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Mamoru Sugiura: Potential Pathways in Nutritional Progress

Ⅰ Introduction

The science of nutrition is entering into a new era, and its dim outlines are beginning to emerge. I wish to write about some of these potential pathways which may lead to nutritional progress, and the researches that have done about some of them in Prof. Lepkovsky Laboratories, University of California.

Ⅱ Dynamic Systems in Nutrition.

Nutrition in animals is the most basic process in animal life, and most of the tissues are involved in this process. Animals eat periodically with alternations of feeding and fasting. Metabolic processes must be appropriate to eating or fasting, and these meta-

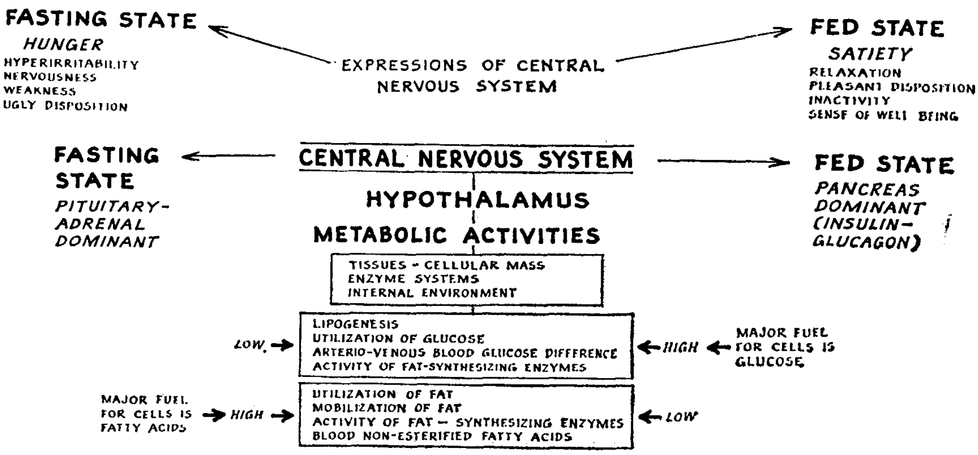

Fig. 1. The dynamic relationship between the nervous system, the endocrine system and the body biochemistry.

bolic processes must be integrated with the endocrine system, all of which must be integrated (Fig. 1)[1] in the central nervous system with expressions of hunger and satiety.

(a) Biochemisry of the Fasting Animal

During fasting the level of blood glucose must be maintained to enable the brain to function, since glucose is its only known source of energy. Many mechanisms participate in the maintenance of the glucose level of the blood of the fasting animal.[2]

Glucose utilization: Glucose utilization is inhibited, through inhibition of the conversion of glucose into fat, glycogen and protein, and impairment of the oxidation of glucose.

Fat utilization: The utilization of fat is increased, and thus the loss of carbohydrate as a source of energy due to the inhibition of the utilization of glucose is balanced.

The mobilization of fat from the adipose tissue is increased and the fat is transported to the other tissues as non-esterified fatty acids.[3] The oxidation of fat is increased.[2]

Synthesis of new glucose: Although the utilization of glucose is inhibited, some glucose is continually used up and some source of glucose must be found. Glycogen is used to meet the immediate demand for glucose, and later more glucose is made available from body protein through gluconeogenesis: through this mechanism the blood glucose may be maintained during long periods of fasting.

Regulation of blood glucose: The blood glucose level is maintained largely through the opposing action of the pituitary and pancreas.[2]

These processes are reflected in the nervous system as hunger. This is accompanied by hunger contraction and other gastric sensations, hyperactivity, weakness, irritability, nervousness, depression and ugly personality.

(b) Biochemistry of the Fed Animal

After eating a high carbohydrate diet, glucose is absorbed from the intestinal tract and pours into the blood. The glucose must be removed from the blood or hyperglycemia ensues, as in diabetes. This is accomplished by changing over the metabolic activities of the animal. The glucose of the blood is utilized rapidly and is converted to glycogen and fat. The fat synthesizing enzymes have been activated, and the newly synthesized fat is deposited in the adipose tissues. The tissues now largely utilize carbohydrates, and the adipose tissues inhibit the release of the non-esterified fatty acids.

