EFFECT OF PHARMACOLOGIC STIMULATION OF DOPAMINERGIC RECEPTORS ON PITUITARY OVARIAN FUNCTION OF RATS WITH AN ANOVULATORY SYNDROME

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Termination of the ovulatory cycle in neonatally androgenized rats (NAR) is connected with disturbance of catecholaminergic regulation of secretion of pituitary hormones: gonadotropins and prolactin. The anovulatory syndrome (AS) in NAR is characterized by hypersecretion of prolactin and a reduction in secretion of luteinizing hormone, due evidently to impairment of the noradrenergic regulatory mechanisms of the hypothalamus [2, 6, 7].

Prolactin is known to depress luteinizing hormone secretion [5]. If hyperprolactinemia is the leading pathogenetic factor in AS, its correction by stimulation of hypothalamic dopamine receptors ought to maintain or restore ovulation in NAR.

To test this hypothesis, it was decided to study the state of pituitary and ovarian functin in adult NAR receiving the dopamine agonist bromocriptine (BC) at different age periods.

EXPERIMENTAL METHOD

Experiments were carried out on female Wistar rats receiving a subcutaneous injection of 0.25 mg testosterone propionate (TP) (experiment) on the 3rd day after birth, or an injection of the solvent (peach oil) (control) on the 3rd day after birth. Some NAR with AS received subcutaneous injections of BC in a dose of 0.1 or 0.5 mg/kg twice a day from the 31st through the 45th day of life, and these animals were decapitated on the 46th day (experiment 1) or at the age of 3.5-4 months (experiment 2). The rest of the rats were given BC by a similar scheme for 15 days, starting from the age of 2.5 months. The animals of this group were killed 2 h after a morning injection of BC (experiment 3). During the last two weeks of the experiment vaginal smears of the sexually mature NAR were studied under the microscope. All animals were decapitated in the estrus stage. The adenohypophyses and ovaries were weighed. The ovaries and the vagina were studied histologically. The prolactin concentration in the adenohypophyses was determined by electrophoresis [1]. Plasma progesterone and estradiol concentrations were determined by radioimmunoassay, using "Steron-P-3H" (USSR) and ESTRK (CIS Internationale, France) kits.

EXPERIMENTAL RESULTS

The results of colpocytologic (persistent estrus) and histologic study of the vagina (increased keratinization of the mucosa) and ovaries (absence of corpora lutea) showed that AS developed in 100% of NAR. The average weight of the adenohypophysis in NAR exceeded the control values, and in experiments 2 and 3 the difference was statistically significant ($P < 0.05$). In all experiments there was a tendency for the weight of the ovaries to decrease. Changes in the hormonal parameters corresponded to the morphologic changes in AS: an increase in the prolactin concentration in the adenohypophysis and a decrease in the plasma progesterone concentration (Table 1).

In all rats receiving BC, regardless of the time of investigation, the prolactin concentration in the adenohypophysis was normal or actually reduced. In experiment 3 the weight

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TABLE 1. Effect of BC on Relative Weight of Adenohypophysis and Ovaries and on Hormonal Parameters of Rats with AS (M ± m)

Experimental conditions	Weight of ovaries, mg/100 g	Weight of adenohypophysis, mg/100 g	Concentration of progesterone in plasma, nmoles/liter	Concentration of estradiol in plasma, pmoles/liter	Concentration of prolactin in adenohypophysis, μg
Experiment 1					
Control (n = 8)	48,6±5,7	3,9±0,51	119,4±7,3	331,6±53,5	31,3±2,1
TP (*n*=8)	36,1±4,6	5,1±0,53	43,1±7,0*	404,0±33,0	48,8±4,8*
TP + 0.5 mg/kg BC (n = 10)	39,1±3,7	4,3±0,32	80,7±21,1	374,1±33,7	37,9±4,1
TP + 0.1 mg/kg BC (n = 9)	41,5±4,1	4,6±0,61	57,1±6,9*	412,0±74,0	38,7±4,1
Experiment 2					
Control (n = 10)	35,4±6,5	4,8±0,32	117,4±8,3	460,0±98,1	32,0±3,9
TP (*n*=10)	20,1±1,8	6,8±0,38*	28,8±4,1*	650,1±108,4	49,7±3,6*
TP + 0.5 mg/kg BC (n = 9)	21,9±1,9	6,1±0,61	44,1±4,2*	429,0±104,1	22,6±2,9
TP + 0.1 mg/kg BC (n = 10)	20,0±1,4	6,3±0,58	40,1±5,18*	352,5±63,8	19,7±1,2*
Experiment 3					
Control (n = 8)	29,0±6,0	4,1±0,17	65,9±9,8	—	33,2±4,9
TP (*n*=9)	17,0±1,2	5,5±0,06*	29,0±5,7*	—	55,0±6,1*
TP + 0.5 mg/kg BC (n = 10)	19,0±0,4	4,5±0,19	44,9±6,0	—	20,1±2,3*

Legend. *P < 0.05 compared with control.

of the adenohypophysis was restored to normal, evidently due to the inhibitory action of BC on the lactotrophocytes. In experiments 1 and 3 BC restored the normal plasma progesterone level. Despite the positive character of these changes, BC could not prevent the development of AS or restore the ovulatory cycle in NAR.

The histologic picture of the ovaries of these animals, just as in NAR, was characterized by an increase in size of the follicles, proliferation of the granuloma, solitary or multiple cysts, and absence of corpora lutea. The vaginal mucosa was thickened, with marked folding and intensive keratinization of the epithelial layer. No cyclic changes were observed in the vaginal smears.

Restoration of the ovulatory cycle and of fertility can be achieved in NAR by injection of ovulation stimulators clomiphene and synthetic LHRH after appropriate progesterone therapy [3]. When hyperprolactinemia is the dominant pathogenetic factor causing inhibition of ovulation, BC was found to be effective in restoring the estrous cycle. The classical example of this action is the positive therapeutic effect of BC (parlodel) in patients with a galactorrhea–amenorrhea syndrome. Restoration of the estrous cycle in rats with long-term diestrus has been reported after administration of BC in a daily dose of 0.5 mg/kg for 3 days [8].

The absence of any such effect of BC in NAR is not grounds for regarding an increase in pituitary prolactin activity as the main cause of AS. A similar conclusion was drawn by workers [4] who obtained the negative result in their attempts to treat AS in neonatally estrogenized rats experimentally with bromocriptine.

The results of the present investigation are in agreement with the view that damage to the noradrenergic system of the hypothalamus plays a leading role in the pathogenesis of AS, associated with a disturbance of sexual differentiation of the brain in NAR [2, 9].

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