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CHARACTERIZATION OF MUSCARINIC RECEPTOR OCCUPANCY IN THE URINARY BLADDER AND SUBMAXILLARY GLAND BY ORAL AND TRANSDERMAL OXYBUTYNIN

Aims of Study

Urge urinary incontinence with bladder instability (detrusor instability or detrusor hyperreflexia) is one of the most common types of incontinence in geriatric patients [1]. Anticholinergic agents such as oxybutynin have been widely used to treat this symptom since parasympathetic innervation is the predominant stimulus for the bladder contraction [2]. However, the use of oxybutynin in therapy is often restricted by its undesirable side-effects such as dry mouth, which present frequently as serious problems in patients receiving oral oxybutynin [3]. In order to reduce or even eliminate serious side-effects of oral oxybutynin, transdermal therapeutic system (TTS) of oxybutynin (CS-801) has been currently suggested to cause less incidence of dry mouth than oral oxybutynin. The therapeutic effect and dry mouth by oxybutynin in patients with bladder instability are mainly mediated through the blockade of muscarinic cholinergic receptors (mAChR) in the bladder and salivary gland, respectively. Our previous studies have shown that the transdermal application of CS-801, compared with oral oxybutynin, reduced significantly the activity of muscarinic receptor binding in the submaxillary gland of rats [4]. To clarify the pharmacological usefulness of transdermal oxybutynin, therefore, we examined comparatively mAChR occupancy in the bladder and submaxillary gland of rats, estimated from binding parameters of [N-methyl-^{3}H]scopolamine (NMS) in these tissues in relation to the plasma concentration of oxybutynin and its active metabolite (N-desethyloxybutynin: DEOB), after transdermal (CS-801) and oral oxybutynin.

Method

At 0.5 to 24 hr after the transdermal (CS-801) and oral administration of oxybutynin, rats were sacrificed by exsanguinations from the descending aorta, and the bladder and submaxillary gland were dissected. The mAChR in each tissue were measured by a radioreceptor binding assay with [^{3}H]NMS as a radioligand [5], and binding constants of apparent dissociation constant (Kd) and maximal number of binding sites (Bmax) for [^{3}H]NMS were estimated by Scatchard analysis. The concentration of oxybutynin and DEOB in the plasma of these rats was also measured by gas chromatography and mass spectrometry (GC/MS). Based on these data, the mAChR occupancy (RO) in the bladder and submaxillary gland of rats were estimated by the following equations: RO(Kd)(%)=[C/(C+EC50)]x100, and RO(Bmax)(%)={[Bmax(cont)–Bmax(drug)]/Bmax(cont)}x100, which C is the concentration of oxybutynin or DEOB and EC50 is the concentration required to produce 50 % of maximal enhancement of Kd for specific [^{3}H]NMS binding in each tissue.

Results

Following the oral administration of oxybutynin (127 mol/kg), there was a significant occupancy of mAChR in the bladder and submaxillary gland of rats. RO(Kd) in the bladder and submaxillary gland was maximal (approximately 40 and 90 %, respectively) at 3 hr after the oral administration of oxybutynin. Furthermore, RO(Bmax) (30-50 %) was seen at 1 to 24 hr later, only in the submaxillary gland. The plasma concentrations of oxybutynin and DEOB were maximal at 1 hr after the oral administration of oxybutynin and it was extremely low at 12 and 24 hr later.

The transdermal application of CS-801 (oxybutynin: 33.6 mol/rat) brought about a significant occupancy of mAChR in the bladder (30 %) and submaxillary gland (70 %) of rats. The RO(Kd) in both tissues was increased with the application time of CS-801, being maximal at 12 hr later. On the other hand, RO(Bmax) was little observed in the submaxillary gland. The plasma concentration of oxybutynin increased with the application time of CS-801, and the maximal level was seen at 12 hr and maintained until the application time of 24 hr. DEOB was not detected in the plasma of CS-801-administered rats.

Conclusions

These data indicate that the transdermal (CS-801) and oral oxybutynin occupies significantly mAChR in the bladder and submaxillary gland of rats and that the sustained occupancy of mAChR in the submaxillary gland characterized by the RO(Bmax) is occurred by oral but not by transdermal oxybutynin. Thus, the present study may provide a rationale for less incidence of dry mouth by transdermal application of CS-801 in the therapy of bladder instability.

References.

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