PONTIFICIA ACADEMIA SCIENTIARVM

COMMENTARII

Vol. II N. 2

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EX AEDIBVS ACADEMICIS IN CIVITATE VATICANA

PONTIFICIA
ACADEMIA
SCIENTIARVM

COMMENTARII
Vol. II - N. 3
pag. 1-8

ROLE OF LIVER INERVATION ON FAT METABOLISM

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SVMMARIVM — In sanguine canum, e quorum iecore nervi ablati sunt, lipida et quaedam acida (NEFA) aucta sunt. Chetonimia autem in canibus, quorum pancreas resectum est, gradatim augetur; minus autem, si a iecore nervi ablati sunt.

The action of the nervous system on carbohydrate metabolism is well known from the classic « piqure » experiment of CLAUDE BERNARD. The sympathetic stimulation transmitted to the liver by the splanchnic nerves produces glycogenolysis by two mechanisms: *a*) intrahepatic direct action due to activation of the phosphorylase which splits the glycogen into glucose and produces hyperglycemia; *b*) stimulation of secretion of adrenaline by the adrenal medulla, which by way of the blood stream reaches the liver and produces also glycogenolysis and liberation of glucose into the blood.

Glycogen formation is accompanied by a simultaneous deposit of potassium in the cell. Glycogenolysis produces a release of potassium in to the blood. Stimulation of splanchnic nerves produces, by the two mechanisms quet mentioned of the sym-

Paper presented on April 22th, 1966 during the Plenary Session of the Pontifical Academy of Sciences.

pathico-adrenal system, a temporary release of potassium into the blood.

The action of sympathetic nerves on the peripheral adipose tissues has been demonstrated. Their stimulation produces lipolysis of the triglycerides and the fatty acids are liberated and transported in the blood as non esterified fatty acids (NEFA).

So far an action of the nerves on the fat metabolism of the liver has not been observed. The work here reported demonstrates its existence (*).

During the catabolism of fatty acids in the liver, ketone bodies are formed which are poured in to the blood and finally oxidized in many tissues (muscle, heart, etc.). When the production of ketone bodies is much greater than their consumption, they accumulate in the blood and there is an increase of ketonemia and ketonuria.

In the diabetes produced by pancreatectomy in the dog glucose consumption is diminished and the utilization of fatty acids is increased. As a consequence, ketone bodies in the blood reach a high level. In table 1 in pancreatectomized diabetic dogs ketonemia is about 10 times greater than in normal animals (table 1).

TABLE 1. — *Hormonal and neural influences on ketonemia in pancreatectomized dogs.*

	Number of animals	Ketone bodies mg/100 ml on the fifth day
Controls pancreatectomized	41	23.7 ± 2.1
With bilateral sympathetic chains removal	8	7.3 ± 6.2
With liver denervated	8	7.5 ± 0.9
Hypophysectomized	11	4.0 ± 2
Adrenalectomized	7	7 ± 1.5
Controls, non pancreatectomized	26	2.4 ± 0.7

(*) Instituto de Biologia y Medicina experimental - Buenos Aires.

The hormonal factors involved in the production of diabetic ketosis in pancreatectomized dogs are: 1) insulin insufficiency; 2) simultaneous presence of two factors, pituitary and adrenal hormones, which increase the severity of the diabetic ketosis (HOUSSAY et al., 1964). The suppression of the pituitary or of the adrenal produces a striking reduction of ketonemia in the pancreatectomized dogs (table 1).

Extirpation of both sympathetic chains, fram T_1 to L_6 (including the stellate ganglia and the splanchnic nerves), in the pancreatectomized dog also produces a diminution of their ketonemia. Hepatic denervation produces also a decrease of their ketonemia (table 1), but with a different mechanism.

In the present note, the results and their discussion are summarized. A paper will be published « in extenso ».

The diabetic hyperglycemia was similar. In the three groups of pancreatectomized dogs. There was no change after sympathisectomy or liver denervation (table 2). The increase of cholesterolemia was also similar in the three lots of animals; the slight differences were not statistically significant.

TABLE 2. — *Blood changes in dogs: pancreatectomized (Pp); pancreatectomized with liver denervation (Pp, liver den.); pancreatectomized with bilateral removal of sympathetic chains (Pp., symp. ex.). Between brackets, number of dogs. Five days of observation.*

Glycemia (mg per 100 ml)

Condition	Basal	1 day	2 days	3 days	4 days	5 days
Pp. . . . . (8)	75±4	228±15	276±10	262±22	286±35	272±11
Pp. liver den. . . (10)	80±3	250±18	291±14	263±99	293±33	352±160
Pp. Symp. ex. . . (9)	85±8	205±21	308±38	348±70	311±37	268±30

Cholesterol (mg per 100 ml plasma)

Condition	Basal	1 day	2 days	3 days	4 days	5 days
Pp. . . . . (8)	115±9	146±11	160±9	153±7	171±16	158±15
Pp. liver den. . . (10)	108±8	128±8	155±13	151±12	141±16	144±8
Pp., Symp. ex. . . (8)	131±15	139±15	159±18	150±13	166±18	170±17

Total lipids (mg per 100 ml of plasma)

