대한마취과학회지 1997; 33: S53~S61

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

Seong Ryong Lee, M.D. and **Jae Kyu Chun**, M.D.*

Department of Pharmacology and Department of Anesthesiology*,
School of Medicine, Keimyung University, Taegu, Korea

= 국문초록 =

Kainate에 기인된 신경독작용에 의한 백서 대뇌의 Polyamine 함량 변동에 대한 Propofol과 Nimodipine의 효과

계명대학교 의과대학 약리학교실 및 마취과학교실*

이 성 룡 · 전 재 규*

서 론: Polyamine의 특정한 생리학적 기전이 잘 밝혀지지 않았지만 최근 많은 연구들을 통해 뇌의 여러 가지 병리학적 상태, 즉 간질발작, 전기적 자극, 허혈, 홍분성 독작용 조건등에서 polyamine의 함량이 현저히 변화하는 것으로 밝혀져 신경세포손상과 밀접한 연관이 있는 것으로 여겨지고 있다. 한편 propofol (2,6-diisopropylphenol)은 새로운 비barbiturate성 마취제로 신경마취에 널리 쓰이고 있으며 뇌보호작용에 대한 가능성에 대해 관심을 고취시키고 있다. 본 연구에서는 kainic acid투여에 의한 발작시의 polyamine함량변동에 대한 propofol의 영향을 nimodipine과 비교하여 보아 보호작용을 가늠하여 보고자 하였다.

방 법: Kainic acid (KA, 10mg/kg) 투여 3시간, 8시간, 및 24시간 후 cortex, hippocampus, 및 striatum을 분리하였고 propofol 및 nimodipine은 각각 25 mg/kg, 30 mg/kg로 투여하였다. Polyamine (putrescine; PU, spermidine; SD, spermine; SM)측정은 HPLC를 이용하였다.

결 과: KA투여 후 PU함량의 현저한 증가를 보이고 시간-의존적이며 이 양상은 propofol과 nimodipine에 의해 억제되었다. SD와 SM함량은 cortex와 hippocampus에서 다소 감소하였다. 이 SD 및 SM 함량변동의 양상 역시 시간-의존적이며, propofol에 의해 다소 억제 되었다.

결 론: KA의 투여에 의한 경련발작시 백서 뇌의 polyamine 함량변동, 특히 PU의 변동을 통하여 볼 때, nimodipine과 함께 propofol이 신경보호작용을 가질 수 있으리라 추정된다. **(Korean J Anesthesiol 1997; 33: S53~S61**

핵심 용어: 뇌: 경련 약리: 니모디핀 정맥마취제: 프로포폴

INTRODUCTION

Propofol (2,6-diisopropylphenol) is a short acting intravenous anesthetic recently introduced into clinical practice for induction and maintenance of anesthesia[1]. It is now widely used not only as an induction, but also a sole anesthetic and sedative agent[2,3] and has barbiturate- like actions and has been shown to improve neurologic outcome and to decrease neurological damage[4]. Although the anesthetic properties of propofol are well established

논문접수일 : 1997년 12월 5일
†본 논문은 대한의사협회 기초의학 진흥기금 연구비로 이루어졌음

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[5-9], and may also be involved in neurodegenerative disorders of different origin[10,11]. Several compounds, structurally related to glutamate and/or aspartate, are also neurotoxic. One of the most potent of these is kainate (KA)[12]. KA is a glutamate analogue that binds to specific excitatory amino acid receptors in the CNS[13]. 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[14].

Calcium plays a major role in regulating the level of neuronal excitability[15] and in the process of long- term potentiation[16]. The calcium channel blocker, nimodipine has been reported to inhibit seizures induced by several experimental models of epilepsy.

The naturally occuring polyamines in mammalian cells are putrescine, spermidine, and spermine[17,18]. 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[19]. 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[20,21] and induce release of excitatory amino acid[22]. 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[23,24].

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-diaminooctane ,and KA were obtained from Sigma (St. Louis, Mo, USA). 4-Fluoro-3-nitrobenzotrifluoride (FNBT, 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 −70C until analysis.