Gluconeogenesis is abolished and body proteins are no longer decomposed to form glucose. Instead, body proteins are synthesized.

These activities go on under the influence of the pancreas, especially of the insulin mechanism.

These processes are reflected through the nervous system as satiety. This is accompanied by the cessation of hunger contractions, relaxation, inactivity, warmth, contentment and a pleasant personality.

(c) Regulation of Biochemical Reactions in the Fasting and Fed Animal.

In the fasting animal, the anterior pituitary gland is activated and the insulin mechanism is inhibited. The fasting condition resembles in many respects that of a depancreatized animal. In the fed animal, the insulin mechaism on the pancreas is activated and the pituitary gland is inhibited. It is suggested that the actions of the pituitary gland and of the pancreas are co-ordinated in the hypothalamus in these nutritional processes.[4)]

Ⅲ. Nutritional Research in Prof. Lepkovsky Laboratories, University of California

The living elements of animals are the cell and they are aquatic organisms living in a specific environment. The nutrients needed by the cell of animals are in the external environment largely as living tissues and in a form unavailable to the cell. To deliver these nutrients to the cell, it is necessary to bridge the gap that exists between the external environment and the cell. The following processes are involved.

1) The animal must have the urge for food to drive it in search for food.

2) Having found the food, the animal must put the food into its mouth and swallow it (Food intake).

The animal must cease eating when it has had enough (Satiety).

3) In the gastrointestinal tract, the food is reduced to nutrients that are available to the cell (digestion).

4) The absorbed nutrients are then delivered to the cell, with some preliminary processing by the liver (disposal of absorbed food).

(a) Food intake and the hypothalamus.

Food intake is under the control of the central nervous system and in this process the hypothalamus plays a key role. In it are so-called nuclei which can be damaged or destroyed and far-reaching changes occur in food intake. One nucleus controls appetiate so that all voluntary eating ceases (aphagia) when these cells are destroyed. When another group of cells destroyed, the animal loses all sense of satiety and eats ravenously (hyperphagia).

Information on food intake is essential for an understanding of obesity in human beings and of the economical use of feeds in the animal industry.

Lesions were put in the hypothalamuses of the rats and chickens.[5)] Hyperphagia has not been produced in female chickens but was produced in male chickens while it has been easily produced in rats. Aphagia has been produced in both rats and chickens. In the rats, the aphagia was temporary. Rats that were kept alive by tube feeding sooner or later resumed eating. The aphagia in chickens seems to be more permanent.

Lesions almost always caused some disturbance of other functions, such as water metabolism, activity, reproduction, temperature regulation, temperament and abnormal distribution of fat in the carcass.

Aphagia in rats is accompanied by a greatly reduced activity and by a cessation of drinking. Resumption of eating and drinking occur more or less simultaneously. Aphagia has been produced in chickens,[6] largely males. Most aphagic chickens will drink water. Activity in chickens was reduced. Defective heat regulation occurred and the chickens did not pant when they were hot their body temperatures rose to high levels, some of them dying. Although their crops were full of feed, the intestines were contracted and suggested that this condition was a protective mechanism against the absorption of food to prevent the heat of digestion. The intestinal tract may play a role in the loss of appetite in hot climates or during fevers.

Lesions in the hypothalamus prevented ovulation in rats as shown by persistent estrus or persistent cornification in the vagina. The ovaries contained many ripe follicles, but they did not ovulate. Replacement therapy showed that injection of I. C. S. H. caused prompt ovulation with disappearance of the cornified cells of the vagina.[7] It was considered that the lesions of hypothalamus interfered with the metabolism of the luteinizing hormone.

