may also be involved in neurodegenerative disorders of different origin. Several compounds, structurally related to glutamate and/or aspartate, are also neurotoxic. One of the most potent of these is kainate (KA). KA is a glutamate analogue that binds to specific excitatory amino acid receptors in the CNS. The excitatory effect of KA leads to generalized convulsions when KA is administered systemically at convulsant doses and has been used to study a variety of CNS disorders involving excitation, excitotoxicity and acute cell loss.

Calcium plays a major role in regulating the level of neuronal excitability and in the process of long-term potentiation. The calcium channel blocker, nimodipine, has been reported to inhibit seizures induced by several experimental models of epilepsy.

The naturally occurring polyamines in mammalian cells are putrescine, spermidine, and spermine. Polyamines (PAs) are present in all living cells and they play a pivotal role in all cellular growth and developmental processes. Endogenous polyamines have multiple effects in the central nervous system and have been suggested to be neurotransmitters or neuromodulators. The polyamine system in brain is sensitive to any kinds of stress: chemical, thermal, physical, or metabolic stress. Changes or disturbances in PA metabolism have also been observed after electroconvulsive shock or agents producing seizures. PA are known to increase the cytosolic calcium ion concentration and induce release of excitatory amino acid. Since KA induced seizure is the model of pathological states in which disturbances in PA synthesis and metabolism. Recently, changes in brain PA levels have been observed after systemic or intracerebral KA administration.

So, to identify the putative neuroprotective effect of propofol, the main objective of this study was to characterize the effect of propofol administration on convulsions induced by KA comparing to calcium channel blocker, nimodipine.

**MATERIALS AND METHODS**

1) **Animals**

Male Sprague-Dawely rats, weighing 230~250 g were used for this study. These animals were kept in cages under light-dark cycle with light on from 7:00 to 19:00 hr. Food and water were available ad libitum.

2) **Chemicals**

The standard compounds putrescine (PU), spermidine (SD), spermine (SM) (as hydrochlorides), 1,8-diaminoctane, and KA were obtained from Sigma (St. Louis, Mo, USA). 4-Fluro-3-nitrobenzotrifluoride (FNBTF, Aldrich) was used in the measurement of polyamine. Propofol was purchased from Zeneca (UK) and was used as supplied as an aqueous emulsion. Nimodipine was purchased from RBI (Natick, MA, USA). Solvents-HPLC grade were purchased from Merck (Germany).

3) **Drug administration**

KA (10 mg/kg), propofol (25 mg/kg, 5 min prior to KA injection), and nimodipine (30 mg/kg, 60 min prior to KA injection) were administered intraperitoneally.

4) **Sample preparation**

At 3, 8, or 24 hr after KA administration (n=5 in each group), rats were killed by decapitation, and brains were removed from the skull. Brains were dissected as cerebral cortex, hippocampus, and striatum immediately. Tissue was also obtained from control saline-injected rats (n=4). Brain regions were weighed and stored in Eppendorf tubes at −70°C until analysis.