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ROLE OF EMOTIONAL STRESS IN DISTURBANCES OF CARBOHYDRATE TOLERANCE

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One of the tests used to determine the state of carbohydrate metabolism is the glucose tolerance test; even if the initial blood sugar level is normal, this test can reveal latent periods of disturbances of carbohydrate metabolism. It is widely used in clinical practice for the diagnosis of diencephalic pathology [4, 5, 7] and also of latent diabetes [1]. Despite evidence that one cause of the transition of latent diabetes in adults and children into its manifest form is psychic trauma [1, 2], we have been unable to find any systematic experimental investigations demonstrating the role of strong or prolonged emotional strain as a primary factor in the onset of lasting disturbances of carbohydrate metabolism. Meanwhile such information would be important when studying the pathogenesis not only of diabetes, but also of ischemic heart disease, for we know that a disturbance of carbohydrate tolerance is one of the risk factors in the development of this disease, especially when combined with hypercholesterolemia and arterial hypertension [9, 10, 15, 16].

The aim of this investigation was to determine whether strong and prolonged emotional strain of negative character can effect changes in the blood sugar level and glucose tolerance. A model of "collisions" between food and nociceptive stimulation, and also stimulation of negative emotiogenic zones of the hypothalamus, were used for this purpose.

EXPERIMENTAL METHOD

Two series of experiments were carried out on 21 rabbits weighing 2.5-3.5 kg. The experiments of series I were performed on 10 animals — five experimental and five control. For 4 months twice a day the experimental rabbits were subjected to "collisions" between food and nociceptive stimuli. All the rabbits were accustomed to receive carrot juice daily from a small (5 ml) syringe, the end of which was connected to a rubber tube introduced painlessly into the mouth between the teeth. After a certain period during which the rabbits became accustomed to this procedure, twice or three times a week a "collision" was created between food and nociceptive stimulation: Simultaneously with receiving carrot juice, the rabbit also received an electric shock (20 V, 60 Hz, 0.5 msec) from an ÉSA-2 stimulator through a wire running alongside the rubber tube. Control rabbits continued to receive only carrot juice as before during this period.

After 1 year the experimental and control rabbits in this series of experiments were subjected to a glucose tolerance test in a dose corresponding to that used in clinical practice. Glucose solution (40%) was injected slowly in a volume of 2 ml/kg body weight into the marginal vein of the ear of the fasting rabbits. Blood samples were taken before and 15, 30, 60, and 120 min after injection of glucose.

In the experiments of series II glucose tolerance was tested after relatively prolonged (10 days) chronic emotional stress caused by stimulation of the negative emotiogenic zones of the hypothalamus, into which bipolar nichrome electrodes were implanted in accordance with

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a stereotaxic atlas [19]. Verification that the electrodes were correctly implanted was given by the appearance of a negative emotional-behavioral response, and after the end of the experiments by morphological examination.

The experiments were carried out on 10 rabbits. Ten days after the behavioral test five experimental rabbits were subjected (for 2 h daily, with several irregular intervals) to prolonged stimulation of negative emotiogenic zones of the hypothalamus with a sinusoidal current from a ZG-10 stimulator. The parameters of stimulation for each rabbit were chosen individually. The strength of the current varied from 50 to 140 μA, the frequency from 50 to 150 Hz, but the duration of the pulses was always constant at 0.5 msec. Stimulation was applied once per second by means of a "Kontrast" time relay.

EXPERIMENTAL RESULTS

The results of the experiments of series I showed that 1 year after exposure to repeated "collisions" between food and nociceptive stimulation the blood glucose level in the experimental and control groups was within normal limits. However, despite this similarity in the initial blood glucose level, the glucose tolerance test revealed great differences in adaptive reactions to glucose loading in the two groups of animals.

