ponded to the inhibition found 150 min after the use of the reversible inhibitor in the presence of spontaneous reactivation of ACE (Fig. 1). The fall in the level of ACE inhibition by galanthamine after treatment with armine took place more rapidly and was more like a "break-away" than a gradual liberation. This "break-away" is most likely linked with a considerable or indeed almost total depression of ACE as a result of the successive action of the reversible and irreversible inhibitors. AC accumulating as a result of this inhibition of the enzyme can evidently displace galanthamine rapidly from the active sites of ACE and reduce the inhibitory effect.

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EFFECT OF PHENFORMIN ON LIPID AND CARBOHYDRATE METABOLISM IN PREGNANT RATS

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A decrease in the blood levels of cholestrol, phospholipids, and free fatty acids was observed in rats receiving the biguanide phenformin (5-25 mg dailyby mouth) from the first to eighth day of pregnancy, but no developmental anomalies of the fetuses or placenta were found. The acceptability of biguanide administration during pregnancy is discussed.

KEY WORDS: pregnancy; phenformin; biguanides; lipid and carbohydrate metabolism.

The similarity between the mechanisms of the changes in energy homeostasis during aging, atherosclerosis, adiposity, several malignant neoplasms, and some other diseases suggests that the same preventive and therapeutic measures could prove useful in all these states [2-4]. Disturbances of lipid and carbohydrate metabolism during normal pregnancy, manifested primarily as hyperlipidemia, are very similar to those observed during aging, and whereas according to some workers they are "physiological" [10, 17], they evidently are not without their effects on the body [1, 4, 19]. The search for methods of eradicating these disturbances or confining them within bounds accordingly merits the closest attention. Recently the antidiabetic biguanides, which include phenformin (Dibotin [5, 7, 18], have become widely used as agents to normalize various disturbances of lipid and carbohydrate metabolism. As long ago as in 1963, Sterne [15] successfully used a biguanide (methformin) during pregnancy to control diabetes mellitus. In 1974, Notelovitz [11] expressed the view that the use of phenformin in diabetes of pregnancy was acceptable. However, the more extensive use of biguanides in pregnant women is prevented by the lack of knowledge of the effect of these preparations on the metabolism and course of normal pregnancy.

In the investigation described below an attempt was made to remedy this deficiency.

EXPERIMENTAL METHOD

Female rats weighing initially 160-180 g were used.

On the 16th-17th day the animals were mated and the discovery of spermatozoa in the vaginal contents of the females next day indicated the first day of pregnancy. The pregnant females were kept in individual cages until the end of the experiment. Some rats from the 1st or 8th day of pregnancy received 5 or 25 mg phenformin

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TABLE 1. Effect of Phenformin on Weight of Pregnant Rats, Fetuses, and Placentas and of Certain Endocrine Organs of the Mother (M ± m)

Index	Group of animals		
	1. pregnant rats (n = 12)	2. pregnant rats + phenformin (n = 17)	3. nonpregant rats (n = 10)
Difference between initial and final body weights of pregnant rats (in g)	101,5±6,7	96,2±5,4	—
Weight of living fetuses (in g)	5,21±0,048 (*n*=114)	5,26±0,041 (*n*=145)	—
Of placentas (in mg)	495,5±9 (*n*=114)	577,2±8 (*n*=145)	—
Percent of dead fetuses	3,39±1,7	2,68±1,3	—
Weight of pituitary gland (in mg)	10,8±0,4	9,4±0,4	8,0±0,3
Of thyroid gland (in mg)	25,1±1,4	24,7±0,6	18,1±1,1
Of adrenals (in mg)	66,3±3,2	72,1±2,5	51,0±2,5
Weight of ovaries (in mg)	87,8±3,7	101,0±3	65,9±2,2

TABLE 2. Effect of Phenformin on Levels of some Indices of Lipid and Carbohydrate Metabolism and 11-Hydroxycorticosteroids in Blood of Pregnant Rats

Index	Group of animals		
	1. pregnant rats (n = 12)	2. pregnant rats + phenformin (n = 17)	3. nonpregnant rats (n = 10)
Sugar (in mg %)	73±2,2	69,3±2,7	86,1±1,8
Cholesterol (in mg %)	63,9±3,3	46,3±1,9	49,5±1,7
Phospholipids (in mg %)	150,1±6 (*n*=7)	120,4±8 (*n*=12)	101,6±5 (*n*=5)
Free fatty acids (in μeq/liter)	605±56	251±19	270±33
11-Hydroxycorticosteroids (in μg %)	17,1±0,8 (n = 7)	17,9±1,0 (*n*=8)	12,1±0,5 (*n*=6)

daily by mouth in 1 ml water. On the average 21.5 days after the beginning of pregnancy the animals were killed, a blood sample was taken from the heart, after which the fetuses, placentas, pituitary, thyroid, and adrenal glands, and the ovaries of the mother were removed, and the numbers of living and dead embryos and of corpora lutea in the two ovaries were counted. The fetuses and placentas were carefully inspected and fixed in Bouin's fluid for 7-10 days. After fixation, the fetuses were studied microanatomically [20]. The concentrations of sugar [8], cholesterol [13], phospholipids [12], free fatty acids [9], and 11-hydroxycorticosteroids [6] in the blood were determined.

EXPERIMENTAL RESULTS AND DISCUSSION

No differences in principle were found between the animals receiving phenformin at different times of pregnancy and in different doses. In Tables 1 and 2 these groups are accordingly considered together.

In no case of phenformin administration were developmental anomalies of the fetuses and placentas found or was the percentage of dead fetuses increased.

The changes discovered in lipid and carbohydrate metabolism, in the 11-hydroxycorticosteroid level in the blood, and in the weight of various endocrine organs during normal pregnancy agreed with data in the literature

[10, 14]. The fall in the fasting blood sugar level likewise did not contradict existing data and was evidently the result of the hyperinsulinemia which develops toward the end of pregnancy [16].

Phenformin caused a significant decrease in the indices of lipid metabolism but left the blood sugar of the pregnant rats virtually unchanged.

The ability of phenformin to change the blood insulin level during normal pregnancy in rats requires further study. However, indirect evidence against it is given by the absence of difference in the final body weight and weight of the fetuses of the pregnant rats receiving and not receiving phenformin. Meanwhile, special experiments showed that phenformin lowers the blood insulin level and the weight of the fetuses of pregnant rats receiving alloxan before the age of sexual maturity.

The increase in weight of the placentas of the rats receiving phenformin was somewhat unexpected, although it was found only if a large dose of the preparation was given (25 mg daily). The mechanism of this effect, like that of the change in weight of the pituitary glands and ovaries during phenformin administration, also requires further study.

Phenformin thus significantly weakens the manifestations of hyperlipidemia in rats during pregnancy and this effect is not accompanied by any visible disturbances of development of the progeny. It can accordingly be concluded that this compound, already used with success in other diseases of compensation [4, 5, 7, 18], can also be used with advantage to correct disorders of lipid and carbohydrate metabolism characteristic of many cases of pregnancy.

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