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[the editor omitted the text in { } "for lack of space". A slightly abbreviated version was published in Headache 2002;42:448]

High-Refined CHO Diet (HRCD), Hyperinsulinism (HI) and Relative Hypoglycemia (rHG): Known but rarely Addressed Critical Etiologies in Migraine. A Synthesis of Old and New Evidence. H Witte (St. Louis, MO)

Seven categories of evidence point to HRCD, HI and rHG as critical factors in migraine pathogenesis.

I. Beyond their disruptive effects on brain metabolism (cerebral hyperosmolality and glucopenia respectively), HI and rHG are predictable etiological factors in migraine as they precipitate or promote its characteristic vasomotor instability **{e.g. vasodilation and abnormal patterns of regional cerebral blood flow},** platelet abnormalities, elevated histamine, **{calcitonin,}** gene-related peptide and cAMP levels, neuronal dysfunctional, spreading depression, neurotransmitter dysregulation (e.g. serotonin depletion), release of nitric oxide and excitatory amino acids and increased NMDA – receptor activation. Furthermore, HRCDs promote inflammation via insulin-mediated increases in proinflammatory prostaglandins, and neuronal hyperexcitability via nutritional depletion (e.g. magnesium deficiency).

II. Migraineurs' conspicuous preference for sweets and a HRCD and their prodromal carb craving is consistent with rHG; it also explains the typical occurrence of migraine: **{during sleep}** at night, early in the morning **{and on weekends}**, upon missing meals, after alcohol, exercise or emotional stress and during the premenses. The decline in frequency of migraine with aging is consistent with the corresponding loss of insulin sensitivity **{and the remission of migraine during pregnancy is consistent with the hyperglycemia attendant to the hypercortisolism of pregnancy}.**

III. HRCDs are commonly seen in patients with anxiety disorders, asthma, **{atopic disorders,}** chronic fatigue, depression, epilepsy, fibromyalgia, hypertension, insomnia, irritable bowel, lupus, **{Menier's, myocardial infarction,}** narcolepsy and stroke. HI and rHG are associated with or significant contributory etiologies in the previously mentioned comorbid disorders. Furthermore, migraineurs typically report many other symptoms which are clear expressions of neuroglycopenia and hyperadrenalinemia.

IV. Consistent with the fact that headaches are classic symptom of spontaneous rHG, migraine headaches can readily precipitated experimentally **{through measures that indirectly or directly lower blood sugar}** in migraineurs

through **{even short fasts, ingestion of}** refined CHOs **{e.g. in glucose tolerance tests}** and physiological doses of insulin and in non-migraineurs through **{prolonged fasts and }** supra-physiological doses of insulin.

V. Many migraineurs report that if they eat something (usually CHOs) early in the prodromal phase they can abort a headache or later on, lessen one.

VI. Consistent with many migraineurs' experience that they can prevent their headaches if they eat regularly, every one of the 7 published studies on dietary restriction of CHOs in over 500 migraineurs has consistently reported benefits ranging from dramatic improvements to complete, lasting remissions in the great majority of cases, (even stress), many of them previously unresponsive to numerous conventional treatments. **{Arguing against a placebo response is that these dietary response rates exceed the known placebo patients were previously unresponsive to numerous conventional treatments}.**

VII. The etiologic role of rHG in migraine is consistent with the proven benefits of biobehavorial interventions since the latter are well known to improve/normalize the kind of excessive sympathetic and parasympathetic activity that adversely affects CHO metabolism**. {Less stressed individuals also eat more healthful diets.}**

In summary, data from varied sources compellingly implicate impaired carb metabolism as a pathophysiological hallmark of migraine. Migraineurs who will likely respond with complete cessation or dramatic improvements alone on a nutritional protocol designed to correct impaired carb metabolism can be readily identified with a questionnaire. Despite the universal acknowledgment that missing a meal and rHG are common migraine precipitants, rHG is very rarely mentioned in the scientific literature and migraineurs are very rarely diagnosed with it or offered the benefits of a comprehensive treatment protocol to correct it **{all of which may partly explain the widely held view that the basic cause of migraine is unknown}**. Integration of such a protocol with conventional, proven therapies would predictably greatly increase the probability for successfully controlling this disease.

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