Study of the Effect of a Chinese Medical Preparation, Hokoei-to, on the Rat Ovary

Takako YOKOZAWA, Atsutoshi TSUJI, Hitoshi MAEDA, and Masao HATTORI

Research Institute for Wakan-Yaku, Toyama Medical and Pharmaceutical University,* 2630 Sugitani, Toyama 930-01, Japan and Laboratory Animal Center, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan. Received December 7, 1993; accepted January 31, 1994

Female rats were given Hokoei-to orally to investigate its effects on hormones. Progesterone and estradiol levels fell markedly in ovariectomized young rats. Administration of Hokoei-to for 25 d produced increased levels of hormones in these rats. A similar effect was found in parous rats, demonstrating replacement of the lost female hormones after Hokoei-to administration.

Keywords Hokoei-to (Pu Gong Ying Tang); progesterone; estradiol; ovariectomy; para; rat

One of the commonest conditions in gynecology is the climacteric change, which arises from hormonal abnormality, i.e., decreased estrogen and excessive gonadotrophin. The most effective treatment for climacteric disturbance is thought to be estrogen supplementation. Specifically, the aim is to suppress gonadotrophin secretion following the increased release of estrogen, by means of the negative feedback mechanism. 1)

Hormone therapy is used widely but these are problems related to the dose and its time of initiation and discontinuation. For this reason the treatment is not entirely satisfactory. Although vitamins, psychotropic drugs and agents regulating the autonomic nervous system may also be used as symptomatic therapies, their efficacy is variable. 2) Development of a new effective therapy is therefore needed.

It has long been known that traditional Chinese medical treatment is effective for indefinite complaints seen in patients undergoing the climacteric change. 3)−7) In this connection, we carried out an experimental study using rats to examine the effects on the ovarian hormones of Hokoei-to, a Chinese medical prescription which is empirically used for the treatment of such indefinite complaints and is known to produce an improvement in subjective symptoms.

MATERIALS AND METHODS

Animals and Treatments Ovariectomized or non-ovariectomized young female rats of the LWH: Wistar strain, with a body weights of 130—140 g (approximately 5-week-old), and those that had been mated since 11 weeks after birth and had lost their reproductive ability after the fourth delivery were used in this experiment. The rats were kept in wire-bottomed cages under conventional lighting with a light/dark cycle. The room temperature (approx. 23 °C) and humidity (approx. 60%) were controlled automatically and the animals were fed a commercial pellet chow (Clea Japan Inc., Tokyo, Japan, type CE-2). Hokoei-to was dissolved in water, and administered orally every day in the drinking water. The dose was adjusted to 120 mg/kg body weight by adjusting its concentration to the water consumption. Control rats were given a corresponding amount of water. After 25 d, rats were killed between 1 p.m. and 2 p.m. to avoid any effect of circadian variation. The estrous cycle of each was determined by microscopic examination of vaginal smears and rats in anestrus were selected. Blood was collected and used for the determination of progesterone and estradiol. There were eight rats in each experimental group and data are expressed as means ± S.E.

Hokoei-to The Hokoei-to preparation was the same as that described by Yakazu. 8) The composition of the sample used in this experiment was as follows: 8 g of Taraxaci Radix (Taraxacum officinale WEBER), 6 g of Angelicae Radix (Angelica acutiloba KITAGAWA), 3 g of Cypers Rhizoma (Cyperus rotundus LINNE), 3 g of Moutan Cortex (Paeonia moutan SIMS) and 4 g of Dioscoreae Rhizoma (Dioscorea batatas DECASIN), Taraxaci Radix came from Germany, Angelicae Radix from Japan, and the other ingredients from China. The extract was obtained by boiling the above crude drugs in 540 ml water for 60 min, and a decoction of about 270 ml was obtained. This was then concentrated under reduced pressure to give a brown residue (Hokoei-to extract) with a yield of about 12.5%.

Statistics The significance of any differences between the control and extract-treated groups was examined using Student's t test.

Analyses Progesterone and estradiol were measured by radioimmunoassay as reported elsewhere. 9,10)

RESULTS

Table I shows the effect of Hokoei-to on the blood levels of progesterone and estradiol after oral administration. In

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Statistical significance: a) p < 0.05, b) p < 0.01 vs. each control group.