Other birds with lesions in the hypothalamus showed diabetes insipidus indicating abnormal function of the posterior pituitary with decreased release of the antidiuretic hormone.[8]

Lesions in the hypothalamus and hypophysectomize in rats and chickens showed the interesting result on tryptophane metabolism.[9][10][11]

(b) Food intake and the adipose tissue

Appetite and satiety must reflect the metabolic processes that are the consequences of eating and fasting. The adipose tissue was investigated as one possible site where control of food intake may be exercised. Rats were fed with and without water. The rats eating without water reduced their food intake. The following results were obtained.

1) Food intake was regulated at the mouth so that only so much food was eaten as could be matched with water that could be mobilized from the tissues the dilute the food in the stomach to a water content of approximately 48 per cent at which it is regulated.[12]

2) The water diluting the food in the stomach came largely from the skin and adipose tissue.

3) Little glycogen was found in the adipose tissues of the rats fed without water and this was presumably due to the withdrawal of the water from the adipose tissue.

There was an association between decreased food intake, dehydration of the adipose tissue and inhibition of the synthesis of glycogen.

(c) The gastrointestinal tract and digestion

1) Regulation. The intestinal tract seems to be regulated as though it were part of the internal environment. The water content of the intestinal contents is regulated as closely as the water content of the blood. Regulation is carried out at the pyloric sphincter in the way food is permitted to enter into the intestinal tract. Ingestion of food is limited by the water that is available, either from the bottle or the tissues to maintain the

water content of the stomach contents at about 48 per cent.

2) Digestion. The enzymes in the intestine needed to digest the food are secreted by the pancreas and the intestinal wall. The stomach contents seem to activate the production and secretion of secretin and pancreozymin which act on the pancreas to secrete the pancreatic juice.

3) The Stomach. Removal of the stomach of the rats results in anemia. It is not clear whether this anemia is the consequence of the deficiency of some essential compound furnished by the stomach or is due to a Bartonella infection.
It is not due to the intrinsic factor because vitamin B_{12} was injected. The stomach may function in an unexplained way to affect hematopoietic processes.

The function of the pancreas of the gastrectomized rats was not greatly impaired as measured by the amounts of the digestive enzymes in the intestinal tract. Presumably food as such will activate the duodenum to secrete the necessary hormones to activate the pancreas to secrete the enzymes needed in the processes of digestion.[13]

4) Regulation of the digestive enzymes. When raw soy bean diets are fed, the antitrypsin of the raw soy beans inactivates the trypsin of the pancreatic juice. The pancreas responds immediately with a "discharge effect"more proteolytic enzymes, lipase and amylase being secreted into the intestinal tract and this is reflected in a decrease in all of these enzymes remaining in the pancreas. The pancreas hypertrophies, the process going on three to four weeks. At that time the production of the proteolytic enzymes in the pancreas has greatly increased in terms of the proteolytic enzymes in the intestinal tract and in the content of the proteolytic enzymes remaining in the pancreas. There is no such adaptation with lipase and amylase.[14] It still remains to be shown how the pancreas knew that antitrypsin was in the gastro-intestinal tract.

5) Amylase and methionine in the chicken. Raw soy bean diets act to decrease the synthesis of amylase in the pancreas of the chicken. Methionine restores to normal the synthetic activity of amylase in the pancreas.[15]

6) Inactivation of digestive enzymes. In both rats and chickens, digestive enzymes are inactivated in the gastro-intestinal tract. Lipase begins to be inactivated in the lower part of the small intestine. In the cecum all the digestive enzyme were rapidly inactivated. This has been checked with germ-free chicks which show:[16]
a) Rapid destruction of amylase and proteolytic enzymes in the cecum of the conventional chicks, but not in the germ-free chicks. b) The amylase activity of the intestinal content of the conventional chicks is about twice as high as that of the germ-free chicks indicating that the intestinal bacteria specifically increase the synthesis of amylase in the pancreas or in the other tissues of chicks.

7) The pancreas as an organ of digestion in the chicken. Depancreatized chickens soon cease laying eggs and cockerels cease producing semen. These functions can be restored by the addition of raw pancreas which increases the digestibility of protein and fat.

