639

Ito Y[1], Matsui M[1], Hikiyama E[1], Yoshikawa E[1], Woo J T[2], Teruya Y[2], Teruya T[3], Yamada S[1]
1. *University of Shizuoka,* ***2.*** *Okinawa Research Center Co., Ltd.,* ***3.*** *University of the Ryukyus*

EFFECTS OF NOBILETIN, A FLAVONE FROM SHEKWASHA (CITRRUS DEPRESSA), ON MUSCARINIC RECEPTORS AND VOIDING FUNCTION IN RATS

Hypothesis / aims of study

Nobiletin, is a polymethoxy flavonoid abundantly present in Citrus fuits including shekwasha (Citrus depressa) produced in southern parts of Japan such as Okinawa. Current studies have shown that nobiletin exhibits anti-inflammatory, antiallergenic, antiatherosclerotic and antitumor activities. This study aimed to clarify the effect of a shekwasha extract containing nobiletin and tangeretin (called as nobiletin mixture), on urodynamic functions in streptozocin (STZ) or acetic acid-injected rats. Futhermore, the binding activity of nobiletin on muscarinic receptors was examined.

Study design, materials and methods

The muscarinic receptor binding activity of nobiletin, tangeretin, quercetin, sinecetin in the rat tissue was examined by radioligand binding assay usin [^{3}H]pirenzepine and [^{3}H]*N*-methyl scopolamin([^{3}H]NMS) as selective radioligands of muscarinic (M_1 selective) and muscarinic (non-selective). The effect of chronic oral administration of nobiletin mixture (50 mg/kg/day) was examined on urodynamic parameters in STZ (50 mg/kg, i.p.) induced diabetic rats. The time of micturition and micturition volume were recorded after 4 weeks administration. Micturition frequency, voiding speed, voiding volume and micturition interval were calculated from the recorded data. The effect of single oral administration of nobiletin mixture (50 mg/kg) was examined on urodynamic parameters in cystometrograms of anesthetized rats induced by intravesical infusion of 0.1% acetic acid.

Results

Nobiletin, quercetin and sinecetin inhibited specific [^{3}H]pirenzepine binding in the rat brain in a concentration dependent manner with Ki values of 12.2, 34.8 and 33.0 μM, respectively. On the other hand, nobiletin and sinecetin partially inhibited specific [^{3}H]NMS binding. Tangeretin had a little effect on the muscarinic receptor binding activity in the rat tissue, evaluated by radioligand binding assays using [^{3}H]pirenzepine and [^{3}H]NMS (Fig.1).Chronic oral administration of nobiletin mixture in STZ induced diabetic rat caused an increase in the voided volume and decrease in the micturition frequency (Fig. 2).Single oral administration of nobiletin mixture in 0.1% acetic acid-infused rat cystometry caused an increase in the micturition interval and voided volume and a significant decrease of micturition frequency during the intravesical infusion of 0.1% acetic acid. The nobiletin mixture had little effect on the threshold pressure and basal pressure, but maximum micturition pressure was significantry increased.

Interpretation of results

Chronic and single oral administration of nobiletin mixture alleviated significantly urodynamic symptoms in hyperactive rat bladders by prolonging the micturition interval and decreasing micturition frequency. Although the precise mechanism which nobiletin mixture improved a hyperactive bladder response in rats remains to be clarified, the binding activity of muscarinic receptor may be partly contribute to the beneficial effect.

Concluding message

Nobiletin improved significantly urodynamic symptoms in hyperactive rat bladders by decreasing the micturition frequency. Thus, the current results may support the clinical efficacy of nobiletin mixture in the treatment of lower urinary tract symptoms accompanying overactive bladder.

