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Is Sugar Addictive?

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The prevalence of obesity began to rise rapidly in the 1980s and since then has more than doubled (1). Sugar (2), sugar-sweetened beverages, and the fructose that they provide have been consistently linked to the risk for obesity (3). Ludwig, Peterson, and Gortmaker (4) provided one of the earliest suggestions that intake of sugar-sweetened beverages might predict weight gain, and this has been supported by an increasing number of studies (5). Because foods can activate the "pleasure" center circuitry, the same circuitry that is activated by drugs of abuse and alcohol (6), the suggestion that sugar might be "addictive" has surfaced from time to time (7,8).

The study by Jastreboff et al. in this issue of *Diabetes* (9), and an earlier pilot study (10), using functional MRI after oral ingestion of either glucose or fructose in 14 lean and 24 adolescents with obesity extends our knowledge of how these hexoses act on the brain. In the lean adolescents, both glucose and fructose increased perfusion of brain areas involved in "executive function and control" (prefrontal cortex) (Fig. 1) but did not activate the "homeostatic" appetite control areas (hypothalamus). A very different picture was seen in the adolescents with obesity where ingestion of either fructose or glucose reduced perfusion of the executive region of the brain (prefrontal cortex) and increased activity in the "reward" or "pleasure" centers. This suggests that obese adolescents may lack the ability to downregulate the hedonic and homeostatic regions of the brain after oral ingestion of fructose or glucose. In addition, the ingestion of fructose produced a greater increase in perfusion of the pleasure or reward centers in the adolescents with obesity—something not seen in the lean adolescents. The authors speculate that the reduced response of the executive centers to fructose/glucose may reduce their ability to control intake of sugar-sweetened beverages.

After absorption, fructose is largely cleared by the liver, leaving only small circulating concentrations. The intriguing question is how fructose produces these effects in the brain. Jastreboff et al. (9) suggest a possible mechanism through changes in the active form of ghrelin (acyl-ghrelin) with a contribution from the higher insulin in the obese. After ingestion of glucose, acyl-ghrelin is significantly suppressed by glucose and more so by fructose in the adolescents with or without obesity. However, circulating levels are higher in the lean than the obese. Changes in ghrelin might provide a signal for the changes in perfusion in various brain regions. Insulin, which responds to glucose, may also play a role through its central nervous system receptors, since the relative increase of insulin in the adolescents with obesity was much greater than in the lean adolescents. However, changes in insulin with fructose were very small, suggesting that lowering of acyl-ghrelin may be a more important messenger for control of central behavior and activation of the pleasure center.

Understanding how adolescents who are obese differ from those who are not is important in framing preventive strategies. The study by Jastreboff et al. (9) describes functional differences in the central nervous system during response to fructose or glucose solutions. First, the executive center in the prefrontal cortex is inhibited in the obese, confirming earlier work in adolescents (11,12) and adults where Volkow et al. (13) showed a significant negative correlation between BMI and metabolic activity in prefrontal cortex and cingulate gyrus. Using leptin as a surrogate for fatness, Jastreboff et al. (9) found that it was inversely related to blood flow in the prefrontal cortex. Second, the hypothalamus, which plays a key role in the homeostatic regulation of food intake, is activated by glucose/fructose in the adolescents with obesity but not in the lean, a change that might stimulate feeding in those with obesity. The pleasure or reward centers in the limbic system and striatum are also activated by fructose/glucose in adolescents with obesity. Much evidence supports the hypothesis that the arcuate hypothalamus plays a direct role in ghrelin-regulated homeostatic feeding and that the ventral tegmental area directly mediates ghrelin-induced hedonic eating (14).

This is a cross-sectional study and leaves at least one key question unanswered: Which came first, the obesity

