Hypoglycemia, Temporal Lobe Disturbance and Aggressive Behavior

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Summary

Two sorts of limbic system disorder have been found to combine in the causation of aggressive behavior. When recurrent hypoglycemia is added to temporal lobe EEC dysfunction, the result will probably include psychomotor disturbances which resemble temper tantrums. The hypoglycemic episodes can combine to kindle or lower the response threshold of dopamine receptors of the ergotropic sympathetic response system. It is proposed that one cause of this temporal lobe disorder is the anoxic damage which occurs during compression of the skull when labor is prolonged. This causes a herniation of the hippocampal gyrus and the major cerebral arteries under the tentorium cerebelli. The hippocampal formation has a particular probability for injury during this temporary obstruction of arterial blood supply. This area helps to regulate and control the amygdaloid nucleus. The amygdala has been shown to activate descending ergotropic response system pathways which stimulate fight or flight behavior. The hippocampal formation has a particular need

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for niacin, zinc and pyridoxine. This is the probable reason that megavitamins and minerals can be a useful addition to therapy which includes diet and phentoin.

The medical profession has a long teaching tradition in which we pretend that every set of symptoms has only one cause. This evolved during the past century when the extensive number of infectious diseases came to be recognized both in their clinical course and their biologic pathology. This helps the medical students during teaching rounds with the professor to learn to recite a differential diagnosis and then to cleverly select the most probable diagnosis. When the medical student begins to practice in the world of real patients, he discovers that they are under a wide variety of stresses and that they usually have two chronic disorders before the current complaints began.

The aggressive behavior which we are concerned with in this paper was shown to result from two causative factors. Yaryura-Tobias and Neziroglu in 1975, reported that hypoglycemia and temporal lobe dysrhythmia combine to cause the person to become prone to aggressive temper tantrum behavior as the result of rather minor stimuli. They reported on therapy with forty-five patients, of whom twenty-three had schizophrenia and seven had organic brain

syndrome. They found that the patients were improved when placed on either the hypoglycemia diet or on phentoin, and that the best behavioral improvement occurred when both were used simultaneously.

Hypoglycemia and the Temporal Lobe

The temporal lobe has long been known to help regulate and control the primary drives which have important relay centers in the limbic system. The circulating blood sugar levels have been shown to very significantly affect the hypothalamic centers which regulate the feeding drive. It is paradoxical that hypoglycemia appears to stimulate primal behavior because a fall in fuel supply should inhibit rather than activate brain function. The fall in blood sugar first inhibits a negative feedback control center which decreases the activity of several adjacent hypothalamic centers which deal with foraging and feeding behavior, and flight or fight responses. Hypoglycemia alters the balance and equilibrium of the ergotropic and trophotropic response systems which have important relay centers in the hypothalamus (Buckley and Gellhorn, 1969).

In 1963, I reported a case of temporal lobe seizures limited to vertigo which were precipitated by reactive hypoglycemia (Buckley, 1963). It was shown that hypoglycemia, metrazol and hypoxia could activate a right temporal lobe focus in this patient. It had previously been found by Tokizani and Sawyer (1958) that prolonged experimental hypoglycemia activated seizures which began in the area of the amygdala and hippocampus of the temporal lobe. In 1966, I proposed that hypoglycemia activated ergotropic pathways in the limbic system. These circuits ascended to the temporal lobe from the hypothalamus. When an irritative lesion is already present in the temporal lobe, activation of these ergotropic response system circuits will significantly increase the probability of a seizure.

In 1978, I proposed that repetitive hypoglycemia amounted to a kindling procedure in which apparently innocuous individual stimuli will sensitize the animal when they occur consistently (Buckley, 1978). It has been found that an increasing responsiveness of the ergotropic system occurs because of a decrease in the threshold of irritability of dopamine receptors in the limbic system (Moskovits et a!., 1978).

