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Section 3 **Autonomous and motor behaviors**

Chapter **12**

Feeding and drinking

Richard J. Bodnar, Sarah R. Lewis, and Benjamin Kest

Systematic analyses of rodent, and particularly mouse, strain differences are important sources of information regarding the genetic control of all aspects of ingestive behavior (see reviews: Reed et al., 1997; West and York, 1998). Such studies not only indicate the presence of genetic variance in ingestive responses, but may also identify strains with divergent sensitivities for quantitative trait loci (QTLs) analyses to localize chromosomal regions, and ultimately genes, critically involved in such differences. In addition to studies examining food and water intake per se and/or macronutrient choice, another behavioral approach has been employed to assess this genetic variance using preference tests between a given ingestive stimulus and a control (e.g., water). A number of studies, particularly the older ones, used either two or a small number of inbred strains to make specific preference comparisons between "sensitive" and "insensitive" strains for a particular response. This approach is also used in many more recent genetic QTL approaches to define gene loci. A second and more recent approach uses large numbers of inbred strains to insure reliability, assess heritability estimates, and facilitate the identification of strains with highly divergent responses in order to increase the success of subsequent QTL mapping. Collectively, recent studies particularly over the past decade and reviewed in detail below, have demonstrated marked strain differences in food and water intake as well as for the following ingestive stimuli: (a) salts, (b) bitter tastants, (c) saccharin, (d) sugars, (e) ethanol, (f) glutamate/umami, and (g) fats. This review also focuses on mechanisms of the above forms of intake as they relate to the development of obesity. The final section of this chapter will examine a series of studies recently conducted in our laboratory to evaluate and compare strain differences in sweet (sucrose) and fat (Intralipid) intake relative to the feeding responses elicited by glucoprivic (2-deoxy-D-glucose: 2DG) and lipoprivic (mercaptoacetate: MA) stimuli.

Salts

Genetic variance between mouse strains was initially observed for intake of moderate concentrations (0.075–0.150 M) of sodium chloride (saline) solutions, with 129/J mice preferring this solution to water in 48 hour preference tests and C57BL/6J mice rejecting this range of solutions (Beauchamp and Fisher, 1993; see also, Bachmanov et al., 1996a, 1998b; Gannon and Contreras, 1993; Kotlus and Blizard, 1998). Genetic variance is quite marked in large analyses of strains as well (Bachmanov et al., 2002a). Increasing choice by using more than two bottles enhanced the salt preferences in 129X1/SvJ mice relative to C57BL/6J mice (Tordoff and Bachmanov, 2003a), and this effect was further enhanced by repeated testing (Tordoff and Bachmanov, 2002). However, in analyzing saline preferences in mice maintained on different maintenance diets, C57BL/6J mice showed a greater preference for a 75 nmol/L sodium chloride solution, particularly on purified diets than 129X1/SvJ mice, indicating that there might be differences due to both the substrain and the underlying diet (Tordoff et al., 2002). Another factor in assessing multiple concentrations of solutions to evaluate strain sensitivity is the order of presentation. Thus, five mouse strains exposed to progressively increasing or decreasing sodium chloride solutions displayed greater preferences for low concentrations of the saline solutions in the ascending as compared to the descending series of stimulus testing. The NZB/B1NJ strain displayed greater NaCl acceptance than 129/J, SM/J, and C57BL/6ByJ strains that in turn displayed stronger responses than the CBA/J strain. Whereas NZB/B1NJ and 129/J mice displayed strong preferences at low concentrations, only the former groups showed persistent preferences at the highest concentrations (Bachmanov et al., 1998b). Further, a subsequent evaluation of 28 mouse strains confirmed that NZB/B1NJ mice avidly consumed high amounts of concentrated sodium, but not potassium or calcium, chloride solutions. At lower sodium chloride concentrations, CAST/Ei mice showed the strongest preferences whereas CBA/J, C3H/HeJ and AKR/J mice showed the strongest avoidance in preference tests (Bachmanov et al., 2002a). A 40 mouse strain survey of water and sodium intake revealed strains with high preference (129S1/SvIm, MA/MyJ, NZW/LacJ, and SWR/J) or indifference (A/J, C57BL/6J, FVB/NJ, and SEA/GnJ) for sodium at all concentrations (Tordoff et al., 2007a). Analysis of normotensive (BPN/3), hypertensive (BPH/2), and hypotensive (BPL/1) mouse strains revealed that hypertensive mice consumed greater fluid and water intakes that normotensive controls, but consumed lower amounts of sodium chloride and

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potassium chloride solutions. In contrast, hypotensive mice consumed higher intakes of potassium chloride at moderate concentrations and lower amounts of calcium chloride (Bachmanov et al., 1998a). A survey of 40 mouse strains revealed strains with consistently high avidity (PWK/PhJ, BTBR T^{+}tf/J, JF1/Ms) and low avidity-high avoidance (KK/H1J, C57BL/10J, CE/J, C58/J) for a wide range of calcium solutions (Tordoff et al., 2007b). A genome screen involving the F2 generation of C57BL/6J mice with low avidity for calcium and PWK/PhJ mice with high avidity for calcium revealed 30 QTLs of which six involved consumption of calcium chloride (Tordoff et al., 2008a). In addition to its importance in sweet intake, the T1R3 receptor also functions as a gustatory calcium-magnesium receptor (Tordoff et al., 2008b). Thus, whereas genetic variance plays a major role in the consumption of salts, it is apparent that a number of methodological factors need to be controlled in assessing such differences; this latter point is reiterated in analyses of other forms of ingestion.

