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Dissertation Abstract:

As obesity and diabetes have emerged as a severe public health crisis, understanding the mechanisms underlying the consumption of sugars and fats has become a topic of vigorous study. From a biological standpoint, genetic dispositions, neurochemical and hormonal influences, and predetermined orosensory and postingestive signals that modulate the hunger and satiety process may govern physiological aspects of the obesity puzzle. In addition to an innate appetite and attraction for simple carbohydrates and fats, learning plays an important role in modulating preferences for sugar- and fat-rich foods in rodents, including inbred mouse strains. Marked genetic variance has been observed among murine strains in sugar and fat appetite as well as the development and persistence of sugar preferences. In particular, SWR and BALB/c inbred mouse strains differ in their sweet taste sensitivity, exhibit robust intakes of sugars and fats, and develop strong and persistent sucrose-conditioned flavor preferences (CFP). These two strains also display strong and divergent sensitivity to dopamine (DA) D1 and opioid receptor antagonists in reducing spontaneous intake of sucrose and fat as well as in the acquisition (learning) and expression (maintenance) of sucrose-CFP. Murine strain differences have also been observed in the ability of sucrose and glucose, but not fructose, to elicit CFP following intra-gastric sugar infusions, and in the differential responsiveness of strains to tpost-oral actions of fructose. Six approaches were employed to further examine the role of genetic variance in responsiveness of and preferences for sugars and fats in inbred SWR and BALB/c mice. A first study examined the relative preference for fructose and sucralose and sucralose + saccharin (S+S) solutions in SWR and BALB/c mice and found that ad-libitum-fed SWR, but not BALB/c mice reversed their initial preference for S+S over fructose after experience. This study also compared initial and subsequent preferences following experience for 8% fructose and 8% glucose solutions in the two strains as an index of the post-oral reinforcing actions of

the two sugars. Both ad-libitum-fed and food-restricted SWR mice strongly preferred glucose to fructose in direct choice tests, whereas food-restricted, but not ad-libitum-fed BALB/c mice displayed this preference. A second study examined whether systemic administration of opioid (naltrexone: NTX) and dopamine D_1 (SCH23390: SCH) receptor antagonists reduced intakes of non-nutritive 0.2% saccharin and nutritive 8% fructose solutions in BALB/c and SWR mice. Although saccharin intake was reduced similarly by SCH and NTX in BALB/c and SWR mice, SWR mice exhibited greater potencies of opioid (1.9-fold) and DA D1 (4-fold) receptor antagonism of fructose intake relative BALB/c mice. A third study examined whether BALB/c and SWR mice exhibited differential sensitivity to NTX and SCH in altering the expression (maintenance) and acquisition (learning) of fructose-CFP. SCH was more effective than NTX in reducing the expression of fructose-CFP in both strains.

Whereas BALB/c mice displayed hastened extinction of acquisition of fructose-CFP following SCH, but not NTX, SCH eliminated fructose-CFP acquisition and NTX hastened extinction of fructose-CFP in SWR mice.

Ahe fourth study examined whether BALB/c and SWR mice exhibited differential sensitivity to the NMDA receptor antagonist, MK-801 in altering acquisition and expression of both sucrose- and fructose-CFP. Although acquisition of fructose- and sucrose-CFP was eliminated by MK-801, NMDA antagonism was more potent in BALB/c relative to SWR mice. MK-801 mildly reduced the magnitude of the expression of sucrose- and fructose-CFP in BALB/c mice, but blocked the expression of fructose-, but not sucrose-CFP in SWR mice. A fifth study examined whether BALB/c and SWR mice exhibit differential sensitivity to NTX and SCH in altering the acquisition and expression of fat-CFP. BALB/c and SWR mice exhibited similar fat-CFP in preferring the CS+ flavor paired with a 5% Intralipid solution over a CS- flavor paired with a 0.5% Intralipid solution. Whereas SCH blocked the expression of fat-CFP in both BALB and SWR mice, NTX reduced this response in BALB/c, but not SWR mice. In contrast, acquisition of fat-CFP was

eliminated by SCH in SWR, but not BALB/c mice. Acquisition of fat-CFP was marginally impaired by NTX in BALB/c, but not SWR mice. A sixth study examined whether BALB/c and SWR mice exhibit differential sensitivity to MK-801 in altering acquisition and expression of fat-CFP. MK-801 eliminated acquisition of fat-CFP in both BALB/c and SWR mice with the latter's response appearing to turn into an avoidance response. Expression of fat-CFP was more effectively eliminated by MK-801 in BALB/c relative to SWR mice. The myriad behavioral differences observed in BALB/c and SWR strains indicate a crucial role for genetic background in mediating the neurochemical and behavioral substrates of sweet and fat intake as well as the development and persistence of sweet and fat preferences.