In both groups the maximal rise of the blood glucose level in response to intravenous injection, within the periods of observation, occurred at the 15th minute. However, whereas in the control animals at this time the glucose concentration was significantly increased from 100.5 ± 5.47 to 194.5 ± 8.28 mg% ($P < 0.001$), in the experimental animals, from an initial level of 111.2 ± 5.19 mg% it rose to 343.4 ± 20.6 mg%. The subsequent time course also was interesting. In the rabbits of the control group the blood glucose level quickly fell to reach its initial level (100.8 ± 9.4 mg%) after 60 min, and even lower (88.5 ± 7.69 mg%; $P < 0.001$) after 120 min. In rabbits of the experimental group, however, the blood glucose level fell more slowly: to 229.0 ± 26.19 mg% ($P < 0.001$) after 60 min, and it was still above the initial level after 120 min (123.8 ± 11.3 mg%; $P < 0.05$).

The experiments of series I thus showed that repeated, strong, prolonged emotional strain leaves its mark on the body, as becomes apparent, despite the seemingly normal initial data, only after an additional strain on the adaptation system, when it is manifested in this case as reduction of glucose tolerance. Under similar experimental conditions the writers previously found lowering of tolerance to cholesterol [13].

In the next series of experiments, to study the effect of emotional stress induced by stimulation of negative emotiogenic zones of the hypothalamus, even after relatively brief (10 days) chronic emotional stress changes in glucose tolerance were observed, with the appearance of a blood sugar curve of diabetic character. For instance, whereas in the control rabbits 15 min after injection of glucose its blood level was increased significantly from 97.0 ± 4.46 to 167.0 ± 7.97 mg% ($P < 0.001$), in the experimental rabbits, from an initial level of 106.2 ± 12.03 mg% the blood glucose level rose to 227.6 ± 19.58 mg%, and it still remained high after 60 min (162.4 ± 16.73 mg%), and it only returned close to the initial level after 120 min (108.0 ± 10.24 mg%; $P > 0.05$). Meanwhile, in rabbits of the control group the glucose concentration actually fell below its initial level, to 81.8 ± 4.74 mg% ($P < 0.05$).

It is interesting to note that as a result of chronic stimulation for 10 days the blood glucose level in two of the five rabbits rose, as high as 146 mg% in one animal, although for the group as a whole it remained within normal limits.

Morphological verification of the position of the electrodes showed that their tips were located in the ventromedial nucleus of the hypothalamus, on the boundary between the ventromedial and dorsomedial nuclei, or in the medial zone of the anterior hypothalamus.

The diabetic type of sugar curve in the rabbits of experiments of series I and II, exposed to different types of repeated emotional stress immediately before testing or in the past, could, it might be supposed, be due to changes in the state of function both of the central regulatory mechanisms responsible for maintenance of the normal blood sugar level, and peripheral mechanisms, mainly the pancreas and liver. Another factor which could be relevant is disturbance of glucose utilization by insulin-dependent tissues — muscle and adipose tissue [1, 17, 18, 20].

These changes in glucose tolerance, due to hypothalamic stimulation, suggest that they may be connected with increased activation of the hypothalamic–hypophyseal–adrenal system.

This suggestion is confirmed by results showing that during stimulation of hypothalamic emotiogenic zones in rabbits the weight of the adrenals was almost doubled: 482 ± 57.7 mg in control rabbits but 971.6 ± 121.6 mg in the experimental rabbits.

A similar increase in weight of the adrenals and in the blood catecholamine and corticosteroid concentrations during prolonged stimulation of the ventromedial hypothalamus was observed by the writers previously [11, 13, 14] and also by other workers [3, 6, 12].

Adrenal hormones, like others whose activity is increased during stress (ACTH, STH, TTH, glucagon), are known to possess contrainsular activity. Whatever the mechanism of elevation of the blood sugar level, the results obtained suggest that emotional stress may be not only an additional factor causing the transition from prediabetes and latent diabetes into its manifest stages [1], but also a primary factor in the genesis of this disease.

Prolonged, chronic stimulation of the negative emotiogenic zones of the hypothalamus thus causes lasting elevation of blood lipid levels (cholesterol and triglycerides), as the writers showed previously [11, 14], but also disturbs carbohydrate tolerance. Consequently, prolonged emotional stress can contribute to the appearance simultaneously of three risk factors in the development of ischemic heart disease, factors which, as epidemiological studies have shown, may aggravate the course of this disease [8, 15].

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