Bitter tastants

Following the initial observation that mice homozygous for the allele Soa^{a} display greater aversions to sucrose octa-acetate (SOA) and strychnine than heterozygous counterparts (Warren and Lewis, 1970), Lush (1981, 1982) characterized the behavioral genetics of tasting of SOA and strychnine in multiple strains of mice. He indicated that SWR/J mice possess taster ability of SOA, and that two allelic forms (Soa^{a}: avoidance and Soa^{b}: indifference) were proposed to explain these genetic differences. SWR/J "taster" mice displayed both strong SOA avoidance in behavioral tests, and potent neural responses to SOA in the chorda tympani and glossopharyngeal nerves in neurophysiological assessments. In contrast, "non-taster" SWR.B6 mice displayed behavioral indifference and weak neural responses to SOA (Inoue et al., 2001). Subsequent assessment of 29 strains consuming either a single concentration (0.8 mM) or a range (0.4–1.6 mM) of quinine solutions in a study by Lush (1984) indicated that A2G, DBA/2, and BALB/cBy strains displayed a moderate quinine aversion (30–43%) in a two-bottle taste test, whereas SWR, 129/Sv and C57BL/6By mice displayed powerful aversions (96–98%) over this range. Subsequent description of a third intermediate demitaster category of mice was provided by Harder et al. (1992), indicating differentiation in avoidance responses between the 0.1 and 1.0 mM range of SOA concentrations, suggesting a third allele (Soa^{c}). A common polygenic basis for quinine and propylthiouracil (PROP) avoidance was subsequently described as well (Blizard et al., 1999; Harder and Whitney, 1998). Interestingly, insertion of two type-A Prp transgenes from taster mice failed to alter SOA avoidance in non-taster mice (Harder et al., 2000). C57BL/6J and C57BL/6ByJ mice displayed greater intake of and preference for citric acid and quinine solutions relative to 129/J and 129Xi/SvJ mice (Bachmanov et al., 1996a), an effect enhanced by the use of purified diets (Tordoff et al., 2002). Both hypertensive (BPH/2) and hypotensive (BPL/1) strains of mice consumed significantly less quinine than their normotensive (BPN/3) counterparts (Bachmanov et al., 1998a). The underlying genetics and recently described polymorphisms in the Soa gene are discussed in Chapter 9.

Saccharin

Strain differences have been observed for saccharin intake in a wide series of studies (e.g., Blizard et al., 1999; Capeless and Whitney, 1995; Inoue et al., 2004b; Reed et al., 2004; Tordoff et al., 2002). An early study using rats by Nachman (1959) found that F1 and F2 generation progeny of saccharin-preferring animals displayed saccharin preferences comparable to those of their parents, whereas water-preferring parents and their progeny failed to display saccharin preferences. In subsequent murine studies by Pelz, a strong preference for a 0.1% saccharin solution relative to water was observed in BALB/cJ, C57BL/6J, I^{S}/Bi mice, but not in 101Bag/R1 mice (Pelz, 1973). Correspondingly, Fuller (1974) found that C57BL6/J mice displayed greater intake of the same (0.1%) saccharin solution than DBA/2J mice. Genetic factors accounted for 78% of the genetic variation associated with consumption of this concentration of saccharin in one outbred and seven inbred strains. This effect was extended to four saccharin concentrations with a rank-order of strain preference scores of 129P3/J, C57BL/6J, BALB/cJ, C3H/HeJ, 129P3/J, and DBA/2J mice (Blizard et al., 1999; Capeless and Whitney, 1995). Intake for a single 1.6 mM saccharin solution in 26 inbred mouse strains by Lush (1989) revealed a pattern of stronger saccharin preferences in A/2G, C57BL/6Ty, C57BL/10, and SWR strains (73–93%) than in AKR, CBA/Ca, C3H/He, DBA/2Ty, and 129/SV strains (53–59%). Extreme responding strains identified for saccharin intake served as progenitors for quantitative trait loci (QTLs) and subsequently, the identification of trait relevant genes. Previous QTLs for saccharin intake using C57BL/6J crosses with DBA/2J or 129P3/J mice revealed both a saccharin (Sac) preference locus and a sweet taste receptor gene,Tas1r3, that are described in detail in Chapter 9.

Sucrose

Similarly to saccharin, genetic variance among mouse strains has been observed for sucrose intake across a wide range of studies (e.g., Bachmanov et al., 1997; Blizard et al., 1999; Inoue et al., 2004b; Lewis et al., 2005). C57BL6/J mice displayed greater intake of five (0.005–1.000 M) glucose and sucrose concentrations than 101Bag/R1 mice in an early study by Stockton and Whitney (1974), and of a 4% sucrose solution than 129P3/J mice (Bachmanov et al., 1997). The greater sensitivity of C57BL/6J to sweetened solutions like saccharin and sucrose relative to 129P3/J mice was extended to maltose, acesulfame-K, sucralose, and SC-45647 as well as to the amino acids, D-phenylalanine, D-tryptophan, L-proline, and glycine (Bachmanov et al., 2001b). Genetic factors accounted for 83% of the genetic variation associated with consumption of 3% sucrose in