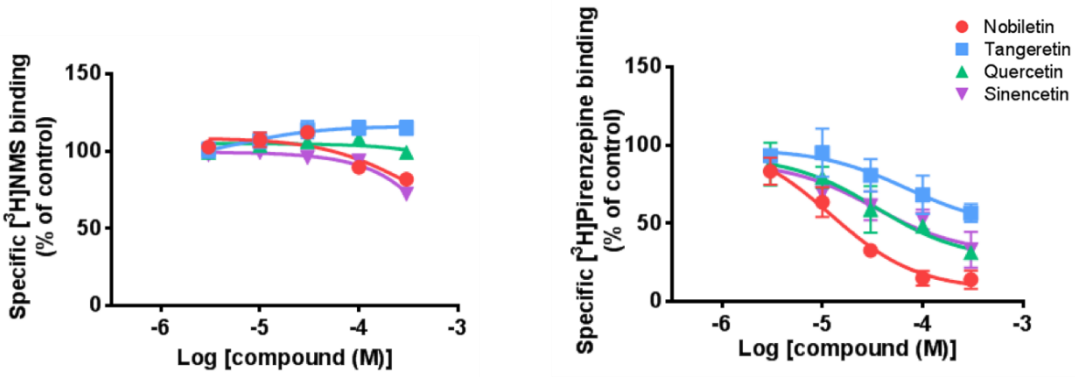
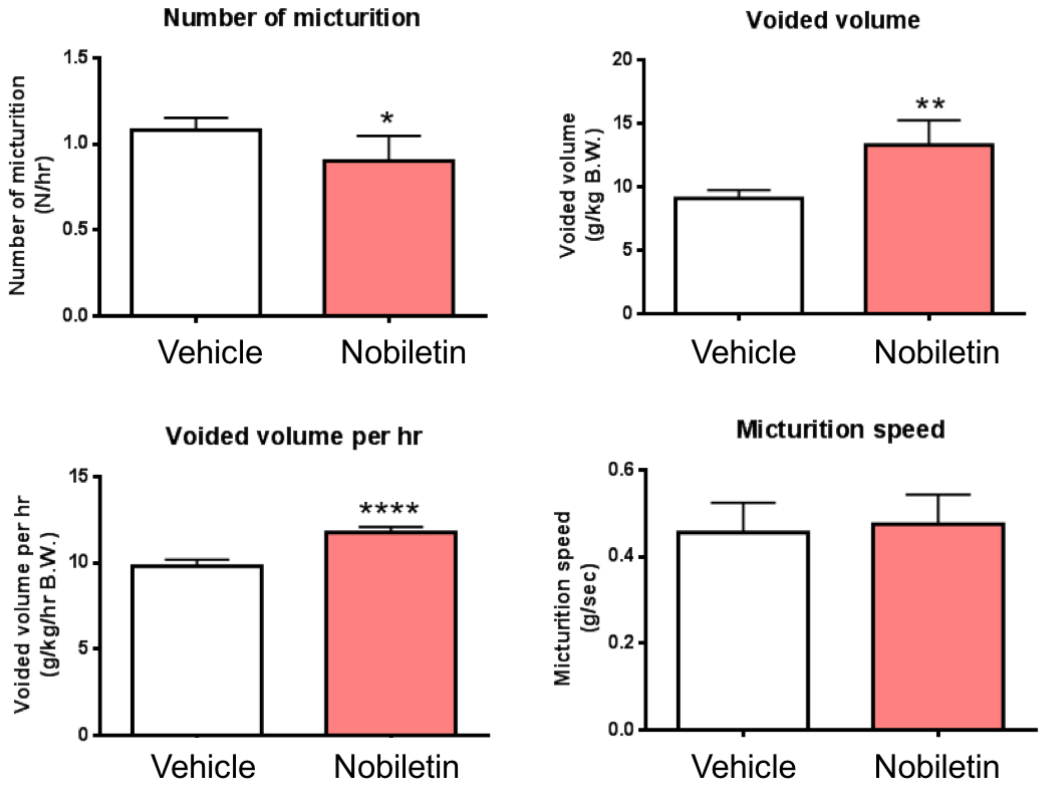


Fig. 1 Inhibition of specific [^{3}H]NMS and [^{3}H]pirenzepine binding in the rat brain by polymethoxy flavonoids.



*P<0.05, **P<0.01, ****P<0.0001 (v.s. Vehicle, t-test), Mean ± S.D. (n= 4-6)

Fig. 2 Effect of chronic oral administration of nobiletin mixture on urodynamic parameters in STZ induced diabetic rats.

Disclosures
Funding: No **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Committee for the care and use of laboratory animals of the University of Shizuoka