Hypoglycemic Kindling of Limbic System Disorder

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Consistent hypoglycemia reactions offer repeated minor stresses to the limbic system. The separate hypoglycemic episodes can be unimportant, but when they are summated, the activated limbic system appears to be "kindled" to have more intense responses. Kindling occurs when repetitive low intensity stimulations decrease the response threshold. When this occurs previously minor stimuli can cause major responses. The ergotropic sympathetic response system then becomes "tuned up" to an increased state of dominance. A wide variety of relatively minor stimuli can then activate the ergotropic response system. It has been shown that stimuli which are initially ineffective in causing a response can eventually cause major responses. Kindling is a variety of conditioning, and time is always required for both conditioning of responses and for deconditioning. This can be the reason that it usually takes two to four weeks in the low-sugar hypoglycemia diet to decondition or "de-kindle" patients. The goal of this dietary therapy is to raise the threshold of responses of the ergotropic system.

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The variety and inconsistency of the hypoglycemic response has long exasperated physicians. Hypoglycemic episodes have been found to be correlated with a wide variety of responses which have ranged from ulcers to epilepsy (Buckley, 1963, 1967). This wide range of responsiveness is one of the reasons for the skepticism with which most physicians view acute hypoglycemia. Another reason is that the depth of the fall often seems unrelated to the severity of the symptoms.

In the past decade a series of experiments activating the limbic system by subthreshold stimuli have been performed. The method has involved both electric activation and such stimulating drugs as cocaine and amphetamine (Post and Kopanda, 1976). These studies have included withdrawal from experimental alcohol administration and electroshock to animals (Pinel and Van Oot, 1975). These findings provide an objective and valid way to change the threshold of sensitivity of the limbic system to various stressors.

These experiments began with depth electrodes inserted into limbic system centers. The amygdala was the center which could be most easily affected by these subthreshold stimulations. Pinel and Van Oot (1975) have reported on kindling

experiments in which the electric stimulations were given twice daily for one second. The pulsations were at 60 cycles per second, and the strength was 400 uA. When this program was used for five months, experimental animals proceeded through a series of spontaneously erratic behaviors to the development of major motor seizures. The threshold of responsiveness has been reduced by the repetition of these once minor stresses. The threshold of limbic system irritability for some other stimuli has also been reduced, and the animal is likely to become irritated by many minor stresses.

A kindling response has been experimentally found to occur after stimulation with cocaine, lidocaine, and amphetamine (Post and Kipanda, 1976). These findings apply to some of the ways that amphetamine abuse leads to the altered CNS response of paranoia (Kramer, 1972). The kindling responses which occurred in these studies have involved activation of ergotropic sympathetic limbic system responses.

There are many changes in autonomic responsiveness which can occur during states of acute hypoglycemia. Buckley (1969) has found that changes in limbic system activity can account for many of the subjective emotional changes which occur during the "hypoglycemic experience."

Ernst Gel I horn (Gel I horn and Loof burrow, 1963; Gellhorn, 1967) has extensively studied autonomic responses to a large variety of stressful stimuli. About 30 years ago he did a series of papers concerned with hypoglycemia, hypoxia, and asphyxiation. He found that hypoxia and hypoglycemia interfere with the same life-support system in a synergistic manner. When both oxygen and glucose were in short supply, the result was even more severe. These responses indicated a sympathetic ergotropic response system activation by hypoglycemic stress (Buckley and Gellhorn, 1969). The acute hypoglycemia reaction is an ergotropic response which often includes tachycardia, palpitations, increased muscle tone, sleep disturbance, sweating, and subjective anxiety.

There are some very important extensions to this finding that the once-kindled limbic system remains sensitive to other sorts of stimulation. This finding supports the proposal of Gellhorn that during a state of increased ergotropic tuning a usually bland stimulus will cause a sympathetic system discharge because it is so close to being released (Gellhorn and Loofburrow, 1963). When the trophotropic parasympathetic system is tuned up and close to dominance, the same bland stimulus will evoke a trophotropic rather than an ergotropic response. This experimental finding helps to account for some of the variability of responses which different persons have to the same stimulus, and which the same person can have on different occasions.