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outbred and seven inbred strains in an early study by Ramirez and Fuller (1976). In examining up to 30 strains of mice for sucrose (50 mM) intake, Lush (1989) found that the patterns of strong preferences for sucrose, like saccharin, were greater in A/J, C57BL/6J, C57BL/10J, and SWR/J strains (73–97%) than in AKR/J, CBA/J, C3H/HeJ, DBA/2J, and 129P3/J strains (51–61%). SWR/J mice displayed increased flavor preferences and lick activity for both sucrose and corn oil compared to AKR/J mice, suggesting greater sensitivity to orosensory flavor factors (Smith et al., 2001). A recent evaluation (Pothion et al., 2004) of sucrose intake at seven supra-threshold (1–50%) concentrations in 11 mouse strains revealed a difficulty in determining clear-cut strain differences because virtually every strain consumed far more sucrose than water for at least one of these higher concentrations. Conditioned flavor preferences induced by intragastric infusions of either a 16% sucrose solution or a 5.6% soybean oil solution appeared to be stronger in C57BL/6J mice than 129 mice, whereas both strains consumed similar amounts of an isosweet solution in preference tests, suggesting that C57BL/6J mice may possess a stronger orosensory response to sugar and fat (Sclafani and Glendinning, 2005). C57BL/6J mice also display conditioned flavor preferences to the intragastric effects of a 8% maltodextrin solution (Sclafani and Glendinning, 2003). Similarly, C57/BL/6ByJ mice display higher consumption and lower preference thresholds for the sweet amino acids, l-glutamine, l-alanine and l-threonine, the monosaccharides glucose and fructose, and malto-oigosaccharide (Bachmanov and Beauchamp, 2008). Age fails to contribute significantly to a wide range of taste preferences observed in C57BL/6J and 129X1/SvJ mice (Tordoff, 2007). Finally, the use of trpm5–/– mice, which lack the cellular machinery for sweet taste transduction, can develop a robust preference for sucrose solutions based solely on caloric content (de Araujo et al., 2008).

Ethanol

In addition to sucrose, ethanol-related phenotypes have been identified in animal models (see reviews: Crabbe et al., 1994, 1999), and the two-bottle choice test in mice appears to produce data relevant to human alcoholism. Interestingly, in preference studies using more than two (e.g., up to six) bottles, alcohol intake is positively and persistently related to the number of alcohol bottles available, and inversely related to the number of water bottles available (Tordoff and Bachmanov, 2003b). Further, restricted, relative to continuous, access to ethanol resulted in greater consumption of ethanol in C57BL/6J and WSC strains (Finn et al., 2005). Moreover, the former strain is also more effective than DBA/2J mice in displaying an animal model of intoxication using blood ethanol concentration as a measure (Rhodes et al., 2005). Indeed, the C57 BL/6J and DBA/2J strains have been respectively identified in high and low consumption of ethanol in such preference tests (Belknap et al., 1997; Melo et al., 1996; Phillips et al., 1994, 1998; Tarantino et al., 1998; Whatley et al., 1999). Indeed, the former strain displayed higher ethanol preferences than 129P3/J mice in a manner similar to that observed for sucrose and citric acid (Bachmanov et al., 1996b). Analyses of 15 mouse strains over a range (3–10%) of ethanol concentrations revealed that C57BL/6J, C57BR/cdJ, and C57L/J mice consumed the greatest amounts of ethanol, whereas DBA/1J and DBA/2J strains consumed the least (Belknap et al., 1993). The C57BL/6J strain avidly consumes ethanol in a drinking-in-the-dark paradigm that fits in well as an animal model for human alcoholism based on its sensitivity to acamprosate (Gupta et al., 2008). Further, supplementing the liquid alcohol diet with chow enhanced alcohol intake in C57/BL/6 mice (Anji and Kumari, 2008).

Quantitative trait loci studies of ethanol preference (3% and 10% concentrations) in C57BL/6By × 129P3/J F2 hybrids, identified two loci on distal chromosome 4 (Ap3q) and proximal chromosome 7 (Ap7q); their presence strongly affected ethanol intake at the high, but not low concentration. Further, an identified male-specific locus on chromosome 8 (Ap8q) affected ethanol preference at the low, but not the high concentration. Additional linkages on chromosomes 2, 9, 12, 13, 17, and 18 were found as well (Bachmanov et al., 2000a). A meta-analysis (Belknap and Atkins, 2001) of eight studies suggested consistent QTLs for ethanol for chromosome 2 (proximal to mid), 3 (mid to distal), 4 (distal), and 9 (proximal to mid). The Ap3q locus on chromosome 4 contains both the saccharin (Sac) preference locus and corresponds to the sweet taste receptor gene, Tas1R3 (Blizard et al., 1999; Phillips et al., 1994). Quantitative trait loci mapping has also revealed a role for the syntaxin binding protein 1 gene for an ethanol preference locus on mouse chromosome 2 (Fehr et al., 2005). In contrast, gene mapping of chronic withdrawal from ethanol revealed loci on chromosomes 1 (proximal), 4 (mid), 8 (mid), 11 (proximal), and 14 (mid) (Bergeson et al., 2003). A recent meta-analysis for alcohol preference in mice based on QTL analysis revealed eight candidate genes the expression of which was localized to the olfactory zone, limbic areas, and the orbitofrontal cortex (Tabakoff et al., 2008).

Glutamate/umami

Although relatively few studies have explored taste preferences for glutamate and umami-type stimuli, the data appear very consistent. Initial acceptance studies using one-bottle tests demonstrated that glutamate could be distinguished from the four other taste substances in mice in early studies by Ninomiya and Funakoshi (1989a, 1989b). C57BL/6J mice: (a) display lower preference thresholds for monosodium glutamate (MSG); (b) prefer MSG over a greater range of concentrations; and (c) consume greater amounts of MSG at high concentrations than 129/J mice. Prior experience with MSG, but not with saccharin, enhanced the subsequent expression of MSG acceptance, an effect also observed with inosine-5'-monophosphate (Bachmanov et al., 2000b). Use of F2 generations of C57BL/6By and 129P3/J mice bred for sucrose preference failed to reveal corresponding changes in MSG relative to sucrose intake preferences,

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suggesting a unique genetic mechanism for this taste (Bachmanov et al., 2000b; Beauchamp et al., 1998). Interestingly, the increased ingestive responses to umami taste in C57BL/6J as compared to 129/J mice are accompanied by either unchanged or decreased neural responses in the chorda tympani or glossopharyngeal nerves, an effect sharply divergent from that described previously for other taste stimuli (Inoue et al., 2004a).