These findings help clarify why temporal lobe EEC disturbance can combine synergistically with hypoglycemia. The limbic system has a very large number of dopamine receptors in its ergotropic neurones. When their response threshold has been lowered by the kindling effect of repeated hypoglycemic episodes, they will become unusually sensitive to relatively minor stimuli. The result can resemble a psychomotor epileptic seizure of the variety of behavior which Jonas described as "Inter-Ictal Neurosis" (1965).

Temporal Lobe Birth Injury

Wilder Penfield headed a neurosurgical group in Montreal which became known for the excision of cortex scars which had become the focus for causing epileptic seizures. They found that the stimulation of special points on the cortex could sometimes inaugurate the aura of a seizure. This was important for identifying the area to be excised. In the course of this work they found that electrical stimulation of the temporal lobe could at times inaugurate complex memory-hallucination of past ex-perience. The memory traces do not reside in the cortex, but can be precipitated when this area is interacting with deeper structures. In their series of 157 cases of temporal lobe seizures, Earle, Baldwin, and Penfield in 1953 reported that a large number had a particular type of pathologic scar tissue which they called incisural sclerosis. They proposed that during difficult delivery, there is a compression of the skull. At this time the increased intracranial pressure can cause a herniation of the uncus and the hippocam-pal gyrus under the tentorium of the cerebellum. At the time of birth, the anterior choroidal artery and branches of the middle cerebral and the posterior cerebral artery are particularly vulnerable to herniation and

compression. In particular, the choroidal artery is larger at birth and supplies a much larger area than it does in the adult. These special scars in the adult appear to be in the distribution of all three of these arteries.

Because there were no reports about such herniation in the pathology reports of the newborn, they studied several stillborn infants. They found that when they simply compressed the skull with a rubber tube and froze the brain, the hippocampus was herniated. This is a reversible herniation, because if they released the rubber tube and then froze the brain, all structures were back in their normal position. Many of the physiological signs of birth injury come from a disturbance of brain stem function. They disappear rather quickly in the infants which survive. Damage to the hippocampus cannot be readily determined at birth because the descending pathways are not myelinated. It is difficult, if not impossible, to detect damage to non-functioning neurones. Injury of the limbic system will become apparent as the infant fails to mature. This development disturbance will be all too easy to blame on the person who cares for the baby.

Fetal Hypoxia in Monkeys

These findings can be better interpreted in view of the experimental studies of fetal anoxia performed on Rhesus monkeys. William Windle reported on this topic in Scientific American in 1969. He found that asphyxia can be induced deliberately in the newborn monkey fetus, and that after only six minutes permanent organic injury could sometimes be found at autopsy. Some sort of injury invariably occurred after twelve minutes of anoxia. This is a particularly important paper, because the neurologic handicap of the deliberately asphyxiated monkeys appeared identical to those of the accidentally injured humans with cerebral palsy. Permanent disorders later developed in some animals which had apparently recovered from this experimental birth trauma. Some of these monkeys were autopsied after the transient damage had disappeared and there were no neurological "hard signs" to confirm the presence of organic

damage. We must conclude that permanent neuronal damage also occurs in the human infant and that this can have a pertinent influence upon later achievement. We can now propose that compression of the skull during birth causes a temporary occlusion of the arteries which supply the medial inferior temporal lobe, and the hip-pocampal formation. When the skull compression during birth lasts longer than twelve minutes it is clearly possible that an injury limited to the temporal lobe can occur. This can seriously interfere with the dynamic interaction between the hippocampal formation and the amygdaloid nucleus immediately adjacent to the lateral hypothalamus which is then relayed to the midbrain. This circuit is involved in fight or flight behavior in cats (Fernandez de Molina and Hunsperger, 1962). Stimulation of another amygdaloid area activates a pathway which inhibits the ventromedial nucleus of the hypothalamus (Buckley, 1972). Inhibition of this negative feedback center will release adjacent ergotropic centers for defensive-aggressive behavior. These are two mechanisms by which increased amygdaloid activity will increase the likelihood of aggressive behavior. Interference with and inhibition of the hippocampus by these sorts of injuries can release the amygdala for inappropriate activation of ergotropic circuits.

