J. Reprod. Fert. (1980) **58**, 387–388 *Printed in Great Britain*

Induction of implantation in the rat by iproniazid*

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Summary. Rats were bilaterally ovariectomized on Day 3 *post coitum* and treated daily with progesterone. Iproniazid, an inhibitor of monoamine oxidase, on Day 8 induced implantation in all rats. Indomethacin treatment prevented this effect.

Introduction

The involvement of prostaglandins (PGs) in decidual cell development (Castracane, Saksena & Shaikh, 1974) and implantation (Lau, Saksena & Chang, 1973; Castracane *et al.*, 1974; Kennedy, 1977) in laboratory animals has been clearly shown. Iproniazid, a potent monoamine oxidase inhibitor recommended as having therapeutic value in mental depression (Koelle, 1970), has an abortifacient action which is mediated through an increased endogenous production of PGs (Chatterjee, Biswas & Pal, 1974). We therefore studied the ability of iproniazid to induce implantation in rats, and also whether indomethacin, a potent inhibitor of PG biosynthesis and release (Vane, 1971; Ferreira, Moncada & Vane, 1971; Rankin, Ledford, Jonsson & Baggett, 1979), can reverse the implantation-inducing effect of iproniazid.

Materials and Methods

Animals. Inbred albino rats weighing 150–170 g were used. They were kept in light controlled conditions of 14 h light/24 h. Pro-oestrous females were caged with males of proven fertility and mating was confirmed by finding spermatozoa in the vaginal smear (Day 1 of pregnancy). Bilateral ovariectomy was performed on Day 3 under light ether anaesthesia. Care was taken to avoid damage to the oviduct. All the rats were killed on Day 12 and the number of implantation sites was recorded.

Drugs and treatments. Iproniazid phosphate, donated by the F. Hoffman La Roche & Co. Ltd, Basle, Switzerland, was dissolved in distilled water and administered subcutaneously (s.c.) as a single injection (0·2 ml) at a dose of 150 mg/kg body weight on Day 8. Progesterone (Proluton Dep: Schering, India) was diluted in olive oil and injected s.c. at a dose of 5 mg/rat/day from Day 3 to Day 11 *p.c.* Indomethacin (I.D.P.L., India) was dissolved in olive oil and administered s.c. at 2·5 mg/kg (0·2 ml) on Days 7, 8 and 9.

Results

As shown in Table 1 daily injections of progesterone were not able to induce implantation, but a single injection of iproniazid to the progesterone-treated animals was successful. Concomitant administration of indomethacin inhibited the iproniazid-induced implantation.

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0022-4251/80/020387-02$02.00/0

Table 1. Effect at Day 12 of iproniazid on implantation in rats bilaterally ovariectomized on Day 3 of pregnancy

Treatment (day of pregnancy)	No. of rats	No. with implantation sites	Mean ± s.e.m. no. of implantation sites
Progesterone (Days 3–11)	6	0	—
Proniazid (Day 8) + progesterone (Days 3–11)	7	7	6·66 ± 0·55
Iproniazid (Day 8) + progesterone (Days 3–11) + indomethacin (Days 7–9)	6	0	—

Discussion

PGF-2α treatment in the mouse prevents the inhibitory effect of indomethacin on implantation (Lau *et al.*, 1973). Iproniazid acts by interfering with the metabolism of catecholamines (Koelle, 1970) which can stimulate the release of prostaglandins in the spleen (Ferreira *et al.*, 1971). Moreover, indomethacin blocks the conversion of arachidonic acid to endoperoxides (Flower & Vane, 1974).

Cyclic AMP is also able to induce implantation (Webb, 1975) and β-adrenergic catecholamine can stimulate adenylate cyclase in pigeon erythrocytes (Davoren & Sutherland, 1963). Endometrial adenylate cyclase is also known to be stimulated by PGE-1 and PGE-2 (Bhalla, Sanborn & Korenman, 1972). The formation of cAMP by cyclo-oxygenase in uterine decidual tissue is inhibited by indomethacin (Rankin *et al.*, 1979).

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Received 7 June 1979