Fat intake and obesity-prone and obesity-resistant animals

The intake of dietary fat also systematically varies as a function of genetic predisposition among a host of other variables (see review: West and York, 1998). Indeed, the analysis of genetic variance has led to the identification of dietary resistance and susceptibility phenotypes in inbred and outbred strains of mice (e.g., West et al., 1992, 1995). These studies led to the identification of particular mouse strains in which only moderate intake of a high-fat diet promoted weight gain and obesity (e.g., AKR/J mice), and other strains in which large intake of the high-fat diet was not accompanied by weight gain (e.g., SWR/J). Although such effects were largely due to variation in the dietary fat content, this latter variable weakly correlated with total energy intake. The AKR/J and SWR/J strains displayed similar effects on intake and compensatory weight changes whether the fat source was shortening, lard or powder, and whether the high and low-fat diets were isocaloric (Smith-Richards et al., 1999). Indeed, whereas AKR/J and C57BL/6J mice self-selected the highest proportion of fat in macronutrient diet selection with ependymal fat correlating with fat consumption, SWR/J and CAST/Ei strains consumed a great deal of fat that was inversely correlated with ependymal fat (Smith et al., 2000). Moreover, whereas the diet-sensitive AKR/J and DBA/2J strains (a) consumed greater amounts of fat; (b) displayed more adiposity; and (c) displayed elevated levels of leptin and insulin; the C57BL/6J strain showed an equal preference between protein and fat, and displayed normal insulin and leptin levels (Alexander et al., 2006). In contrast, the obesity-resistant SWR/J and A/J mice that consumed more fat than carbohydrate, yet failed to gain weight, did so potentially because of (a) lower insulin levels; (b) increased capacity of skeletal muscle to metabolize fat; (c) enhanced paraventricular galanin; and/or (d) reduced arcuate Neuropeptide Y (Leibowitz et al., 2005). Maintenance on a very high-fat diet (60%) resulted in type 2 diabetes for C57BL/6J mice and normoglycemic responses in A/J mice (Gallou-Kabani et al., 2007). Mapping of a series of multiple genetic loci (mob 1–4), located on chromosomes 9 and 15, appeared to explain some of these genetic variations for fat and obesity (e.g., Bachmanov et al., 2001a; Fisler et al., 1993; Smith-Richards et al., 2002; Warden et al., 1995; West et al., 1994a, 1994b). A 40 mouse strain survey of body composition revealed profound genetic variance in percentage of body fat that ranged from 16 (C58/J) to 39% (NON/LtJ) (Reed et al., 2007). Increased body fat has also been associated with a novel p-locus fat-associated ATPase on mouse chromosome 7 (Dhar et al., 2000). Moreover, loci on chromosomes 2, 4, 9, and 16 have been identified for body weight, body length, and adiposity in a genome scan of an F2 intercross between the 129P3/J and C57BL/6ByJ mouse strains (Reed et al., 2003). Using a C57BL/6J × PWK/PhJ mouse intercross, a genetic loci analysis identified 28 suggestive or significant linkages for four traits (body weight, adjusted lean and fat weight, and percent fat) (Shao et al., 2007). Moreover, using C57BL/6ByJ × 129P3/J F2 hybrids, absolute depot weight was linked to chromosomes 5, 11, and 14, relative depot weight was linked to chromosomes 9, 15, and 16, and both types were linked to chromosomes 2 and 7 (Reed et al., 2006). Finally, using mouse lines divergently selected for food intake, chromosomes 4 and 19 were associated with white and brown adipose issue, and chromosome 9 was associated with white adipose tissue depots (Rance et al., 2007). Therefore, fat intake, and its attendant changes (or lack thereof), appears to be under the influence of genetic variability.

Recent strain survey studies from our laboratory

Our laboratory examined strain differences among 11 inbred (A/J, AKR/J, BALB/cJ, CBA/J, C3H/HeJ, C57BL6/J, C57BL10/J, DBA/2J, SJL/J, SWR/J, 129P3/J) and one outbred (CD-1) mouse strains in four different paradigms that analyzed sweet (sucrose) intake (Lewis et al., 2005) and fat (Intralipid) intake (Lewis et al., 2007), as well as feeding responses elicited by glucoprivic (2DG: Lewis et al., 2006a) and lipoprivic (MA: Lewis et al., 2006b) stimuli. In the first pair of studies (Lewis et al., 2005, 2007), we presented animals in each strain a choice of nine different subthreshold, threshold, and supra-threshold sucrose (0.0001–20.0%) and Intralipid (0.00001–5.0%) concentrations using two-bottle 24-hour preference tests. We controlled for relevant methodological variables such as ascending and descending presentations of different sucrose/Intralipid concentrations (Harder et al., 1989), the relative positions of the two bottles containing sucrose/Intralipid and water (Bachmanov et al., 2002b), measured kilocalorie intake as sucrose/Intralipid or chow, and examined such effects in absolute terms or relative to body weight. In the second pair of studies (Lewis et al., 2006a, 2006b), we used either the anti-metabolic glucose analogue, 2DG or the free fatty acid oxidation inhibitor, MA to elicit respective glucoprivic or lipoprivic states to examine whether genetic variance was present in the ingestive responses to these regulatory challenges. We employed systemic dose ranges of 2DG (200–800 mg/kg) and MA (50–100 mg/kg) that in previous studies both elicited feeding, while controlling for the order of ascending and descending 2DG and MA doses. Finally, we examined the presence of potential relationships in common or differential genetic variance between sweet and fat intake and between glucoprivic and lipoprivic responses.

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Table 12.1 Baseline water (ml, ±SEM) and chow (g, ±SEM) intake and body weight (g, ±SEM) in 12 mouse strains in analyses of sucrose and Intralipid intakes.

