Pathophysiological Significance of a Novel Vasopressin Receptor (Vp) in Stroke-prone Spontaneously Hypertensive Rat Kidneys. Hitoshi Endou and Michio Takeda. Department of Pharmacology and Toxicology, Kyorin University School of Medicine, Tokyo-to 181.

Objectives of this study were to evaluate the receptor subtypes of arginine vasopressin (AVP) within the single nephron of rat kidneys and to investigate a possible involvement of a novel receptor subtype named Vp in hypertension.

The animals used in this investigation were male Sprague-Dawley rats (8-10 week-old), young (4-5 week-old) and adult (14-16 week-old) Wistar-Kyoto (WKY) and age-matched stroke-prone spontaneously hypertensive (SHRSP) rats. Kidneys were perfused with 0.1% collagenase and slices were incubated at 37°C for 30 min. Nephron segments microdissected under a stereomicroscope were early proximal tubule (S1), medullary thick ascending limbs of Henle's loop (MTAL), and outer medullary collecting tubules (OMCT). Intracellular free calcium ([Ca++]i) was determined using the fluorescent indicator Fura-2AM, and intracellular ATP content was quantified by the luciferin-luciferase bioluminescence method.

Physiological concentration (±10⁻¹²M) of AVP in MTAL and OMCT mobilized [Ca++]i in a dose-dependent manner, but relatively high concentration (±10⁻⁹M) of AVP in S1 increased [Ca++]i. AVP (10⁻⁷M) transiently increased [Ca²⁺], followed by sustained phase for 14-18 min in these nephron segments. Moreover, pretreatment with both V1 and V2 antagonists in MTAL or OMCT completely inhibited the AVP-induced [Ca++]i transient, but in S1 partially blocked it. DDAVP (10⁻⁷M), a specific V2 agonist, in MTAL and OMCT transiently mobilized [Ca++]i, but not that in S1 of both strains. Using several AVP analogues, a relative distribution of AVP receptor subtypes was tentatively calculated in each nephron segment, indicating that although these nephron segments possess V1, its density was very low (about 10%). The majority (about 90%) of AVP receptor in MTAL and OMCT was V2, while that in S1 was a new subtype (Vp) which is insensitive to V1 and V2 antagonists. AVP (10⁻⁷M)-induced [Ca++]i transient in S1 from SHRSP was significantly lower than that in S1 from age-matched WKY, and the attenuation in adult rats was remarkably higher than that in young rats. [Ca²⁺] transients by AVP in MTAL and OMCT from SHRSP were similar to those in MTAL and OMCT from age-matched WKY. To evaluate physiological significance of Vp receptor, AVP-mediated cellular ATP change was measured. Cellular ATP content in S1 was significantly increased by 10⁻⁷M AVP, but in MTAL it was significantly decreased by the same concentration of AVP. Similar to SD rats, the cellular ATP content in MTAL of WKY and SHRSP was significantly decreased by incubation with 10⁻⁷M AVP under no substrate, but ATP in S1 of WKY was increased. Interestingly, cellular ATP content in S1 of adult SHRSP significantly decreased with the addition of 10⁻⁷M AVP.

This study suggests that a novel AVP receptor exists in isolated rat S1, and its physiological significance may be the inhibition of ATP-consuming ion transport system. Its property in hypertensive rat S1 is gradually attenuated by aging. Accordingly, Vp receptor could be considered an important regulator involved in manifesting volume-expanded hypertension.