

LONG-TERM BROMOPRIDE TREATMENT INDUCES MORPHOLOGICAL CHANGES IN FEMALE RATS

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INTRODUCTION

Bromopride [N - (diethylaminoethyl) - 2-methoxy-4-S-bromobenzamine] is a widely used drug in gastroenterologic clinic, not only because of its central and peripheral actions on gastrointestinal motility but also for its antiemetic properties.

Long-term treatments are frequently performed with this drug. It is known that bromopride acts on the central nervous system blocking dopaminergic receptors (1,4), leading to an increase in serum prolactin levels through receptors blockage at the tubero-infundibular dopaminergic system (6). This increase in prolactin levels is an undesirable side effect in patients chronically treated with this drug (6).

In this report it is presented the assessment of long-term bromopride treatment on the morphology of mammary glands, ovaries, uterus and fallopian tubes of rats.

MATERIAL AND METHODS

Adult virgin female rats (Wistar origin) aging 90 days at the beginning of the treatment were used in this study.

Daily vaginal smears were sampled to monitor estrous cyclicity and 20 animals showing two consecutive 4-day-estrous cycle were used.

Three rats were maintained per each cage under controlled light (12h light, 12h dark; lights off at 7:00h p.m.) and temperature (22-23°C) conditions. Food and water were available ad lib.

Pure bromopride powder generously provided by ROCHE was dissolved in 0.2 M monopotassic phosphate solution and pH was adjusted to 5.0 with 0.5 N hydrochloric acid.

Half of these animals received 60.0 mg/kg of drug subcutaneously (S.C.) twice a day during 28 days (experimental group). The remaining rats were treated only with bromopride solvent in the same schedule (control group). From the tenth day of the treatment until the 28th day, the vaginal smears were observed once a day at the same time (8:00h a.m.) in order to monitor estrous cyclicity. The animals were sacrificed twenty four hours after the last injection, and the

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SUMMARY: There were morphologically examined the ovaries, uterus, fallopian tubes and mammary glands of adult female rats, that were long-term treated with bromopride. Large corpus luteum, uterus in a secretory stage and hipertrophiated mammary gland were observed in treated animals. These marked morphological changes were correlated to the neuroendocrinal effects of the drug, considering what it is able to block tuberoinfundibular dopamine (DA) receptors leading to an increase in prolactin levels.

UNITERMS: Bromopride; Estrous cycle, diestrous; Prolactin

uterus, ovaries, fallopian tubes and mammary glands were removed for histological examination. After removal, tissues were immediately immersed in Bouin fixative, included in paraffin, cut (thickness: 5µm) and stained with hematoxylin and eosin for ordinary optical microscopic observation.

The tissues were examined by one of the authors, who previously knew nothing about the treatment the animals had received.

RESULTS

The vaginal smears, monitored during 18 days had shown that the animals of experimental group were permanently in diestrous. On the contrary, rats of control group had normal cyclicity.

As demonstrated histologically in Fig. 1A the ovaries of the control rats showed follicles in different developmental stages and corpus luteum corresponding to a normal cycle. In the experimental ones, the follicles were not observed and the corpus luteum were well developed, presenting proliferation of granulous cell layer, amorphous intercellular substance, better cellular organization and connective tissue with many vessels (Fig. 1B). Further, different morphological features were also observed in the uterus of control animals according to the cyclic phase they presented at the time of their sacrifice. The rats of the experimental group were in a diestrous phase, i.e., a secretory stage. Whereas normal mammary glands were observed in the control rats, hypertrophic and edematous glands with lactic secretion in the galactophorous ducts were found in rats long-term treated with bromopride.

Finally, the fallopian tubes of animals of both groups showed no differences.

DISCUSSION

Long-term bromopride treatment can induce permanent diestrous in rat. Ovaries showing absence of follicles, with well developed corpus luteum, uterus in a secretory stage and other his-

tological changes mentioned are histological correlates of the diestrous observed in the vaginal smears.