Strain	Sucrose water (ml)	Intralipid water (ml)	Sucrose chow (g)	Intralipid chow (g)	Sucrose weight (g)	Intralipid weight (g)
A/J	5.6 (0.7)	4.6 (0.2)	4.4 (0.3)	3.8 (0.2)	26.2 (1.4)	19.6 (0.5)
AKR/J	5.7 (0.6)	8.6 (0.2)	4.6 (0.1)	4.1 (0.1)	33.6 (1.4)	26.6 (1.0)
BALB/cJ	5.6 (0.1)	7.4 (0.2)	5.4 (0.2)	6.7 (0.2)	27.9 (0.8)	23.5 (0.2)
C57BL/6J	4.9 (0.3)	4.8 (0.4)	4.1 (0.1)	3.6 (0.2)	27.9 (0.6)	27.8 (0.8)
C57BL/10J	5.5 (0.3)	6.9 (0.5)	3.7 (0.1)	4.8 (0.2)	26.8 (0.5)	22.7 (0.3)
CBA/J	5.3 (0.3)	6.7 (0.2)	3.8 (0.1)	4.0 (0.2)	32.3 (1.5)	22.6 (0.5)
CD-1	7.8 (0.4)	9.3 (0.8)	5.8 (0.3)	4.1 (0.4)	37.7 (0.8)	37.0 (1.0)
C3H/HeJ	5.2 (0.4)	5.5 (0.2)	4.2 (0.1)	4.4 (0.2)	28.4 (0.5)	18.5 (1.1)
DBA/2J	5.1 (0.1)	6.5 (0.2)	4.4 (0.2)	5.3 (0.2)	27.0 (0.8)	23.7 (0.2)
SJL/J	5.7 (0.3)	6.6 (0.1)	3.5 (0.2)	3.6 (0.2)	25.6 (0.2)	21.1 (0.3)
SWR/J	7.3 (0.3)	9.2 (0.3)	4.6 (0.2)	3.9 (0.1)	27.2 (0.3)	18.3 (0.6)
129P3/J	7.1 (0.4)	5.9 (0.4)	NA	5.0 (0.4)	30.5 (0.4)	22.6 (0.4)
Correlation	$r = 0.65$	$P < 0.05$	$r = 0.42$	NS	$r = 0.77$	$P < 0.05$

NA: not applicable; NS: not significant, SEM: standard error of mean.

Baseline food, water, and weight responses

A previous analysis of food intake and body weight in male mice from 28 inbred strains indicated high narrow-sense heritability estimates, particularly for body weight ($h^2 = 0.87$: Bachmanov et al., 2002b). Baseline 24 hour intake of chow and water (across two bottles) intake as well as body weight were measured for the 12 tested strains (Lewis et al., 2005, 2007). Table 12.1 summarizes the means of these three variables for both studies; significant correlations were observed for water intake ($r = 0.65$) and body weight ($r = 0.77$) as a function of the 12 strains in these two studies. Indeed, water intake in strains tested by both Bachmanov et al. (2002b) and our laboratory (Lewis et al., 2007) yielded positive and significant correlations as well ($r = 0.67$). Such data indicate that baseline responses elicited by the 12 different strains appear consistent between studies both within and across laboratories.

Sucrose

Our evaluation (Lewis et al., 2005) of genetic variance in sucrose intake revealed strong and marked differences in terms of sensitivity to sucrose concentrations (Figure 12.1c), the absolute magnitude of sucrose intake (Figure 12.1a), and the evaluation of the amount of kilocalories consumed as sucrose (Figure 12.1b). In this regard, A/J, C57BL/6J, CD-1, and SWR/J strains consumed the greatest (11.6–22.0 ml) amounts of sucrose (Figure 12.1a), whereas the A/J, C57BL/10J, SJL/J, and SWR/J strains consumed the greatest (44–56%) percentages of kilocalories as sucrose (Figure 12.1b). Among these strains only the CD-1 and SWR/J consumed significantly more sucrose than water at each of the nine concentrations tested (Figure 12.1c). The BALB/cJ and 129P3/J strains displayed intermediate responsiveness in terms of sensitivity to sucrose concentrations (Figure 12.1c). In contrast, the AKR/J, CBA/J, C3H/HeJ, and DBA/2J strains consumed the least (6.9–7.9 ml) amount of sucrose (Figure 12.1a), and displayed low (20–30%) percentages of kilocalories consumed as sucrose (Figure 12.1b). Correspondingly, the DBA/2J and C3H/HeJ strains significantly increased sucrose intake over water intake only at the two highest concentrations, indicating less sensitivity (Figure 12.1c). The consistently higher sucrose responses observed in C57BL6/J mice relative to 129P3/J mice is consistent with other recent findings (Sclafani, 2006a, 2006b). A number of previous studies have employed as a measure of preference the percentage of sweetener consumed as a function of total fluid intake over a very restricted range of sucrose concentrations (e.g., Capeless and Whitney, 1995; Fuller, 1974; Lush, 1989; Pothion et al., 2004). This appeared not to be a reliable measure in our study because strains that showed both large (e.g., C57BL/6J, C57BL/10J, SWR/J, SJL/J) and small (e.g., C3H/HeJ) magnitudes of sucrose intake invariably showed very high (≥95%) preferences for sucrose. This underlines the importance of studying multiple strains across a greater range of sucrose concentrations.

A further noteworthy finding of our first study (Lewis et al., 2005) was that 24 hour sucrose over-consumption produced strain-dependent effects on overall kilocaloric intake. Whereas A/J, C57BL/6J, C57BL/10J, CD-1, SWR/J, and SJL/J strains all displayed the most pronounced compensatory decreases in chow intake as the percentage of kilocalories consumed as sucrose increased, the AKR/J, C3H/HeJ, and DBA/2J strains failed to significantly alter chow intake even at high sucrose concentrations. This very rapid compensation to the energy provided by sucrose suggests that some strains have either a greater sensitivity to changes in energy and/or a quicker ability to both adapt and respond to these changes in energy.