Condition	Basal	1 day	2 days	3 days	4 days	5 days
Pp. . . . . . . (8)	437±50	715±159	1223±153	1046±209	908±240	854±204
Pp. liver den. . (10)	439±3.9	714±7.7	1260±271	1117±308	799±201	701±119
Pp., Symp. ex. (8)	571±92	659±118	844±151	795±107	752±246	731±109

Non esterified fatty acids (*NEFA*) (microequivalents per litre of plasma)

Condition	Basal	1 day	2 days	3 days	4 days	5 days
Pp. . . . . (8)	594±90	1437±184	1549±268	1594±165	1867±139	1741±155
Pp. liver den. (8)	539±62	1745±101	1691±143	1757±169	1454±92	1481±168
Pp., Symp. ex. . . . (8)	407±76	776±123	1588±137	1434±98	1604±219	1340±311

Ketone bodies (mg per 100 ml of plasma)

Condition	Basal	1 day	2 days	3 days	4 days	5 days
Pp. . . . . . . (7)	2.7±0.9	7.2±1.1	10.5±2 4	13.6±4.3	19.0±4.1	25.1±3.6
Pp. liver den. . (10)	1.0±0.2	3.7±0.4	6.5±0.9	7.5±0.9	11.0±2.8	14.4±2.7
Pp., Symp. ex. . (8)	3.3±0.6	3.5±0.5	5.4±1.1	7.3±6.2	11.1±5.3	12.0±4.6

Bilateral removal of sympathetic thoraco-lumbar chains provoked marked changes: lower values of lipemia, free fatty acids (NEFA) and ketonemia. There was a diminished mobilization of fatty acids from the peripheral adipose tissue and then a smaller increase of lipemia and less formation of ketone bodies.

After liver denervation, the increase of lipemia and non esterified fatty acids were as high as in the pancreatectomized dogs, but there was a marked decrease of the ketonemia in the pancreatectomized dogs with liver denervation.

In the pancreatectomized dogs with or without liver denervation, the peripheral mobilization of fatty acids was intense and similar in both lots of animals.

The fatty liver aspect was observed in the three groups of pancreatectomized dogs, but the chemical analysis of the liver was made only in pancreatectomized animals, pancreatectomized with liver denervation and in normal dogs. In both groups of pancreatectomized dogs the total lipid increased to 5-6 times the normal value. This increase was due mainly to triglycerides (table 3) the phospholipids changes were slight. The cholesterol values were increased in both lots of pancreatectomized dogs.

Striking changes were observed in the free fatty acids (NEFA). They were markedly increased in the pancreatectomized dogs (16 times, over the normal value), but only very slightly (1.5 times) in the pancreatectomized dogs with denervated liver (Table 3).

The blood ketone bodies increased progressively after pancreatectomy, but in the pancreatectomized dogs with liver denervation the values were always lower (about 44 per cent) (Table 4).

The diminution of hepatic NEFA and blood ketone bodies produced by the liver denervation in the pancreatectomized dogs is an indication of the intrahepatic diminution of lipolysis of triglycerides and the catabolic oxidation of fatty acids and subsequent ketogenesis.

TABLE 3. — *Composition of the liver lipids of normal dogs (N); pancreatectomized (Pp); pancreatectomized with liver denervation (Pp. l. d).*

Dogs (*)	Free fatty acids µEq/g	Total lipids g/100 g	Triglycerides as total lipids g/100 g	Phospholipids as total lipids g/100 g	Cholesterol mg/100 g
74 Pp. l. d.	16.4	35	32.3	2.6	431
76 Pp. l. d.	11.5	30	23.6	2.1	760
79 Pp. l. d.	11.6	25	21.7	2.6	690
	13.1	30	25.8	2.3	627
77 Pp.	132	25	20	2.7	960
83 Pp.	80	18.7	16.8	1.95	483
81 Pp.	120	30	23.6	2.03	715
82 Pp.	217	25	23.2	2.0	—
	137	25	21	2.1	719
81 N.	12.2	5.4	4.2	1.4	286
82 N.	3.3	4.3	2.5	1.9	315
83 N.	10.8	8.8	7.6	1.9	232
	8.7	6.2	4.8	1.7	277

(*) Experimental condition and serial numbers.

TABLE 4. — *Changes in fat metabolism of pancreatectomized dogs produced by liver denervation.*

	Blood		Liver			Blood
	Total lipids g/100 ml	NEFA µEq/l	Total lipids g/100 g	Triglycerides g/100 g	NEFA µEq/g	Ketone bodies mg/100 ml
Pancreatectomized	949	1637	25	21	229.0	17.0
Pancreatectomized, liver denervation	968	1625	30	25	19.4	9.8

BIBLIOGRAPHY

HOUSSAY B. A., A. D. MARENZI and REBECA GERSCHMAN, « C. R. Soc. Biol. », París, 1936, *124*, 383 et 384.

WERTHEIMER E., « Pflüg. Arch. ges. Physiol. », *213*, 262 and 280 (1926).

HOUSSAY B. A., E. J. URGOITI, C. T. RIETTI, M. E. GALLI, E. J. DEL CASTILLO, Pontificia Academia Scientiarum, Commentarii, 1964, 1, n. 42, 1.