Bromopride is a DA antagonist (1,4). Thus, this kind of drug is able not only to increase serum levels of PRL but also to induce diestrous in rats (5) since DA seems to be one of the prolactin inhibiting factors (2,3). Probably this is the reason for the rise in PRL levels in healthy women and after long-term bromopride treatment (6). The histological changes observed in mammary glands are the typical ones of increased PRL levels. An elevated PRL concentrations have profound effects on reproductive cyclicity. Apparently PRL disrupts essential preovulatory neurochemical events in selected brain areas involved in the regulation of LHRH as well as the ovarian steroid secretion patterns that accompany the estrous cycle (7,8).

The ovarian changes observed are in agreement with the hormonal changes described by Wise (8) and the uterine histological features were the ones expected in this kind of ovarian functional modification. Possibly it seems that drug-induced ovarian modifications may be the cause of the menstrual disorders observed in patients treated with other ortopramides such as clebopride, metoclopramide and sulpiride (6).

The long-term bromopride treatment induces morphological changes in female rats arising out of the neuroendocrinal effects of the drug. Although high doses were presently used, it is necessary to have in mind this kind of side effect when long-term use of the drug is considered, especially in gastroenterologic clinic. Patients should be aware of some possible undesirable side effects of the drug like gynecomastia in men, galactorrhea, menstrual disorders and even infertility in women.

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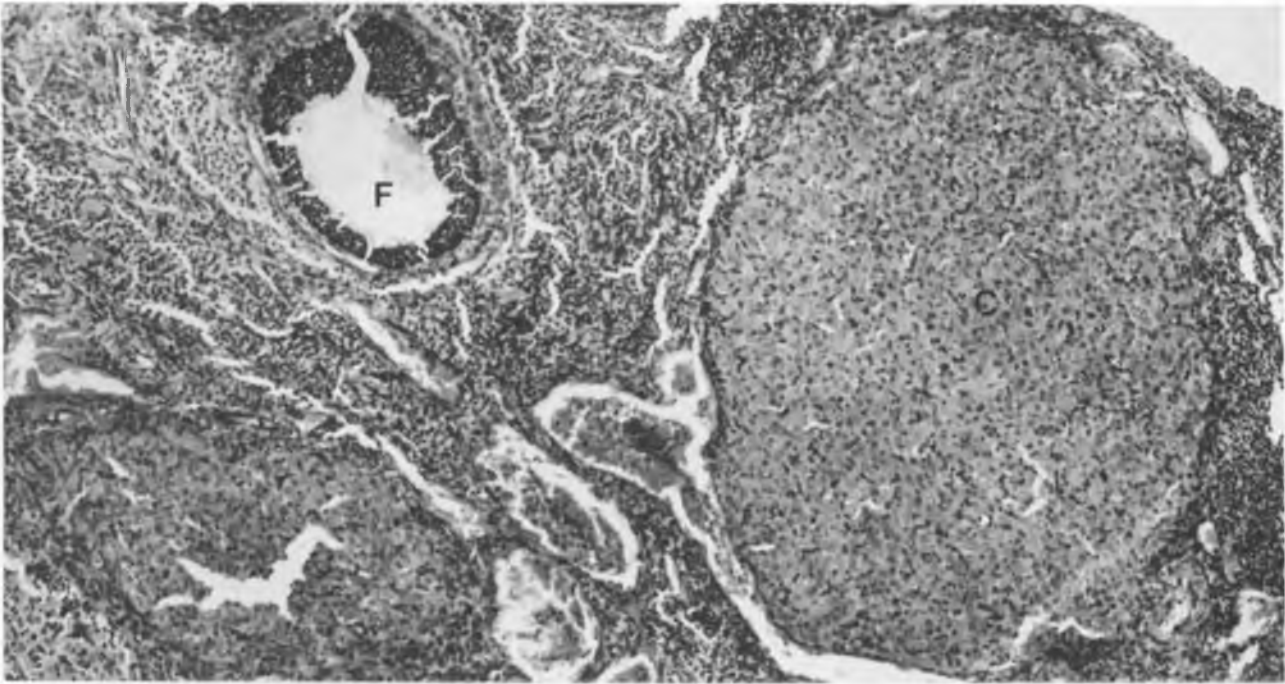