Glucose and Primary Drives

The glucoreceptor center is the ven-tomedial hypothalamic nucleus. It is the area of the brain which is most sensitive to the acute deprivation of oxygen and sugar, and it is responsive to acute changes in the circulating insulin level (Debons et al., 1970). It serves as a negative feedback center which inhibits adjacent ergotropic centers which regulate feeding behavior. For this reason it has been called the satiety center. When it is inhibited by hypoglycemia, it releases the feeding center in the lateral hypothalamus so that the animal can renew his foraging behavior. We can propose that a primary drive involves a series of neuronal connections which include a governor mechanism to keep the system from becoming too active. Primary drive behavior results when the animal must perform some act or secure some goal in order to regulate the governor mechanism. This can be readily seen in the feeding drive:

(1) Food deprivation inhibits the VMH glucoreceptor center.

(2) The feeding center of the lateral hypothalamus is released.

(3) Primal drive foraging and feeding are activated.

(4) Eating the food will elevate the blood sugar and the secretion of insulin.

(5) Both glucose and insulin act on the VMH which is activated to inhibit the feeding center.

One result of acute elevation of blood sugar

is that the insulin release alters the concentration of amino acids in the blood. This release leads to an elevation of tryptophan which is converted to serotonin, which causes the drowsy, sleepy, response after a heavy meal (Femstrom and Wurtman, 1974).

Since glucose is the major fuel for the brain, it is paradoxical that its reduction activates rather than inhibits. This is explained by the fact that the ergotropic response system is released to perform primary drive self-preservation behavior. The E-system also causes release of epinephrine which can elevate the blood sugar if hepatic glycogen stores are intact.

Hypoglycemia and Temporal Lobe Activity

Experimental hypoglycemic seizures were found to begin in the temporal lobe by Tokizani and Sawyer (1957). They reported changes in activity in the amygdala and hippocampus.

Since acute hypoglycemia releases hypothalamic centers which project to the temporal lobe, the probable cause of Tokizani and Sawyer's finding was a release of these circuits because of VMH inhibition. Keller et al. (1975) have found that destruction of the glucoreceptor mechanism will prevent hypoglycemia seizures. This may occur because the brain is no longer sensitive to acute rise or fall of the blood sugar. The amygdala can be activated by low blood sugar reactions. It is also the area which is most sensitive to electrokindling. It is likely that the activation of the amygdala during hypoglycemia serves to kindle a state of ergotropic system sensitivity, provided the hypoglycemic episodes are frequent enough.

Buckley (1963) has reported a patient with recurrent hypoglycemia who had temporal lobe epileptic seizures which could be activated by both mecholyl and hypoglycemia. This seizure was limited to vertigo. Penfield and Kristiansen (1951) have found that eight out of nine patients who had vertigo as part of their seizure aura could have the aura repeated by stimulation of the posterior temporal gyrus. Moorhouse (1956) found that five out of 20 patients with hypoglycemia complained of vertigo. These clinical findings confirm that acute hypoglycemia can be correlated with disturbances in temporal lobe function. When the kindling occurs due to temporal lobe hypoglycemia responses, the decreased threshold for irritability will remain for a period of time when other minor stresses can more easily annoy the person with hypoglycemia.

It has been found that hypoglycemic episodes activate the temporal lobe and that the amygdala is the most sensitive center in the brain for kindling abnormal responses. The work of Fernandez DeMolina and Hunsperger (1962) concerning the amygdala as a major center for ergotropic responses should now be considered. They found that a growling, hissing response could be elicited from depth electrodes in the amygdala, the lateral hypothalamus, and the brain stem. Moreover, they showed that a pathway exists from the amygdala through the hypothalamus to the brain stem. Destruction of the hypothalamic area prevented stimulation of the amygdala from reaching the brain stem to trigger this response. This is part of the ergotropic system "road map" which has some application here.

