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THE EFFECTS OF E2110, A NOVEL SELECTIVE 5-HT1A RECEPTOR ANTAGONIST, ON THE MICTURITON REFLEX IN CEREBRAL INFRACTED RATS AND SPONTANEOUSLY HYPERTENSIVE RATS.

Hypothesis / aims of study

The relationships between the function of serotonin1A (5-HT1A) receptor and the control of micturition are suggested. It is well known that 5-HT1A agonists induce the frequent micturition in conscious rats. The action sites of 5-HT1A receptor agonist are thought to be Raphe nuclei in brainstem and Onuf's nucleus in spinal cord. E2110 is a novel 5-HT1A receptor antagonist that has been developed for the treatment of overactive bladder syndrome. The purpose of this study was to examine the effects of E2110 on activated bladder function using the cerebral infarcted rats and spontaneously hypertensive rats (SHR).

Study design, materials and methods

(1) Fifty male Sprague-Dawley rats were used. Cerebral infarction was induced by middle cerebral artery occlusion. Cerebral infarcted rats were divided into five groups; vehicle group (n=10), solifenacin group (n=10), E2110 0.03 mg/kg group (n=10), E2110 0.1 mg/kg group (n=10) and E2110 0.3 mg/kg group (n=10). E2110 was administered intravenously. To evaluate the efficacy of E2110, the micturition interval, single micturition volume, basal pressure, micturition pressure and residual volume were measured.
(2) Ten female WKY/Hos rats and forty female SHR/Hos rats were used. SHR were divided into four groups; vehicle group (n=10), E2110 0.3 mg/kg group (n=10), E2110 1.0 mg/kg group (n=10) and E2110 3.0 mg/kg group (n=10). E2110 was administered perorally. To evaluate the efficacy of E2110, the frequent micturition, micturition interval and single micturition volume were measured.

Results

(1) The cerebral infarcted rats showed a shortening in the micturition interval and decrease in the single micturition volume and an increase in residual volume, but no change in micturition pressure. E2110 and solifenacin significantly prolonged the micturition interval and increased the single micturition volume without change in micturition pressure (Table.1).
(2) SHR showed frequent micturition compared with WKY rats. E2110 significantly reduced frequency of micturition along with prolongation of micturition interval and increase in the micturition volume (Table.2).

Interpretation of results

(1) The after administration values for micturition interval and single micturition volume in each group showed significant prolongation compared to before administration. Even in the vehicle group, some prolongation was noted in comparison to the before administration value. This is commonly noted in urinary disorder models. In addition, though the values of before and after administration were changed slightly, significant differences were noted due to the individual data being uniform in the vehicle group. With the values for micturition interval and single micturition volume following administration in the vehicle group understood as the range of spontaneous recovery, comparison of each dose group with the vehicle reveals significant prolongation in the micturition interval in the E2110 0.03 mg/kg group as well as significant increase in single micturition volume in the E2110 0.03 and 0.3 mg/kg groups. Comparing the ratios of change, the solifenacin, E2110 0.03 and 0.3 mg/kg groups showed significantly high rates of change in voiding interval compared to the vehicle group.
(2) The E2110 1.0 mg/kg and 3.0 mg/kg groups exhibited reduction in frequency of micturition along with prolongation of micturition interval and increase in the micturition volume, based on which it was judged that E2110 has ameliorating effect on frequent micturition. The E2110 0.3 mg/kg group showed neither the reduction in micturition frequency or the prolongation of micturition interval, but the prolongation of micturition interval were noted in the preliminary study, suggesting that 0.3 mg/kg is a borderline dosage for appearance of pharmaceutical effect by E2110. However, as frequency of micturition and micturition interval remained unchanged while micturition volume increased, it seems likely that E2110 has a bladder volume increasing effect.

Concluding message

These results suggest that E2110 may improve detrusor overactivity without causing urinary retention and may be a promising drug in the treatment of patients with overactive bladder syndrome.

Table.1 Effect of E2110 on micturition intervals, single micturition volume, basal pressure, micturition pressure and residual volume in cerebral infarcted rats.

