

Post-Coital Contraceptive Effect of 2-Br- α -Ergocryptine (CB-154) in the Rat

Diencephalic dopaminergic systems appear to play a significant role in the control of the hypothalamic releasing factor (RF) mechanisms subserving anterior pituitary hormone secretion¹⁻³. The compound 2-Br- α -ergocryptine methanesulfonate (CB-154, Sandoz, Basel), a dopaminergic receptor stimulant⁴, has been shown to be an effective inhibitor of pituitary prolactin secretion^{5,6} and an ovulation blocker⁷.

In view of the effect of CB-154 on neuroendocrine-reproductive events, a study was undertaken to determine the effect of this drug on pregnancy in the rat.

Materials and methods. Female Sprague-Dawley rats weighing an average of 325 g (range: 310–350 g) were used. Animals (5/group) were caged with fertile males on the evening of proestrus. The presence of vaginal sperm the next morning was considered day 1 of assumed pregnancy. CB-154 was then administered either s.c. or orally (p.o.) from days 1–7 of pregnancy. Animals were sacrificed on day 14 of pregnancy. The number of uterine implantation sites was recorded and fetuses were examined under a dissecting microscope for the presence of teratogenic signs. The presence of at least one normal fetus was the criterion of pregnancy.

CB-154 also was evaluated for estrogenic activity by recording uterine weight in young, mature ovariectomized mice (7/group). Total dose of the drug was administered

s.c. over a 3-day period; animals were sacrificed the next day. Estrone was administered as a positive estrogen control.

Results and discussion. Figure 1 demonstrates the effect of CB-154 on pregnancy in the rat. The drug is effective in inhibiting pregnancy by either the s.c. or p.o. route. The estimated minimum 100% effective daily s.c. dose is 1500 μ g/kg; that for oral treatment is 6000 μ g/kg. In the mouse estrogen test (Figure 2), CB-154 was devoid of activity. The absence of estrogenicity at post-coital contraceptive doses of CB-154 would argue against any steroid-like effect.

In general, the ergot alkaloids have been shown to possess abortifacient and anti-implantation properties, most likely due, in part, to their oxytocic activity⁸.

CB-154 is a highly active cerebral dopaminergic stimulant; its ability to dramatically lower serum prolactin levels and inhibit galactorrhea is well documented^{9,10}. The presumed mechanism is via inhibition of hypothalamic prolactin-inhibitory factor. It is tempting to speculate that CB-154's post-coital contraceptive action also is mediated via a hypothalamic system, perhaps by interfering not only with prolactin secretion, but also through a disruptive effect on luteinizing hormone RF, all of which may be necessary for corpus luteum formation, progesterone secretion and eventual maintenance of uterine integrity. However, it should be borne in mind that CB-154 also may act directly at the level of the anterior pituitary^{11,12}.

Résumé. Le CB-154, un stimulant du récepteur dopaminergique central, administré post-coïtum, pendant 7 jours, par voie s.c. ou orale, possède chez les rats une activité inhibitrice de la grossesse (en fonction de la dose). Aux doses contraceptives, le produit n'a aucun effet oestrogène. Les résultats suggèrent que le mécanisme hypothalamo-dopaminergique joue un rôle dans le maintien de la grossesse.

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10 June 1974.

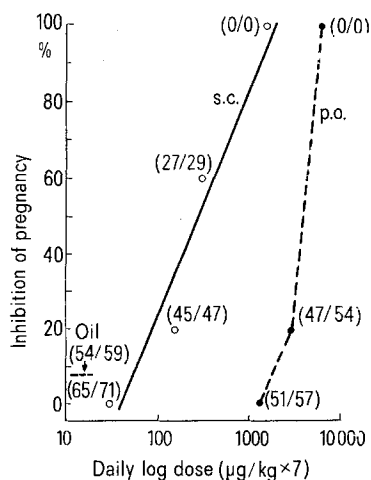


Fig. 1. Effect of CB-154 on pregnancy in the rat. Numbers in parenthesis = implantation sites normal/total.

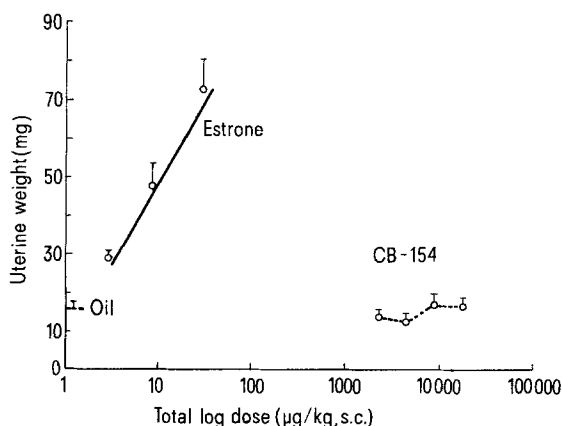


Fig. 2. Test for estrogenicity: effect of CB-154 on uterine weight of ovariectomized mouse.

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- 12 The technical assistance of Ms. P. DOVE is gratefully acknowledged.