Hypoglycemic episodes have been known to be associated with emotional disorders for over 30 years. Salzer (1966) found them to be associated with almost the entire range of psychopathy. These findings do not indicate whether hypoglycemia was the cause or the result of these disorders. This has been investigated in regard to tension-depression. In 1942 Rennie and Howard reported that these patients had hypoglycemia during their disorder, but when they had recovered, the curve had also returned to normal. Buckley (1975) has reported that 41 out of 45 outpatients with tension-depression had hypoglycemia during the five-hour test. They had a blood sugar level which was 20 mg percent or more below the fasting level, and they would activate some variety of symptoms such as dizziness, hunger, headache, body chills and shivering, or gastric acidity. Six of them were placed on the high-protein,

sugar-free diet before prescription of antidepressant medications. Four of these six reported relief from some of their tension symptoms, but not from their depression.

Gellhorn concluded that depression is a state of abnormal trophotropic system dominance. Depression is associated with increased parasympathetic activation of insulin release. This leads to recurrent hypoglycemia which releases the sympathetic system and causes tension and anxiety to be added to the depression. This proposal gains support from the work of Mueller and associates (1969). Hospitalized psychotic, depressed patients were given the intravenous glucose-tolerance test. They had an increased level of circulating plasma insulin, even when the glucose levels remained normal on an excellent hospital diet. These findings indicated that the high-protein and refined sugar- and starch-free diet should be a useful component to the therapy of all sorts of depressive disorders.

The disorders of carbohydrate metabolism found in schizophrenic patients are much more variable than those seen in depressives. The abnormal responses during the glucose-tolerance test include both elevated and lower profile curves. The disruption of limbic system function caused by hypoglycemia will complicate their recovery (Buckley, 1969). Many studies of glucose metabolism have been made with chronically hospitalized patients who have been eating the high-starch meals which are served there. The high refined sugar and starch of this diet makes them prone to an abnormal GTT. Recent work on food sensitivity found in schizophrenics has found that a very significant percentage are sensitive to wheat. Singh and Kay (1976) have found that actively disturbed schizophrenics will improve more quickly when they have been placed on a gluten-free diet. When gluten is surreptitiously added, the patient regresses and previous symptoms return. These findings indicate that a food sensitivity can disrupt limbic system function in ways that are similar to hypoglycemia. It has even been shown that hypoglycemia can occur as one of the responses to a food allergy, even if the food contains no refined sugar at all.

These findings place renewed emphasis on the value of an appropriate diet. The schizophrenic should be on a gluten-free diet (Hills, 1976) which specifically excludes refined sugar.

Conclusion

Hypoglycemic episodes disrupt limbic system function by an inappropriate release of ergotropic sympathetic responses. When the glucoreceptor center in the hypothalamus is inhibited by acute hypoglycemia, limbic system pathways to the temporal lobe are released. The amygdaloid nucleus of the temporal lobe is the brain area which is most sensitive to the kindling effect caused by subthreshold electric stimulation. This kindling response is a lowering of the response threshold of the ergotropic system. It is proposed that repeated episodes of hypoglycemia kindle the ergotropic system to abnormal responses to many kinds of relatively minor stimuli. These responses will complicate any sort of emotional disorder which happens to be present.

REFERENCES

BUCKLEY, R.E.: "Vertiginous Temporal Lobe Seizures by Functional Hyperinsulinism." JAMA 186:726-727, November 16,1963.

BUCKLEY, RE.: "Induction of Hyperglycemia as Treatment for Peptic Ulcers." The Lancet: London 11:7514:497-499, September 2,1967.

BUCKLEY, RE.: "Hypoglycemic Symptoms and the Hypoglycemic Experience." Psychosomatics 10 (11:7-14, January-February, 1969.

