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THE ROLE OF PROSTAGLANDIN E2 (PGE2) IN CEREBRAL INFARCTION ASSOCIATED WITH DETRUSOR OVERACTIVITY. AN EXPERIMENTAL STUDY ON THE OCCURRENCE OF NEUROPLASTICITY

Hypothesis / aims of study

We have previously reported that, in the etiology of overactive bladder in cerebrovascular ischemia, the signal transfer that begins with the opening of glutamate receptors in the neurons of dorsal pontine tegmentum (DPT) is necessary, as are RNA transcription from DNA and the appearance of genes such as c-fos/zif268 and COX-2. In this study, we elucidate the way in which prostaglandins (PGs) which is the products of COX-2 downstream PGE synthase (PGES)/PGD synthase (PGDS) is related to detrusor overactivity (DO) after left middle cerebral artery occlusion (MCAO), and the location of neuroplasticity in micturition. We also report a study on the effects of PGE2 administration into rat intracerebroventricular (ICV), dorsal pontine tegmentum (DPT), and periaqueductal gray (PAG) tissues on micturition reflexes.

Study design, materials and methods

Ten-week-old Sprague-Dawley female rats were utilized. After MCAO, timed procurement of DPT/PAG areas was performed, followed by quantitative measurement of mRNA by real-time PCR. Also, in the measurement of PGs such as PGE2/PGD2/PGF2alpha, the EIA kit (Cayman) was utilized after microwave irradiation to the brain. We paid special attention to PGE2 and studied its effect on micturition reflexes by intracerebral administration. After a cystostomy was performed, the rat was prepared through the insertion of an ICV stainless steel tube under halothane anesthesia. When the rat awakened, PGE2 was administered through the stainless tube. The concentrations of PGE2 administered were 28pmol~2.8nmol. Then, under urethane anesthesia, a microsyringe insertion to DPT and a stainless steel tube insertion to PAG were done along with administration of PGE2. We further prepared a group of rats for PGE2 administration into PAG after intravenous administration of EP1 receptor antagonist (ONO8711) in an effort to determine whether or not the effect of PGE2 occurs via the EP1 receptor. The concentration of EP1 receptor antagonist administered were 0.1mg/kg.

Results

The appearance of PGES mRNA peaked at 5 hours afterMCAO and gradually decreased thereafter. PGDS mRNA increased till 24 hours post-infarct. PGE2 showed significant increases at 3 and 5 hours. PGD2 failed to show significant increases. In ICV and DPT, PGE2 (20µg/ml) administration increased bladder capacity by an average 33% and an average 38%, respectively. On the other hand, administration of PGE2 (28pmol) to PAG caused a significant average 35% decrease in bladder capacity. This effect was blocked by the EP1 receptor antagonist (ONO8711).

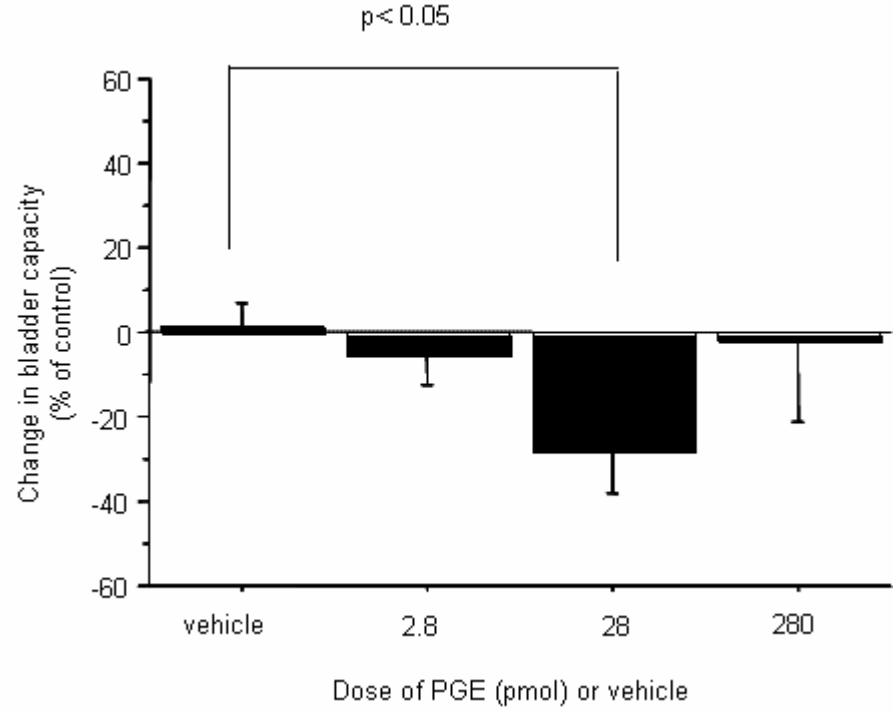

Figure Effect of PGE2 into PAG on bladder capacity. Significant decrease in bladder capacity was recognized at 2µg/ml PGE2 administration into PAG in rats.

Interpretation of results

In this study, PGE2 level was increased in the DPT/PAG areas after MCAO. By administration of PGE 2 into the ICV and DPT, the bladder capacity was increased. In PAG, on the other hand, the bladder capacity was significantly

decreased. Therefore, PGE2 was thought to mediate DO after cerebrovascular ischemia in rats, and the causative region of DO was believed to be the PAG.

Concluding message

After cerebrovascular ischemia, the arachidonic acid cascade is dynamically activated in the PAG and DPT. The results of this study suggested the possibility of PGE2 as a causative mediator of DO via the EP1 receptor.

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