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Divergent responders may be a model for studying and identifying genetic substrates associated with this ability to regulate kilocalorie intake across a variety of energy sources. The fact that AKR/J, C3H/HeJ, and DBA/2J strains persist in consuming normal chow intake in addition to their increased kilocalories consumed at high sucrose concentrations make these strains potential models in chronic studies that might show increased weight gain, obesity, and diabetic symptoms. By testing a sufficient number of randomly chosen inbred strains, this study design also allows for the valid estimation of genetic correlations (Hegmann and Possidente, 1981). Thus, in determining whether sucrose consumption in the present study correlated with Tas1R3 polymorphisms in mouse strains (Reed et al., 2004), significant correlations were observed between these polymorphisms and moderate (0.01%: $r = 0.83$; 0.1%: $r = 0.91$; 2.5%: $r = 0.86$), but not higher (5–20%) sucrose concentrations. Thus, marked genetic variance was observed for the sensitivity to and consumption of sucrose.

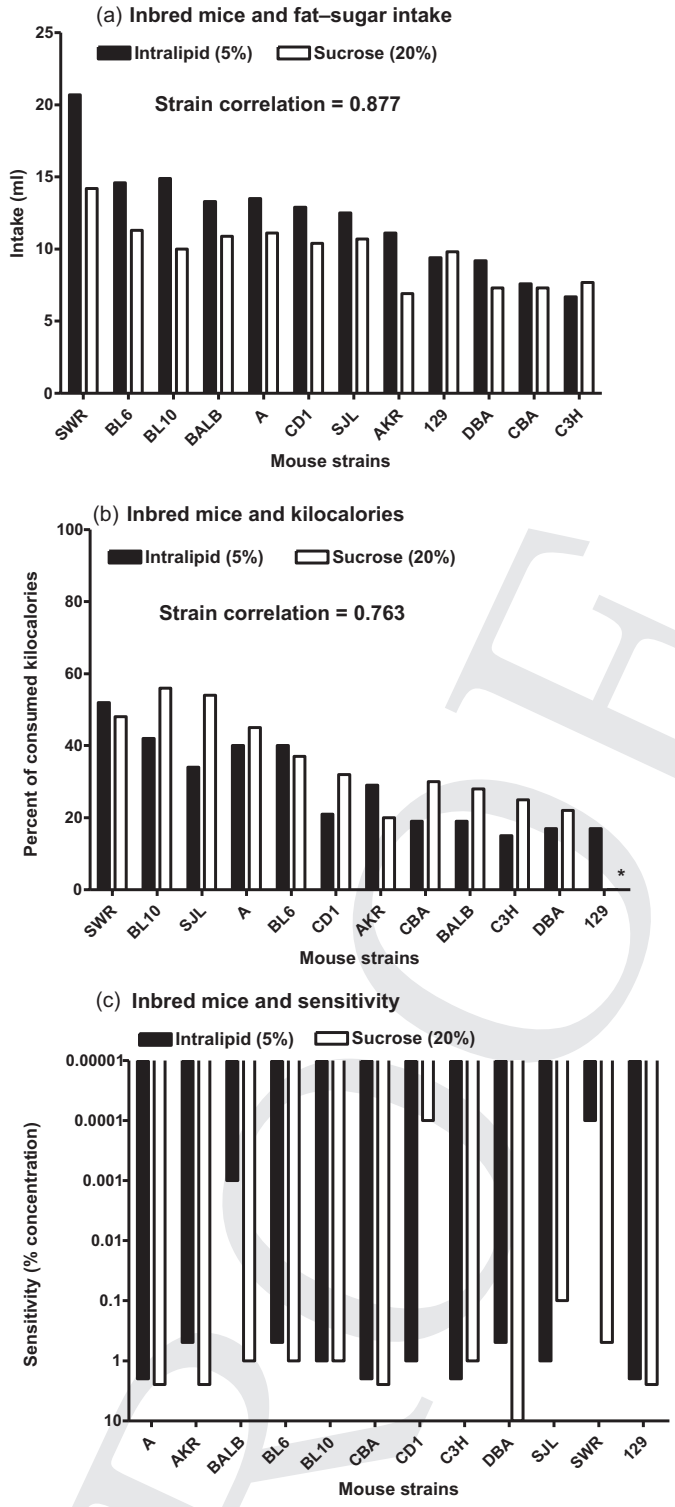

Figure 12.1 Comparison of inbred mouse strains in their responsiveness to intake of Intralipid (5%) fat, and sucrose (20%) solutions across three dimensions. Panel (a) displays systematic strain-specific differences in Intralipid and sucrose intake over 24 hours, and indicates a highly significant ($r = 0.87$) correlation among strains in their intakes of the fat and sugar solutions. Panel (b) displays systematic strain-specific differences in the percentage of kilocalories consumed as Intralipid and sucrose over 24 hours, and indicates a corresponding and highly significant ($r = 0.76$) correlation among strains in their ability to consume fat and sugar solutions as part of their total caloric daily intake. Panel (c) displays the sensitivity to different nine different concentrations of either Intralipid (0.001–5%) or sucrose (0.0001–20%) wherein these forms of intake over 24 hours were significantly higher than water in two-bottle preference tests. In contrast to intake per se and percentage of kilocalories consumed, significant strain-specific differences in sensitivity failed to correlate between sucrose and Intralipid ($r = -0.06$). (*Spillage in the sucrose study in 129P3/J mice precluded careful measurement of chow intake, and therefore the percentage of kilocalorie intake consumed as sucrose could not be ascertained.)

