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THE ROLE OF 5-HT$_{2A}$ RECEPTORS IN THE BLADDER SMOOTH MUSCLE OF DIABETIC RATS

Aims of Study

It is well known that cystopathy occurs frequently in diabetes mellitus. In general, diabetic cystopathy has been characterized by impaired bladder sensation, increased bladder capacity and decreased bladder contractility, resulting in increased residual urine, urinary retention or overflow incontinence[1)]. Due to the impaired bladder sensation, the subjective symptoms of diabetic cystopathy do not always match diabetic progression in the patient. Finding a cure for diabetic cystopathy is therefore often difficult.

On the other hand, 25-55% of patients with diabetic cystopathy have detrusor hyperreflexia[2,3)]. It is difficult to assess whether the presence of detrusor hyperreflexia in patients is inherent to diabetes. Not only osmotic diuresis but also detrusor hyperrflexia may give rise to urinary frequency. Although anticholinergic drugs are often administered to patients with urinary frequency, it is difficult to cure. It appears that non-adrenergic and non-cholinergic (NANC) neurotransmitters may be related to diabetic cystopathy in some way. We thus paid attention to 5-hydroxytryptamine (5-HT), one of the NANC neurotransmitters.

The bladder smooth muscle of streptozotocin-induced diabetic rats contracts at lower concentrations of 5-HT than that in controls and such concentrations are inhibited by the 5-HT$_{2A}$ receptor antagonist, sarpogrelate hydrochloride[4)]. In diabetic rats, an alteration of the 5-HT$_{2A}$ receptors has been suggested, although it remains to be elucidated whether the characteristics of the 5-HT$_{2A}$ receptor are in fact altered. This experimental study was therefore designed to characterize the 5-HT$_{2A}$ receptors in the bladder smooth muscle of streptozotocin-induced diabetic rats by employing radioligand binding assays, and the characteristics of the 5-HT$_{2A}$ receptors in the diabetic rats were compared with those in normals.

Methods

Streptozotocin was administered to 8-week-old male Wistar rats. Age-matched control rats received the same volume of vehicle alone. Four weeks after, bladder domes were dissected and membrane specimens were obtained.

Using [^{3}H]ketanserin (1 nM and 10 nM) and [^{3}H]DOB (10 nM), comparisons were made between the control and diabetic group. The non-specific binding was determined in the presence of 10 mM sarpogrelate hydrochloride (for [^{3}H]ketanserin binding) and 100μM DOI hydrochloride (for [^{3}H]DOB binding). The specific binding was expressed as the difference between the total binding and non-specific binding.

The Kd and Bmax values were estimated using a computer-assisted iterative program. The significance of differences between the two groups was assessed by Student's t-test. A p-value of less than 0.05 was considered as significant.

Results

In the diabetic group, the binding of [^{3}H]ketanserin tended to decrease in comparison with that in the controls. In both groups, the [^{3}H]ketanserin binding was inhibited in a dose-dependent manner by sarpogrelate hydrochloride, however the diabetic group was inhibited by lower concentrations of sarpogrelate hydrochloride than the control group.

The [^{3}H]DOB binding in the diabetic group was significantly lower than that in the control group ($p<0.05$). Scatchard plots of the [^{3}H]DOB binding exhibited a single binding site in both groups. The Kd value in the control and diabetic group were 23.1±4.7 μM and 7.7±3.2 μM, and the Bmax values were 1270±350 pmol/mg protein and 305±84 pmol/mg protein, respectively. The affinity for [^{3}H]DOB binding in the diabetic group was significantly higher than that in the control group ($p<0.0001$). The Bmax value in the diabetic group tended to be lower than that in the control group, but no significantly difference was observed between the two.

Conclusions

Our results clearly demonstrated that the affinity for 5-HT$_{2A}$ receptors in the rat bladder smooth muscle was significantly increased in diabetes mellitus. The contractile response of the bladder smooth muscle is related to the 5-HT$_{2A}$ receptors, but the question remains as to whether or not 5-HT$_{2A}$ receptors antagonist can be applied clinically. Sarpogrelate hydrochloride, a 5-HT$_{2A}$ receptors antagonist, has been employed clinically for arteriosclerosis obliterans. At present, we are attempting to use sarpogrelate hydrochloride in patients with diabetes mellitus and urinary frequency.

References

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