BUCKLEY, RE.: "Hypothalamic Tuning, Hypoglycemic Episodes, and Schizophrenic Responses." Schizophrenia 1 (11:14-24,1969.

BUCKLEY, RE.: "A Neurophysiologic Proposal for the Amphetamine Response in Hyperkinetic Children." Psychosomatics 13 (21:93-99, March-April, 1972.

BUCKLEY, RE.: "Autonomic-Metabolic Components of Depression." Presented at the International Academy of Metabology Conference, March, 1975.

BUCKLEY, R.E., and GELLHORN, E.: "Neurophysiological Mechanisms Underlying the Action of Hypo-and Hyperglycemia in Some Clinical Conditions." Confin. Neurol. 31:247-257.1969.

DEBONS, **A.F., KRIMSKY, I.,** and **FROM, A.: "A** Direct Action of Insulin on **the Hypothalamic Satiety** Center." American **Journal of** Physiology 219 **(4): 938-943,** October, 1970.

FERNANDEZ-DeMOLINA. A., and HUNSPERGER, R.: "Organization of the Subcortical System Governing Defense and Flight Reactions in the Cat." Journal of Physiology 160:200-213,1962.

FERNSTROM, J.D.. and WURTMAN, R.J.: "Nutrition and the Brain." Scientific American 230 (2) :84-91, February, 1974.

GELLHORN, E.: "Autonomic-Somatic Integration." University of Minnesota Press, Minneapolis, Minnesota, 1967.

GELLHORN, E., and LOOFBURROW, G.: "Emotions and Emotional Disorders. A Neurophysiologic Study." Harper and Row, NY.. 1963.

HILLS, H.E.: "Good Food Gluten Free." Keats Publishing Co., New Canaan, Conn., 1976.

KELLER. K.J.. LANGLEY, AC, MARKS, B.H.. and O'NEIL, J.: "Vent-romedial Hypothalamus. Involvement in Hypoglycemic Convulsions." Science 187:746,1975.

KRAMER. JC: "Introduction to Amphetamine Abuse in Current Concepts on Amphetamine Abuse." National Institute of Mental Health Pub. 72-9085. Ed. by Ellenwood, E.H., and Cohen, E. Washington DC. U.S. Government Printing Office, pp. 177-184, 1972.

MOORHOUSE, D.: "Some Neurological Manifestations of Hypo glycemia." Brit. MedicalJournal 2: 1512-1514, 1956.

MUELLER, PS., HENNINGER. G.R.. and McDONALD, R.K.: "Intra venous Glucose Test in Depression." Arch. Gen. Psychiat 21:470 477, October, 1969.

PENFIELD. W., and KRISTIANSEN. E.: "Epileptic Seizure Patterns; Study of Localizing Phenomena in Focal Cortical Seizures." C.C. Thomas, Springfield, III., 1951.

PINEL. J.P., and VAN OOT, PH.: "Generality of the Kindling Phen omenon, Some Clinical Implications." Canadian Journal Neurological Sciences 2:467-476, November, 1975.

POST, R.M., and KOPANDA, R.T : "Cocaine, Kindling, and Psycho sis." American Journal of Psychiatry 133161:627-634, June. 1976.

RENNIE, AT., and HOWARD, J.E.: "Hypoglycemia and Tension Depression." Psychosomatic Medicine 4:273-283.1942.

SALZER, H.M.: "Relative Hypoglycemia as a Cause of Neuropsy chiatric Illness." Journal Nat Med. Assoc. 58(11:12-17, January, 1966.

SINGH, MM., and KAY, S.R.: "Wheat Gluten as a Pathogenic Factor in Schizophrenia." Science 191:401 -402, January 30,1976.

TOKIZANI, T., and SAWYER, C.H.: "Sites of Origin of Hypoglycemic Seizures." Arch. Neurol, and Psychiat. 77:259-266,1957.

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