Fat (Intralipid)

A goal of a parallel study (Lewis et al., 2007) was to assess similarities or differences in genetic variance observed for sucrose intake relative to genetic variance in fat intake. However, unlike sucrose, typical difficulties in using different liquefied fat sources presented at different concentrations include their inability to stay in solution over a time course (e.g., 24 h) that is necessary to study murine intake. Intralipid is an emulsified fat solution (20%) made almost exclusively from soybean oil (20 g in 100 ml), and thereby insures that the fat is equally distributed in solution across a wide range of concentrations. Indeed, Intralipid solutions are readily consumed in a manner similar to sucrose and other palatable solutions (e.g., Higgs and Cooper, 1998a, 1998b). Further, a number of strains previously evaluated for sucrose intake (Lewis et al., 2005) also display three divergent patterns of fat intake: high fat intake with weight gain (e.g., AKR/J, C57BL/6J, DBA/2J: Alexander et al., 2006; Smith-Richards et al., 1999; West et al., 1992, 1995), high fat intake without weight gain (e.g., A/J, SWR/J: Leibowitz et al., 2005; Smith et al., 2000), and low fat intake (BALB/cJ, C3H/HeJ SJL/J, 129/J: Alexander et al., 2006; Smith et al., 2000). Our second study (Lewis et al., 2007) employed Intralipid as the source of fat.

First, it was clear that all strains displayed significant increases in Intralipid intake relative to water intake in

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24 hour, two-bottle preference tests (Figure 12.1a). As expected, strong and systematic strain differences were observed for Intralipid preference and intake. Thus, sensitivity analyses (Figure 12.1c) revealed significant increases in Intralipid relative to concomitantly offered water intake to the greatest degree (0.001–5.0% Intralipid concentrations) in BALB/cJ mice, and to progressively lesser degrees in AKR/J, C57BL/6J, DBA/2J, and SWR/J inbred strains (0.5–5.0%), in outbred CD-1 and inbred C57BL/10J and SJL/J strains (1–5%), and to the least degree in A/J, CBA/J, C3H/HeJ, and 129P3/J inbred strains (2–5%). Congruent sensitivity data were observed for the percentage of fluid intake consumed as Intralipid with significant increases noted in BALB/cJ mice at the seven highest concentrations, in SWR/J mice at the five highest concentrations, in C57BL/6J, C57BL/10J and DBA/2J mice at the four highest concentrations, and in A/J, AKR/J and SJL/J mice at the two highest concentrations (Figure 12.1a). However, the percentage of fluid intake consumed as Intralipid was only significantly greater at the highest concentration in outbred CD-1, C3H/HeJ, and 129P3/J mice, but failed to differ at any concentration in CBA/J mice (Figure 12.1b). Moreover, Intralipid intake per se (Figure 12.1a) or Intralipid intake adjusted for body weight (ml/30 g body weight) indicated that SWR/J mice (25.9 ml adjusted) consumed by far the most among inbred strains, followed by A/J, BALB/cJ, C57BL/10J, and C57BL/6J mice (12.9–15.6 ml adjusted), followed then in turn by SJL/J, AKR/J, and 129P3/J mice (10.9–14.7 ml adjusted), and finally by DBA/2J, C3H/HeJ, and CBA/J mice (8.0–9.5 ml adjusted). Correspondingly, strains differed in the percentage of kilocalories consumed as Intralipid across concentrations (Figure 12.1b) with SWR/J mice displaying significantly greater consumption of Intralipid as a function of total intake at the three highest concentrations, A/J, AKR/J, C57BL/6J, CBA/J, and SJL/J mice displaying significantly greater consumption of Intralipid as a function of total intake at the two highest concentrations, and the other six strains displaying this effect at only the highest concentration. Further, compensatory decreases in chow intake were noted at the highest Intralipid concentration only in A/J, AKR/J, BALB/cJ, C57BL/10J, and SWR/J strains. Finally, we observed significant positive correlations for both the magnitude of intake and the percentage of kilocalories consumed as Intralipid among the four highest (0.5, 1.0, 2.0, and 5.0%) concentrations, indicating consistency of the effects. Interestingly, a more recent study (Glendenning et al., 2008) using Intralipid demonstrated that the Tas1r3 genotype does not modulate orosensory stimulation from oil, and that orosensory and post-ingestive mechanisms respectively modulate dilute and concentrated Intralipid solutions.

We then systematically analyzed whether genetic variance in sucrose intake was related to genetic variance in Intralipid intake. Although the threshold sensitivity for the 12 strains for sucrose intake and for Intralipid intake failed to display significant relationships ($r = -0.06$, ns; Figure 12.1c), a highly significant positive correlation ($r = 0.87$, $P < 0.01$; Figure 12.1a) for the peak magnitude of sucrose intake and Intralipid intake was noted among the 12 strains. Moreover, significant positive correlations were also observed when comparing Intralipid (5%) intake with sucrose intake at concentrations of 5% ($r = 0.82$), 10% ($r = 0.85$), and 20% ($r = 0.88$). An identical pattern of positive correlational effects was observed when one analyzed the percentage of kilocalories consumed as Intralipid (5%) relative to the percentage of kilocalories consumed as sucrose at concentrations of 5% ($r = 0.81$), 10% ($r = 0.89$), and 20% ($r = 0.76$, Figure 12.1b). These data support the notion that genetic variance in the consumption of sweets and fats are highly related to each other.