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COMMENTARY

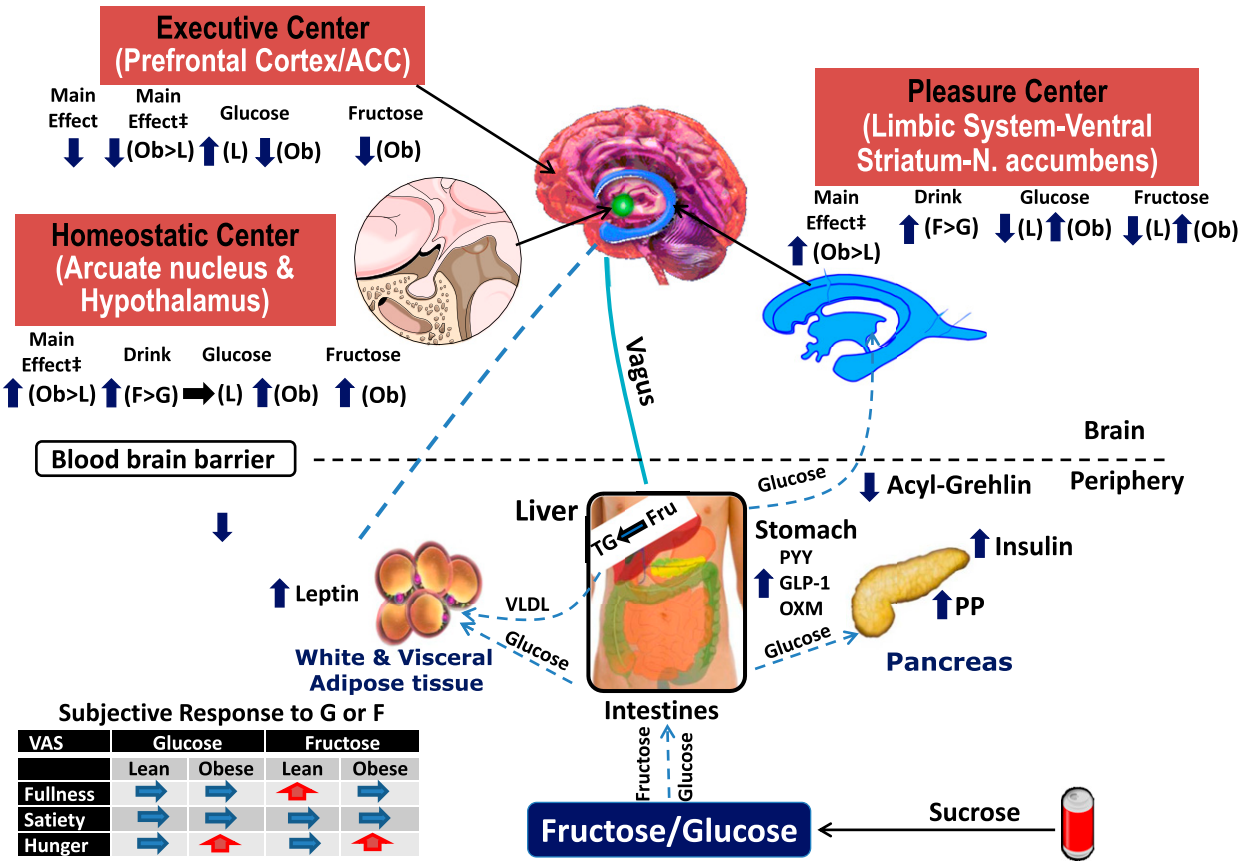

Figure 1—Signaling in the brain of adolescents in response to glucose or fructose: schematic representation of changes in the periphery and brain after the ingestion of glucose or fructose. Subjective responses using variable analog scales (VAS) are shown in the lower-left corner for hunger, fullness, and satiety where differences were detected. Both glucose and fructose are absorbed, but fructose is largely cleared in the liver, where it stimulates de novo lipogenesis. Glucose is taken up by many tissues and stimulates insulin release from the pancreas more so in the adolescents with obesity than in lean adolescents. Both monosaccharides reduce circulating acyl-ghrelin concentrations. Effects of glucose and fructose on cerebral blood flow relative to baseline are shown by arrows in major regions of the brain: the prefrontal cortex, which has major executive functions; the hypothalamus, which modulates appetite; and the limbic system and striatum-thalamus, which encompass the reward feature of food. Solid lines represent neural connections and dashed lines circulating connections. ‡Adjusted for acyl-ghrelin and insulin. ACC, anterior cingulate cortex; F, fructose; Fru, fructose; G, glucose; GLP-1, glucagon like peptide 1; L, lean adolescents; N. accumbens, nucleus accumbens; Ob, adolescents with obesity; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, polypeptide YY; TG, triglyceride.

or the changes in brain response? The idea that sugar might be addictive or habituating surfaced over 40 years ago (7,8), in part related to the finding that endogenous opioids (endorphin and enkephalin) stimulate feeding, as do endogenous cannabinoids, which were identified after noting that "marihuana" stimulated feeding.

In addition to the association of sugar (glucose/fructose) intake with the risk for developing obesity, diabetes, and heart disease, fructose seems to have other possibly detrimental metabolic effects (15,16). Fructose stimulates de novo lipogenesis and liver fat (17), increases visceral adipose tissue (16), and increases triglyceride levels (15). Drinking sugar-sweetened beverages for 6 months can replicate the findings of the metabolic syndrome (18). Both glucose and fructose provide energy, but fructose in addition provides a more intense sweetness than glucose and, as shown in the study by Jastreboff et al. (9), stimulates the striatal complex, which may provide a hedonic override of the homeostatic control of feeding (19).

Evidence supporting features of addiction to sucrose come mainly from studies in experimental animals (7). Withdrawal from a "sugar-rich" diet is associated with behavior suggestive of "withdrawal" symptoms. Clinical support for this idea comes from a study by Drewnowski et al. (20), who used naloxone to block opioid receptors in women who were binge eaters and those who were not. In the binge eaters, naloxone reduced the preference for sweet taste and the actual amounts consumed. The findings of Jastreboff et al. (9) that glucose and fructose stimulate the striatal system more in the adolescents with obesity than in lean individuals indicate that these molecules have addictive or habituating potential. In many cases sucrose is consumed in sugar-sweetened beverages that also contain caffeine, a drug that stimulates the central nervous system. It would be of great interest

to find out whether caffeine added to the glucose or fructose produced more profound effects on the striatal system of adolescents with obesity.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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