FIGURE 1A – Ovary of a control rat with follicles in different developmental stages (F) and *corpus luteum* (C) corresponding to a normal cycle (hematoxylin and eosin, x 80)

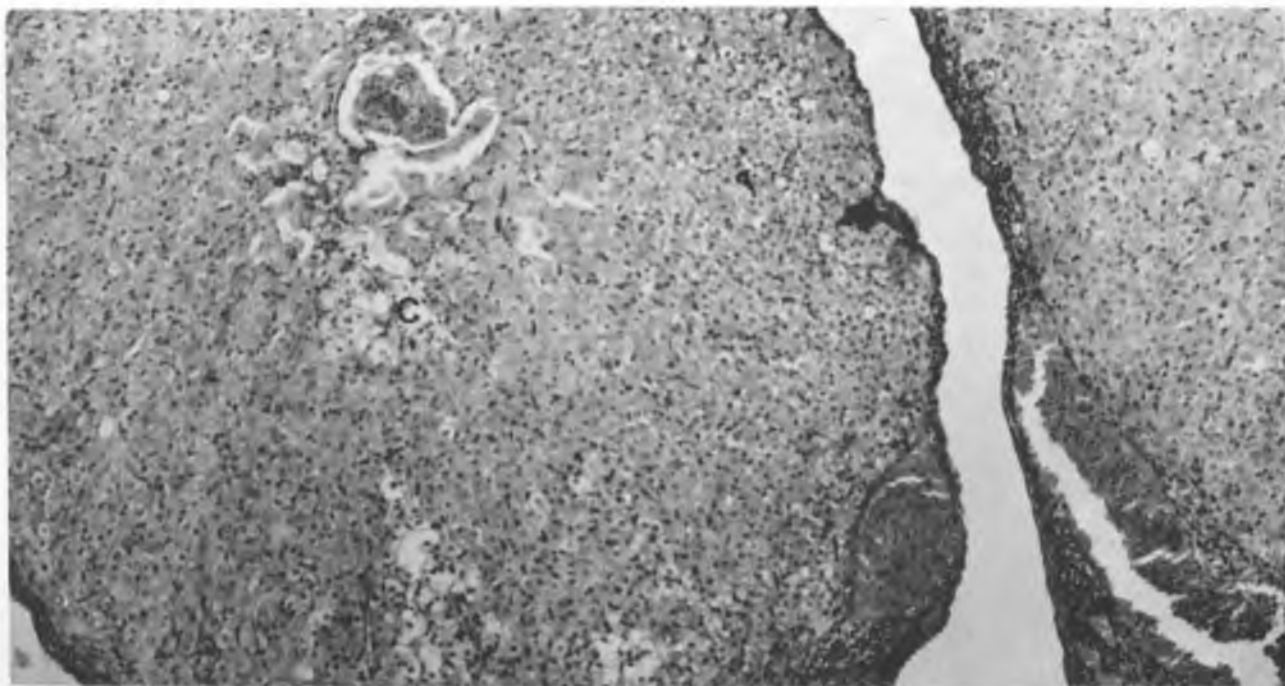


FIGURE 1B – Ovary of a long-term bromopride treated rat without follicles, hypertrophic *corpus luteum* (C) (hematoxylin and eosin, x 80)

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RESUMO: Foram examinados ovários, úteros, trompas de falópio e glândulas mamárias, provenientes de ratas tratadas prolongadamente com o bromopride. Foram observados

corpos lúteos muito desenvolvidos, úteros em fase secretória e glândulas mamárias hipertrofiadas. Estas alterações morfológicas marcantes estão correlacionadas com os efeitos neuroendócrinos da droga, pois esta é capaz de bloquear os dopaminocetores do sistema tuberoinfundibular, aumentando, assim, os níveis séricos de prolactina.

UNITERMOS: Bromopride; Ciclo estral, diestro; Prolactin

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