Glucoprivic and lipoprivic responses

Most of the above studies examining genetic variance in ingestive responses employed hedonic and/or orosensory stimuli in distinguishing responsiveness across murine strains. To extend the analysis of genetic variance in ingestive responses to homeostatic mechanisms, our laboratory (Lewis et al., 2006a, 2006b) examined whether different mouse strains varied in their feeding responses induced by glucoprivation and lipoprivation. Glucoprivic feeding can be induced by the anti-metabolic glucose analogue, 2DG. Our first study (Lewis et al., 2006a) surveyed 11 inbred and one outbred strain for variations in feeding responses following a wide range of systemic 2DG doses (200–800 mg/kg) across a 4 hour time course (Table 12.2). Similar to outbred CD-1 mice that displayed orderly time and dose-dependent increases in 2DG-induced feeding, genetic variability was observed in the inbred strains with dose-dependent increases in 2DG-induced feeding observed across all four doses (DBA/2J), across the three highest doses (BALB/cJ, SJL/J and 129P3/J), and across the two highest doses (CBA/J and AKR/J). In contrast, some mouse strains (A/J and C3H/HeJ: 800 mg/kg; C57BL/6J: 400 mg/kg) displayed very limited instances of 2DG-induced feeding, failed to show any increase (C57BL/10J), or actually significantly reduced intake (SWR/J). Such effects could not be predicted by any difference in baseline intakes. Moreover, although there was significant cross-correlation between 2DG doses of 200, 400, and 600 mg/kg, they in turn failed to correlate with the highest 800 mg/kg 2DG dose. Interestingly, significant correlations between sucrose intake (Lewis et al., 2005) and 2DG food intake failed to occur across the 11 inbred strains. Thus, although both experimental paradigms are thought to provide insight into glucosensing processes, the present differential pattern of strain sensitivity in each suggests differential genetic organization.

Using the free fatty acid oxidation inhibitor, MA that significantly increases food intake following systemic administration, our second study in this series (Lewis et al., 2006b) surveyed the 11 inbred and one outbred strain for variations in feeding responses following a wide range of systemic MA doses (5–100 mg/kg) across a 4 hour time course (Table 12.2). Strain-specific effects for MA-induced feeding were observed following the three highest (35–100 mg/kg) MA doses in inbred

Table 12.2 Comparison of sensitivity (minimum dose) to feeding responses to 2-deoxy-D-glucose (2DG) and mercaptoacetate (MA) and the greatest magnitude (g) of food intake following the glucoprivic and lipoprivic stimuli. Sensitivity is defined as that dose that significantly increases intake over vehicle values after 4 hours. Magnitude is the defined as the increased intake after 4 hours following 2DG or MA over vehicle values.

Strain	2DG sensitivity (mg/kg)	MA sensitivity (mg/kg)	2DG magnitude (g)	MA magnitude (g)
A/J	800	>100	0.5	0.04
AKR/J	600	35	0.4	0.4
BALB/cJ	400	100	0.7	0.7
C57BL/6J	800	100	0.2	0.1
C57BL/10J	>800	>100	0.1	0.3
CBA/J	600	100	0.5	0.1
CD-1	200	70	0.5	0.7
C3H/HeJ	800	5	0.6	0.4
DBA/2J	200	35	0.5	0.6
SJL/J	400	100	0.4	0.2
SWR/J	>800	>100	0.01	0.2
129P3/J	400	>100	0.3	0.3
Correlation	$r = 0.26$	NS	$r = 0.48$	NS

2DG: 2-deoxy-D-glucose; MA: mercaptoacetate; NS, not significant.

DBA/2J mice and the two highest (70–100 mg/kg) doses in outbred CD-1 mice. Dose-specific increases in intake were observed following the two middle (35–70 mg/kg) MA doses in AKR/J mice, only the 5 mg/kg MA dose in C3H/HeJ mice, only the 35 mg/kg MA dose in BALB/Cj, and CBA/J mice, only the 70 mg/kg dose in SJL/J and SWR/J mice, and only the 100 mg/kg dose in C57BL/6J mice. In contrast, MA failed to significantly increase food intake at any dose in this wide range in A/J, C57BL/10J and 129P3/J mice.

Functional comparisons between lipoprivic (MA) and glucoprivic (2DG) feeding in rats have revealed similar c-fos responses in the nucleus of the solitary tract, lateral parabrachial nucleus, central nucleus of the amygdala, and the dorsal motor nucleus of the vagus (Ritter and Dinh, 1994) as well as elevated sympathoadrenal plasma levels of epinephrine and norepinephrine (Scheurink and Ritter, 1993). However, there are marked differences in sensitivity to different physiological manipulations between MA-induced and 2DG-induced feeding responses following vagotomy (Ritter and Taylor, 1990) and lesions placed in the lateral parabrachial nucleus (Calingasan and Ritter, 1993) or the central nucleus of the amygdala (Ritter and Hutton, 1995). Importantly, our correlational analyses of genetic differences in feeding responses elicited by 2DG and MA failed to find significant strain-specific relationships in terms of either sensitivity (the dose range to elicit feeding) or magnitude (the actual amount of intake elicited by each dose) of effects (Table 12.2). Similarly, significant genetic correlations between Intralipid intake and MA-induced intake failed to occur despite the recent finding (Matsumura et al., 2008) that MA attenuated the oral acceptance of fat in BALB/c mice. Thus, the differences among diverse mouse strains in their ingestive responses to lipoprivation and glucoprivation suggest that they employ different neural circuitry, and indeed provide evidence that these two homeostatic responses operate via different genetic mechanisms of action.

Conclusions

This chapter has evaluated a great deal of recent empirical evidence examining genetic variance in inbred, outbred, and crossbred murine strains across a wide array of ingestive behaviors. However, for other ingestive states, the complexity of the response, the differences in procedures, and the wide variety of tested strains precluded a more thorough investigation of the genetic substrates of these responses, particularly involving fat intake and obesity. Yet, it is becoming increasingly clear that the two major approaches in examining these responses, either the use of a small number (2–4) of mouse strains for "sensitive" and "insensitive" responders on behavioral and QTL analyses, or the use of large numbers of strains across a wide array of ingestive stimuli and concentrations, have together provided insights into the complex, multi-genomic mechanisms mediating feeding behavior. Together with studies using knockout and knockdown genetic approaches, feasible strategies for the analysis of genetic contributions of normal, intact genetically varied strains in evaluating feeding responses have clearly emerged, allowing us to analyze complex genetic × environmental interactions in the etiology of both normal and disordered feeding behaviors.

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