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ROLE OF THE HYPOPHYSIS ON KETONEMIA AND FATTY LIVER OF THE PANCREATECTOMIZED DOG

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SVMMARIVM — Hypophysectomia attenuat diabetem ex pancreatectomia provenientem; efficit etiam ut cetonemia non amplius augeatur, et ut iecoris pinguedo minuatur. Si in canem, qui hypophysectomiam et pancreatectomiam passus sit, hormo pituitarius incrementi iniectetur, et cetonemia et iecoris pinguedo (triglycerides) augentur. Citosis in pancreatico diabete duas habet causas: a) insulinae absentia; b) concurrens et hypophysis (vel eius hormonis) et subrenis (vel eius hormonum) actio.

Hypophysectomy produces in pancreatectomized dogs a striking attenuation of the pancreatic diabetes.

This attenuation is present in: 1) carbohydrate metabolism: less increase of glycemia, less glycosuria; 2) protein metabolism: less increase of gluconeogenesis, less increase of urinary nitrogen; 3) and in the lipid metabolism: less increase of lipemia, FFA, and ketone bodies in blood and urine, less triglyceride deposit in liver.

The action on carbohydrate metabolism is well known but the action on fatty metabolism is more striking. In the hypophysectomized-pancreatectomized dogs there is less lipolysis and less transport of peripheral fat to the liver and especially

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a striking lack of increase of ketone bodies in blood. This action on ketosis was discovered by C. T. RIETTI (1930, 1932) in the pancreatectomized-hypophysectomized dogs studied by HOUSSAY and BIASOTTI (1930). He fonnd also the attenuation of ketosis in dogs with phlohizin diabetes (1932).

Previous experiments (1963) have demonstrated that *the production of diabetic ketosis in pancreatectomized dogs is dependent on the obligatory presence of two main groups of hormonal factors*: 1) the first is the lack *of insulin*; 2) the second is the simultaneous presence of *the pituitary and the adrenal glands (or their hormones). The presence of only one of these glands (or its hormones) is not sufficient; both of them must be present for the production of diabetic ketosis in the dog.*

The ketonemia of normal dogs is 3.2 mg/100 ml (average of 22 animals); after 5 days from pancreatectomy the value increases to 24 ± 2.8 mg/100 ml (average of 12 dogs). After hypophysectomy in pancreatectomized dogs the increase of ketonemia is almost prevented, being the value 4.0 ± 2.0 mg/100 ml; average of 11 dogs).

In hypophysectomized-pancreatectomized dogs, cortisol alone cannot restablish the diabetic level, due to the absence of the hypophysis.

In the pancreatectomized dog hyperketonemia is also diminished by adrenalectomy, and somatotrophin cannot restablish it, due to the absence of adrenal glands. Cortisol restores the hyperketonemia of pancreatectomized-adrenalectomized dogs, because they have their hypophysis intact and cortisol replaces the adrenal glands. But cortisol has no ketonemic action in the pancreatectomized-hypophysectomized dogs (hypophysis has been removed) (fig. 1).

The combination of both hormones (somatotrophin and cortisol) has an intense hyperketonemic action in all of our experimental groups (pancreatectomized-hypophysectomized, pancreatectomized-adrenalectomized or pancreatectomized-adrenalectomized-hypophysectomized). The level of hyperketonemia

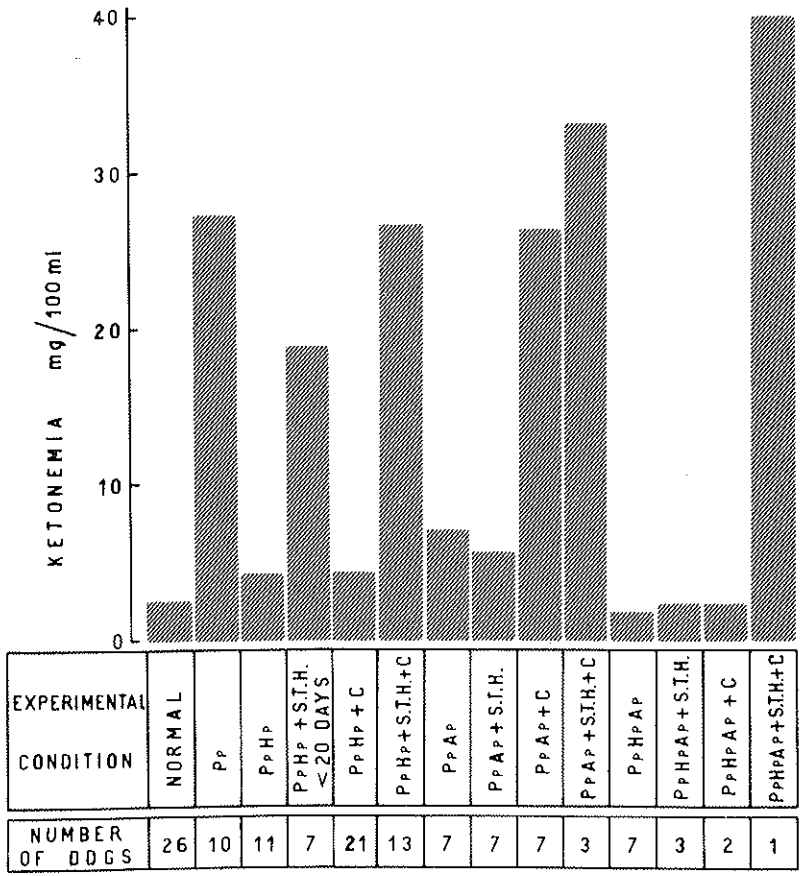

FIG. 1 — Blod ketone bodies (mg/100 ml) in different groups of dogs.

obtained is similar or higher than in animals having been pancreatectomized only.