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non-ovariectomized young rats, the levels of progesterone and estradiol were 8.49 and 103.50 pg/ml, respectively, whereas the corresponding values in rats given Hokoei-to were 21.40 and 112.63 pg/ml, respectively. Thus the progesterone level was 152% higher than the control value, while Hokoei-to had no effect on the estradiol level. The progesterone level in ovariectomized young rats was about 73% lower, and the estradiol level about 45% lower, than in the young non-ovariectomized controls. However, in the rats given Hokoei-to, the progesterone rose by 56% from 2.28 to 3.56 pg/ml ($p<0.05$). The estradiol level also rose significantly from 57.13 to 77.36 pg/ml (a 35% change, $p<0.01$) when Hokoei-to was given. Oral administration of Hokoei-to also increased the hormone levels of parous rats, as shown in Table 1, with Hokoei-to causing an 88% increase in progesterone from 8.54 to 16.08 pg/ml ($p<0.01$) and a 30% increase in estradiol from 76.00 to 98.63 pg/ml ($p<0.05$).

DISCUSSION

The ovary is an endocrine gland: the ovarian follicle secretes estrogen and the luteal body secretes progesterone to regulate the secondary sex characteristics and the estrous cycle.

In the present study, the levels of progesterone and estradiol in ovariectomized young rats were 2.28 and 57.13 pg/ml, respectively, significantly lower than the corresponding levels, 8.49 and 103.50 pg/ml, in non-ovariectomized young rats. Thus, the effects of ovariectomy are marked. Although the values were low, the above results show that the ovariectomized group still had measurable blood levels of these hormones, indicating substantial biosynthesis from androstenedione and testosterone by aromatase in tissues such as fat and the adrenal cortex. In contrast, the progesterone and estradiol levels in ovariectomized rats given Hokoei-to orally for 25 days increased significantly to reach levels similar to those in non-ovariectomized young rats. This indicates replacement of the hormonal loss.

The climacteric change, which may result in osteoporosis, arteriosclerosis or obesity occurs in the process of the switch from a reproductive to a sterile state with age. It is an inevitable physiological change in many women and is associated with a reduction in estradiol. For this reason, we need a drug treatment that suppresses the lowering of endogenous hormone levels and allows the endocrine system to change smoothly from middle age to senility while maintaining fluid homeostasis. To this end, we have examined the effects of Hokoei-to on the female hormones of multiparous rats. The progesterone levels in rats that experienced four deliveries were similar to those in 5-week-old rats, but the estradiol was about 27% lower in the former group. In parous rats given Hokoei-to, however, the low estradiol level recovered significantly, in parallel with a significant increase in progesterone, a precursor of estradiol. Thus, Hokoei-to has been shown experimentally to suppress the fall in female hormones, allowing us to expect a therapeutic effect on ovarian dysfunction.

Hormonal therapy is theoretically and practically effective in climacteric disorders. However, since this condition occurs in the transitional period from sexual maturity to senility and requires long-term treatment, treatment involves certain problems, such as the choice of dosage and the time of administration and, ultimately, its discontinuation. For these reasons, hormonal therapy is not the best treatment. As palliative treatment, medication with autonomic nervous system-stabilizing agents and vitamins is used for indefinite symptoms, but their efficacy is not as clear-cut as hormones. Therefore, development of a more effective treatment would be desirable.

Hokoei-to, the drug examined in the present study, was originally prescribed in the medical book "Hoyoei," published in the Edo period in Japan, with a description suggesting that it had some effect on the endocrine system. When ovariectomized or parous rats were given daily oral doses of Hokoei-to, their progesterone and estradiol blood levels increased significantly. As far as other traditional medicines are concerned, the luteal function-regulatory effect of Toki-shakuyaku-san (a prescription consisting of Paeoniae Radix, Atractylodis Lanceae Rhizoma, Alismatis Rhizoma, Hoelen, Cnidii Rhizoma and Angelicae Radix) and the estrogenic effect of red ginseng have been reported by Usuki et al., Koyama, Samukawa and Ogita. Hokoei-to is a very interesting preparation because it exhibits a combination of these effects.

REFERENCES

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