Conclusions:

$P2X3^{-/-}$ mice (5-6 months old) have significantly increased urinary bladder filling capacity and decreased micturation frequency, suggesting that P2X3 receptors play an important role in urinary bladder sensory activity. The increased urinary bladder capacity was not apparent in young $P2X3^{-/-}$ mice (2 months old), suggesting that this bladder dysfunction develops over time. Given these findings, it is proposed that P2X3 antagonists may be useful in the treatment of conditions of poor bladder compliance, e.g., overactive bladder.

Figure 1

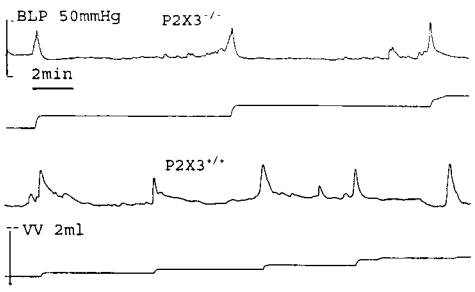
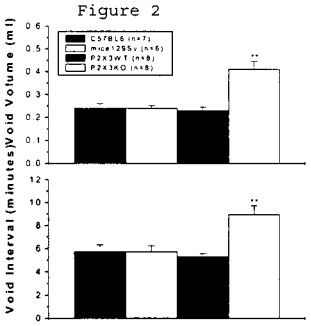


Figure 2



References:

1. A P2X purinoceptor expressed by a subset of sensory neurons, *Nature*, (1995) 377: 428-431.

2. Distribution of P2X purinoceptors in the urinary bladder and the ureter of the rat, (2000) *J.Urol*, In press.

3. Purinergic sensory neurotransmission in the urinary bladder: an *in vitro* study in the rat, *BJU international*, (1999) 84: 854-860.

24

Author(s):
S. Matsuura, T. Shiga, T. Mitsui, H. Kakizaki, K. Ameda, H. Tanaka, C. Katoh, N. Tamaki, T. Koyanagi

Institution, city, country:
Departments of Urology and Radiology Section of Nuclear Medicine
Hokkaido University School of Medicine, Sapporo, Japan

Title (type in CAPITAL LETTERS, leave one blank line before the text):

A POSITRON EMISSION TOMOGRAPHY (PET) STUDY ON BRAIN CONTROL OF URINE STORAGE IN HUMANS

Aims of study It is broadly accepted that the brain control is crucial to maintain the urinary continence. In fact patients with cerebrovascular disease often have urge incontinence. However, little is known regarding which lesions in the brain cause such urine storage dysfunction in human. As the first step to answer this question, this study was performed to clarify the human brain regions involved in the voluntary urine storage, using positron emission tomography (PET).

Methods Brain activation was measured in male healthy and right-handed volunteers (n=8, age range 27-41, mean age 33 years). With the head fixed in an air-pressured mold, the subjects were placed in a horizontal position in the PET camera (ECAT EXACT HR+, Siemens-CTI, TN, USA). Beforehand 8 Fr. catheter was indwelled in each subject and the bladder was made empty. A

transmission scan of 10 minutes was first made for attenuation correction of the emission scans, followed by 3 scanning sessions (6 scans in total). Each scanning session consisted of two measurements, scan-1 in the empty bladder phase and scan-2 in the full bladder, and was repeated three times. Before each scan, 300 MBq of $H_2{}^{15}O$ in saline was intravenously injected. Data acquisition was initiated 40 seconds after the beginning of injection and continued for 90 seconds. To decrease the radiation levels to the background, at least 10 minutes were allowed to elapse between the injections. For filling bladder, distilled water was dripped via the catheter, and the infusion was stopped when the volunteer felt the maximum desire to void. Once a scan-2 was completed, the bladder was emptied again via the catheter for a next scan. The data of each scan were summated and further analyzed using the Statistical Parametric Mapping procedure (SPM95, the Wellcome Department of Cognitive Neurology, London, UK) on a computer. The SPM95 software was used for anatomical realignment, normalization, smoothing and statistical analysis. A corrected P-value less than 0.001 was considered significant.

Results The mean bladder capacity was 400 ml (300-480 ml). During active urine storage, significantly increased blood flow was found in the anterior cingulate gyrus, the thalamus and the upper level of the midbrain, predominantly on the left side. Only the lower part of the midbrain periaqueductal gray showed significant activation on the right side.

Conclusions Our data suggest that the midbrain as well as more rostral regions are involved in the urine storage function in the human brain. Blok et al. previously reported the cortical and pontine micturition sites to be located on the right side [1]. In our PET study, however, significant brain activation associated with urine storage occurs predominantly on the left side.

Reference [1] Brain, 120 (1997) 111-121.

25

K. Kaidoh, *H. Takeda, *Y. Yamazaki, *S. Akahane, *H. Miyata, *Y. Ajisawa, Y. Igawa, O. Nishizawa & **K. -E. Andersson

Department of Urology, Shinshu University School of Medicine, Matsumoto, *Central Research Laboratories, Kissei Pharmaceutical Co., Ltd., Hotaka, Japan and **Department of Clinical Pharmacology, Lund University Hospital, Lund, Sweden

EFFECTS OF SELECTIVE β2- AND β3-ADRENOCEPTOR AGONISTS ON DETRUSOR HYPERREFLEXIA IN CEREBRAL-INFARCTED RATS

AIMS OF STUDY It is well known that excitation of the sympathetic nerves during the filling phase, relaxes the bladder via activation of β-adrenoceptors. We have demonstrated using an in vitro functional study that the subtypes of β-adrenoceptor that contribute to the detrusor relaxation in the rat are β2- and β3-adrenoceptors (1).

A rat model of detrusor hyperreflexia associated with cerebral infarction has been recently developed (2). In the present study, we investigated whether selective β2- and β3-adrenoceptor agonists could suppress detrusor hyperreflexia in conscious cerebral-infarcted (CI) rats.

METHODS Female Sprague-Dawley rats weighing 210-260 g (n=132) were used. Under general anesthesia with ketamine and xylazine, a catheter was implanted into the bladder through the dome and a separate catheter into the right jugular vein for drug administration. Three or four days after the operation, cystometric investigations were performed without any anesthesia as a base-line study. Then, the rats were anesthetized again with halothane and the left carotid artery was exposed. The left middle cerebral artery was occluded with a 4-0 monofilament nylon thread introduced from the carotid bifurcation by 17 mm in CI group. In sham-operated animals, the left carotid artery was exposed, but no further procedures were performed. Two hours after the operation, cystometric investigations were repeated without any anesthesia. Then, the effects of intravenous (i.v.) administration of saline (1