The blood FFA are increased by pancreatectomy and decreased by hypophysectomy (table I).

TABLE I — *Blood changes in dogs: normal (N); hypophysectomized* (Hp); *pancreatectomized-hypophysectomized* (PpHp); *and pancreatectomized* (Pp). *Between brackets number of dogs.*

Dogs	N (22)	H_p (22)	P_pH_p (11)	P_p (12)
Glycemia mg/100 ml	73 ± 0.2	60 ± 1.2	161 ± 33	275 ± 10
F.F.A. μEq/l	480 ± 22	350 ± 36	632 ± 107	1880 ± 152
ketone bodies mg/100 ml	3.2 ± 0.3	4.0 ± 0.5	4.0 ± 2.0	24.0 ± 2.8
Total lipids mg/100 ml	419 ± 52	424 ± 32	554 ± 93	854 ± 182
Cholesterol mg/100	92 ± 7	83 ± 7	121 ± 14	156 ± 11

After pancreatectomy there is a striking increase of liver fat, and the macro-and microscopical aspect is of a fatty liver. The value in normal dogs is 3.5 g/100 g of total lipids; after pancreatectomy the increase is 8 times higher, 25 g/100 g. But hypophysectomy diminishes this increase, the average being 8.6 g/100 g and in many cases the aspect is not of a fatty liver.

The increase of fat is due to the deposit of triglycerides. Phospholipids have little variation and the cholesterol content is increased in the pancreatectomized dogs (table II).

In pancreatectomized-hypophysectomized dogs the injection of somatotrophin produces a marked increase of liver fat (18 g/100 g) (table III).

Bilateral removal of the thoraco-abdominal ganglionic chains of the sympathetic system produces an attenuation in the intensity of the pancreatic diabetes which is probably due to

the diminution of peripheral fat lipolysis and mobilization after pancreatectomy. This attenuation of the pancreatic diabetes is less intense than after hypophysectomy.

TABLE II — *Changes of liver composition in dogs: normal* (N); *pancreatectomized* (Pp); *pancreatectomized-hypophysectomized* (PpHp) *and hypophysectomized* (Hp). *Between brackets number of dogs.*

Dogs	F.F.A. µEq/l	Total lipids g/100 g	Triglycerides g/100 g	Phospholipids g/100 g	Cholesterol mg/100 g
N (6)	5.6 ± 1.0	3.5 ± 0.45	2.5 ± 0.5	1.8 ± 0.5	175 ± 28.6
P_p (9)	5.0 ± 0.5	25.4 ± 3.6	23.2 ± 3.6	2.0 ± 0.2	483 ± 15.6
P_pH_p (6)	4.1 ± 0.2	8.6 ± 2.0	6.6 ± 2.1	2.3 ± 0.1	510 ± 84.8
H_p (6)	4.1 ± 0.7	2.7 ± 0.42	1.2 ± 0.2	1.8 ± 0.2	266 ± 23.6

TABLE III — *Changes of liver composition in dogs: pancreatectomized-hypophysectomized* (PpHp); *pancreatectomized-hypophysectomized + somatotrophin* (PpHp + STH) *and pancreatectomized* (Pp). *Between brackets number of dogs.*

Dogs	F.F.A. µEq/l	Total lipids g/100 g	Triglycerides g/100 g	Phospholipids g/100 g	Cholesterol mg/100 g
P_p (9)	5.0 ± 0.5	25.4 ± 3.6	23.2 ± 3.6	2.0 ± 0.2	483 ± 15
P_pH_p (6)	4.1 ± 0.3	8.6 ± 2.0	6.6 ± 2.6	2.3 ± 0.1	570 ± 85
P_pH_p + STH (4)	6.3 ± 0.2	18.4 ± 2.3	16.1 ± 2.2	1.9 ± 0.3	428 ± 101

The injection of somatotrophin in pancreatectomized-gangliotomized dogs restores the intensity of the pancreatic diabetes. The infusion of norepinephrine in pancreatectomized-hypophysectomized dogs increases the blood ketone bodies.

Some pituitary hormones have a lipolytic action « in vivo » and « in vitro » and increases ketonemia, including: adrenocorticotrophin, somatotrophin, melanotrophin, thyrotrophin and many polypseptides (lipotropin of ANSELMO and HOFFMANN, β — and γ — lipotropin of LI and coll., lipid mobilizing factor of Trygstad; substances described by RUDMAN and coll., ASTWOOD and coll.). The chemical structure of the β lipotropin has been determined by LI.

In diabetic animals a lipolysis of the triglycerids of the adipose tissue is observed « in vivo ». Glycerol, which is the quantitative index of lipolysis, passes to the blood and is metabolized. Fatty acids also pass to the blood as free fatty acids (FFA), one part being resynthetized as fat, another one used by the tissues and the other transformed by the liver in ketone bodies.

These ketone bodies are used by the tissues (brain, heart, muscle) but when their production is excessive, an accumulation in the blood (hyperketonemia) and in the urine (hyperketonuria) is seen.

In normal animals a prolonged injection of growth hormone produces supernormal formation of protein and increased abnormal growth. There is a marked diminution of fatty tissue and an increase of water and potassium in the tissues.

The pituitary gland has an important role in the regulation of the metabolism of lipids in the body under normal and pathological conditions.

The diabetic ketosis of the pancreatectomized animals is due to two factors: 1) lack of insulin; 2) simultaneous presence of the hormones of the hypophysis and adrenal glands. Due to these factors there is an increase of lipolysis and mobilization of the adipose tissue, triglycerides, with increase of lipemia, FFA, ketonemia and accumulation of triglycerides in the liver (fatty liver) and other organs.

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