The amygdala and hippocampus have a more complicated interaction style than the straight forward "reciprocal inhibition" which exists between the anterior and posterior hypothalamus. In his last major book, Gellhorn (1967) described this as a state of "antagonism" between the amygdala and the hippocampus. He does report that stimulation of the amygdala can activate the secretion of ACTH. It was found that activation of the hippocampus did not. They then found that when the hippocampus was activated first, it inhibited the amygdala, because stimulation here was now unable to cause ACTH secretion.

My major proposal here is that compression of the skull for longer than twelve minutes can cause brain damage by obstruction

of the choroid artery. The resultant damage to the hippocampus can then interfere with the way the amygdala activates the fight or flight responses, in the circuits described by Fernandez de Molina and Hunsperger.

Hippocampal Vitamin needs

The hippocampus has been found to have particular needs for niacin and zinc. These facts were discussed by Paul.MacLean in his important 1958 paper on the limbic system. In particular he reported that the H-3 sector of the hippocampus was damaged when the animals were given 3-acetylpyrine (3-AP). This chemical is a competitive antagonist which counters the effect of niacin. The particular sensitivity of this section to 3-AP indicates that it has an unusual need for niacin. This finding in mice was investigated in other species which were not damaged to the same degree. This does not mean that the mouse hippocampus is unique among mammals in its need for niacin. It can mean that mice have a relatively higher need than other animals. This should be experimentally studied by applying different sorts of chronic stress to the other species which have been studied, to see if they would then reveal that specific biochemical deprivation of niacin caused particular damage to the hippocampal formation.

This same location was found to have an unusually high concentration of zinc. This was found because the H-3 sector is stained with the chelating agent dithizone. This topic of zinc and the hippocampus was well summarized by Crawford and Connor in 1975. Because zinc and pyridoxine are known to function together as parts of several enzymes, I expect that pyridoxine also has particular importance in the hippocampus.

The birth trauma brain damage which is severe enough to cause diagnosable temporal lobe epilepsy will occur in only a small proportion of those who suffered some injury. Most of the injuries will involve a reduction in the number of neurones which will disturb the effectiveness of temporal lobe function. This sort of injury can be the basis for the irritable and uncomfortable responses which cannot be called "epileptic" and yet which are helped by the use of phentoin.

These patients have a decreased number of neurones with which to respond to incoming stimuli. When they fail to function adequately the amygdala will not be properly controlled and the ergotropic response system will be released for inappropriate aggressive "fight or flight" behavior. The decreased number of neurones will still be stimulated by incoming nerves because these neurones activate multiple cells. When there is a decreased number of cells to do this work, the metabolic need for nutrients becomes enhanced. It is then likely that increasing the extra-cellular levels will enhance transmembrane transport for improving enzyme repair.

This could only be one of the ways that mega-vitamin dosages improve performance. Linus Pauling (1973) has shown that upset newly admitted schizophrenics have a much greater utilization of mega dosages of vitamins than the normal population. The basis for this response is different from a mere enhancement of trans-membrane transport. Libuse Cilka (1978) has found that schizophrenic patients have a metabolic block on the tryptophan-niacin pathway. They have high urinary levels of abnormal derivatives of the amino acid tryptamine and some tryptophan derivatives have psychotogenic properties.

Conclusion

This paper has presented a physiologic rationale for both factors which Yaryura-Tobias and Neziroglu (1975) found to be synergistically contributing to disturbing aggressive behavior. It has been proposed that transitory obstruction of the choroid artery when the skull is compressed during birth will damage the way the hippocampus and amygdala interact with each other. This injury can be the cause of the EEC dysrhythmia which Yaryura-Tobias reports. The recurrence of hypoglycemia for a long enough time has effects which are very

similar to the kindling which can occur after repeated subthreshold stimulation of the amygdala. A synergism of responses can occur because both of the CNS events cause the ergotropic system to have a greater state of dominance. This can lead to a variety of fight or flight aggressiveness which is both inappropriate and yet related to the environment and events which appear to stimulate it.

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