Treatment	n	Micturition interval (sec)		Single micturition volume (g)	
		Pre-administration	Post-administration	Pre-administration	Post-administration
Vehicle	10	311 ± 29	383 ± 28 *	0.13 ± 0.02	0.20 ± 0.02 *
			(1.3 ± 0.1)		(1.7 ± 0.2)
Solifenacin	10	295 ± 40	457 ± 44 **	0.17 ± 0.03	0.27 ± 0.03 **
			(1.7 ± 0.2)#		(1.8 ± 0.2)
E2110 - 0.03mg/k	10	334 ± 27	546 ± 70 **	0.17 ± 0.02	0.36 ± 0.05 *
			(1.7 ± 0.2) #		(2.9 ± 1.1)
E2110 - 0.1mg/kg	10	339 ± 35	509 ± 79 *	0.17 ± 0.03	0.31 ± 0.08 *
			(1.5 ± 0.1)		(1.8 ± 0.2)
E2110 - 0.3mg/kg	10	311 ± 26	569 ± 89 *	0.18 ± 0.03	0.36 ± 0.07 *
			(1.8 ± 0.2) #		(2.4 ± 0.7)

Treatment	n	Basal pressure (mmHg)		Micturition pressure (mmHg)		Residual volume (g
		Pre-administration	Post-administration	Pre-administration	Post-administration	
Vehicle	10	11.1 ± 1.2	11.0 ± 1.0	30.5 ± 2.4	32.3 ± 3.6	0.06 ± 0.01
			(1.0 ± 0.1)		(1.1 ± 0.1)	
Solifenacin	10	11.7 ± 1.7	11.7 ± 1.8	34.6 ± 3.5	32.7 ± 3.5	0.08 ± 0.01
			(1.0 ± 0.0)		(1.0 ± 0.0)	
E2110 - 0.03mg/k	10	11.1 ± 0.6	10.8 ± 0.8	35.3 ± 2.5	36.9 ± 3.2	0.11 ± 0.03
			(1.0 ± 0.0)		(1.1 ± 0.0)	
E2110 - 0.1mg/kg	10	10.5 ± 0.4	10.2 ± 0.5	29.1 ± 1.1	29.3 ± 0.9	0.09 ± 0.02
			(1.0 ± 0.0)		(1.0 ± 0.0)	
E2110 - 0.3mg/kg	10	10.1 ± 0.4	10.5 ± 0.5	33.2 ± 1.5	33.4 ± 1.4	0.11 ± 0.03
			(1.1 ± 0.1)		(1.0 ± 0.1)	

Each value represents the mean ± S.E.

(Values in parenthesis are the changes from before administration)

*: p<0.05,**: p< 0.01; Significant difference from before administration (paired t-test)

#: p<0.05; Significant difference from vehicle group (t-test)

Table.2 Effect of E2110 on frequency of micturition, micturition interval and single micturition volume in SHR.

Treatment	n	Frequency of micuturition (times)		Micturition interval (sec)	
		Before	After	Before	After
WKY / Vehicle	10	5 ± 1	9 ± 0	4660 ± 1388	1631 ± 174 a
SHR / Vehicle	10	9 ± 1 *	10 ± 1	1703 ± 169 *	1649 ± 190
SHR / E2110 - 0.3mg/kg	10	8 ± 1	8 ± 1	1808 ± 236	1930 ± 227
SHR / E2110 - 1.0mg/kg	10	8 ± 1	6 ± 1 #,a	2098 ± 250	2769 ± 353 #
SHR / E2110 - 3.0mg/kg	10	10 ± 2	6 ± 1 #	1639 ± 227	2297 ± 322

Treatment	n	Single micturition volume (g)	
		Before	After
WKY / Vehicle	10	0.56 ± 0.30	0.15 ± 0.02
SHR / Vehicle	10	0.23 ± 0.03	0.19 ± 0.03
SHR / E2110 - 0.3mg/kg	10	0.18 ± 0.03	0.35 ± 0.07 a
SHR / E2110 - 1.0mg/kg	10	0.21 ± 0.03	0.46 ± 0.08 ##,a
SHR / E2110 - 3.0mg/kg	10	0.19 ± 0.03	0.40 ± 0.04 #,aa

Each value represents the mean ± S.E.

*: p<0.05; Significant difference from WKY group (Student's t-test)

#: p<0.05,##: p<0.01; Significant difference from vehicle group (Dunnett's multiple test)

a: p<0.05,aa: p<0.01; Significant difference from before administration (Student's t-test)

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Institutuinal animal Ethical Committee of Eisai Co., Ltd.**