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EFFECT OF GOSHA-JINKI-GAN, A HERBAL MEDICINE, ON BLADDER ACTIVITY AND THE AUTONOMIC NERVOUS SYSTEM IN RATS.

Aims of study
Recently, traditional Chinese medicine (called Kampo medicine in Japan) has become more popular worldwide, and is now used as a form of complementary therapy in Western medicine. Gosha-jinki-gan (GJG) is one of the traditional Kampo drugs that has been widely used for the treatment of various symptoms in Japan. Some studies have suggested that GJG ameliorates symptoms and improves the vibration threshold in patients with diabetic neuropathy. GJG is also used clinically for the treatment of lower urinary tract symptoms (LUTS). In animal experiments, it has been demonstrated that GJG inhibits bladder contraction and increases bladder capacity, and that it reduces the systolic blood pressure in spontaneously hypertensive rats (1). Regarding the influence of blood pressure on LUTS, a high blood pressure has been reported to worsen these symptoms (2), while administration of an adrenergic alpha-1 blocker has been shown to improve both voiding symptoms and storage symptoms in patients with benign prostatic hyperplasia (3). In the present study, we investigated the effect of GJG on bladder activity and the autonomic nervous system in rats.

Materials and methods
Forty-two female Sprague-Dawley rats were divided into two groups, which were a control diet group (n = 21) and a GJG group (n = 21). Rats from the control diet group were fed a standard diet, while animals from the GJG diet group were fed a special diet containing 1.08% GJG (Tsumura Co., Japan). After 4 weeks, 28 rats (14 from the control diet group and 14 from the GJG diet group) were anesthetized with urethane (1.2 g/kg) and their body weight was measured. For continuous cystometry, a polyethylene catheter was inserted into the bladder through the urethra. Then physiological saline was infused into the bladder at 0.05 ml/min and bladder activity was monitored via the urethral catheter. After bladder contraction had been stable for at least 30 min, cystometry was done with physiological saline in 7 rats from the control diet group and 7 from the GJG diet group, while the other 7 rats from each group underwent cystometry with a 0.1% acetic acid solution instead. Cystometry was performed for at least 60 min with each test solution, and the changes of bladder activity were recorded. We measured serum amino acid levels (glutamate and glycine) and plasma monoamine levels (noradrenaline, adrenaline, dopamine, and serotonin) in the remaining 14 rats (7 from the control diet group and 7 from the GJG diet group). Results are reported as the mean ± standard deviation. Student's unpaired t-test was used for statistical analysis, and $P <$
0.05 was considered to indicate statistical significance.

Results
The body weight was significantly lower (decreased by 8.7%) in the GJG diet group than in the control diet group after 4 weeks of feeding. During continuous cystometry with physiological saline, the amplitude of bladder contraction pressure was significantly lower (decreased by 23.8%) in the GJG diet group compared with the control diet group. When continuous cystometry was done with 0.1% acetic acid, the interval between bladder contractions became significantly shorter in both the control diet group (reduced by 70.1%) and the GJG diet group (reduced by 40.3%) compared with the rats tested using physiological saline. However, the interval between bladder contractions induced by 0.1% acetic acid was significantly longer in the GJG diet group than in the control diet group. Moreover, the duration of bladder contraction was significantly longer (prolonged by 36.3%) in the GJG diet group than in the control diet group. Laboratory tests revealed that the plasma dopamine and serotonin levels were significantly lower (decreased by 52.3% for dopamine and 61.4% for serotonin) in the GJG diet group than in the control diet group.

Interpretation of results
GJG decreased the amplitude of bladder contraction pressure on continuous cystometry during physiological saline. When continuous cystometry was done with 0.1% acetic acid, the interval between bladder contractions and the duration of bladder contraction were significantly longer in the GJG diet group than in the control diet group. These results suggest that GJG not only acts on the afferent limb, but also the efferent limb, of the micturition reflex pathway. GJG also decreased the plasma dopamine and serotonin levels. Dopamine is a catecholamine released by the adrenal medulla or sympathetic nerves, while it has been suggested that serum serotonin level reflects the activity of the parasympathetic nervous system. Therefore, GJG may inhibit bladder activity by maintaining the appropriate balance between the sympathetic and parasympathetic nervous systems at a low level.

Concluding message
Gosha-jinki-gan may inhibit bladder activity by acting on both the afferent and efferent limbs of the micturition reflex pathway, and by maintaining the correct balance between activities of
the sympathetic nervous system and the parasympathetic nervous system at a low level.

References
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