Little increase in the digestibility of starch was noted. The anticipated increase in digestive enzymes in the intestinal tract due to the feeding of the raw pancreas were not found when the intestinal contents were assayed for these enzymes. This picture is further complicated when it was recently observed that raw muscle meat like raw pancreas in the feed acts to restore egg production.[17] The role of muscle meat in the production of semen is under investigation.

8) The pancreas and blood cholesterol.

Depancreatized chickens showed lower blood cholesterol than normal ones. Incom pletely depancreatized chickins behaved like normal chickens. Pancreatic juice seems to influence the blood cholesterol of chickens. Tryptophane metabolism of depancreatized chickens was done by Matsumura.[18]

9) The pancreas and the iron contents of the liver.

Depancreatized chickens including partially depancreatized chickens show higher iron contents of the liver than normal ones. Apparently, pancreatic juice plays a role in the absorption of iron or storage of iron in the liver.

10) Fate of absorbed carbohydrates. Conversion of glycogen.

The fate of absorbed carbohyrats was followed by glycogen synthesis in liver, muscle, skin, brain and the following fatty tissues: brown interscapular, brown "renal", mesentric, retroperitoneal and subcutaneous. All the tissues except muscle contained little or no glycogen at fasting and reached a peak in their accumulation of glycogen at 7 to 9 hours after eating. There are differences among all the tissues in their synthesis of glycogen and the following differences may be noted:

a) Liver glycogen was low in fasted rats and at 7 to 9 hours after eating increased to as much as 3 to 5 per cent.

b) Muscle glycogen changed very little from fasting to fed rats.

c) The skin had little glycogen in the fasting state (about0.02%) and after eating, the glycogen rose to a maximum of 0.10 per cent.

d) Glycogen in the brain was uninfluenced by the metabolic processes that are going on the rest of the animal.

e) The interscapular brown fatty tissues contained little or no glycogen at fasting and accumulated as much as 2 to 3 per cent of glycogen 7 to 9 hours after eating.

f) The brown fatty tissue between the kidney and the adrenal acted very differently from the surrounding white fatty tissues. This tissue accumulated as much as 1 to 2 per cent of glycogen whereas the visceral, retroperitoneal and subcutaneous fatty tissues accumulated but a few tenths of a per cent of glycogen of these, the mesenteric fatty tissue was most active and the subcutaneous the least.[19]

11) Fate of absorbed carbohydrates. Conversion to fat.

At fasting, the lipogenic activity of the liver was much greater than that of the other tissues. After eating, the increase inlipogenic activity of the liver was 3 to 7 times while that of the fatty tissues increased 10 to 40 times so that at this time some of the fatty tissues showed as high a lipogenic activity as the liver. Among the fatty tissues the mesentric and renal fatty tissues were the more active and the subcutaneous the least.

IV) Co-operation research with Prof. Lepkovsky in future.

I will have the co-operation research with Prof. Lepkovsky (University of California) on mechanisms that regulate the action of the pancreas and how the pancreas regulates digestion and absorption by grant of National Science Foundation.

In the study we shall examine:

1) Mechanisms that regulate the synthesis of the protease, lipase and amylase of the pancreas.

2) The role of the stomach in regulating the release of the enzymes from the pancreas. It does so in two ways. a) Stomach distention, and b) supplies the hydrochloric acid with the gastric juice which triggers the secretion of pancreatic juice.

3) Mechanisms that act upon the pancreas to regulate the secretion of the digestive enzyme. a) The secretin and pancreozymin mechanisms. These hormones are elaborated in the intestinal mucosa and act upon the pancreas. b) Neurogenic mechanisms

4) Adaptive changes in the pancreas enabling the pancreas to regulate the concentration of the protease, amylase and lipase in the intestine.

Our studies indicate that pancreas regulates the synthesis of these enzymes in accordance with need which is communicated to the pancreas through the information it receives from the intestine upon the status of these enzymes in the intestine.

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