A Systematic Scoping Review of Surgically Manipulated Adipose Tissue and the Regulation of Energetics and Body Fat in Animals

Anarina L. Murillo1, Kathryn A. Kaiser2,3, Daniel L. Smith Jr2,4, Courtney M. Peterson2,4, Olivia Affuso2,5, Hemant K. Tiwari1, and David B. Allison5

Objective: Surgical manipulations of adipose tissue by removal, or partial lipectomy, have demonstrated body fat compensation and recovered body weight, suggesting that the body is able to resist changes to body composition. However, the mechanisms underlying these observations are not well understood. The purpose of this scoping review is to provide an update on what is currently known about the regulation of energetics and body fat after surgical manipulations of adipose tissue in small mammals.

Methods: PubMed and Scopus were searched to identify 64 eligible studies. Outcome measures included body fat, body weight, food intake, and circulating biomarkers.

Results: Surgeries performed included lipectomy (72%) or transplantation (12%) in mice (35%), rats (35%), and other small mammals. Findings suggested that lipectomy did not have consistent long-term effects on reducing body weight and fat because regain occurred within 12 to 14 weeks post surgery. Hence, biological feedback mechanisms act to resist long-term changes of body weight or fat. Furthermore, whether this weight and fat regain occurred because of “passive” and “active” regulation under the “set point” or “setting point” theories cannot fully be discerned because of limitations in study designs and data collected.

Conclusions: The regulation of energetics and body fat are complex and dynamic processes that require further studies of the interplay of genetic, physiological, and behavioral factors.

Introduction

Despite many efforts to lose or maintain weight loss through behavioral strategies (e.g., diet, exercise) or through surgical means (e.g., bariatric surgery, fat-specific liposuction), many individuals regain weight after experiencing temporary weight loss. To explain why it is so difficult to lose weight, it has been proposed that biological mechanisms may directly oppose changes in weight or that our biology works to resist changes in either weight or body fat (BF), both at the energy balance intersection. Through our basic understanding of biology, we know that organs, such as the heart and lungs, have a narrow range of sizes or weights relative to body size, suggesting that their sizes are tightly regulated. However, other body components, such as adipose tissue (both visceral and subcutaneous), differ widely across individuals and can vary substantially within individuals over time. Given this heterogeneity, whether and how weight and BF stores are regulated, and even what is regulated, is currently not well understood.

A combination of evidence, anecdote, and intuition suggests that there is likely some type of biological feedback system that controls, or regulates, body weight (BW) or a close correlate of weight, such as BF, or
body energy stores, such as glycogen in liver and muscle. Energy balance, which can be defined as the difference between energy input and output, is governed by a complex and dynamic system that regulates the accumulation and partitioning of energy stores. While short-term energy imbalances lead to weight gain (energy intake > energy output) or weight loss (energy intake < energy output), physiological (e.g., metabolic hormones) and behavioral (e.g., energy intake, type of diet, physical activity) factors may adapt and work together to favor returning BW to a specific “set point.” For example, studies of diet-induced obese mice (via a high-fat diet [HFD] or Western diet) have found that the mice returned to their baseline weights after switching to a normal chow diet (1), suggesting that there is a “body-inherent” weight, referred to as the body’s set point. Speakman et al. (2) defined set point as an “active feedback mechanism linking adipose tissue (stored energy) to intake and expenditure via a set point encoded in the brain” and “setting point” as a “passive feedback [mechanism] between the size of the body stores and aspects of expenditure.” In summary, the complex interplay among behavioral, physiological, and genetic factors regulating BW and whether changes in weight/fat occur because of “passive” and “active” regulation under the set point or settling point theories are not well understood.

Kennedy (3) postulated that any deviation in fat mass from the body’s ideal level triggers an error signal detected by the central nervous system; specifically, the hypothalamus acts as the coordinating release or response center of hormones of the autonomic nervous system and controls homeostatic processes, such as appetite. This response, in turn, triggers short-term changes in food intake (FI) to regulate BF and thereby BW in the long term. To study the regulation of BW or fat, small mammal experiments involving the surgical removal of BF (partial lipectomy) and inserts of adipose tissue from one animal into another (implant/transpose) have been used. Many lipectomy experiments have been performed since the 1950s to explore Kennedy’s “lipostatic theory” yet have reported conflicting results, with some studies reporting a return baseline-equivalent fat level (4) and others not (5).

The purpose of this scoping review is to describe what has been reported about the regulation of fat mass from one particular class of intervention studies, namely those that surgically manipulate adipose tissue in small mammals, primarily rodents. We review studies that have surgically manipulated, such as removal (partial lipectomy), insertion (transplant/implant), or both, fat depots in small mammals as a model to probe which subcomponents of energetics and body composition are regulated and in what manner. In this paper, first, we describe the methodological framework implemented for the scoping review; second, we summarize key findings from the literature, focusing on its ability to support inferences about the regulation of BW, BF, and energy stores; and finally, we summarize our conclusions and recommendations for future work.

Methods

Study design

A scoping review of small mammal literature was performed to determine what has been reported about the regulation of BW and BF. Data were extracted from studies that surgically manipulated adipose tissue in small mammals, and then the subsequent changes in BW, BF, and other extracted variables were documented. In this work, our methods used both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (6) and Arksey and O’Malley’s (7) proposed methodological framework for synthesizing and writing the scoping review.

Inclusion and exclusion criteria

The study characteristics using the Population, Intervention, Comparison, and Outcome framework for inclusion were as follows: participants/population, small mammals such as rats, mice, hamsters, squirrels, rabbits, gerbils, and prairie voles; intervention/study design, randomized controlled experimental and/or quasi-experimental designs with pre- and post-surgery measures and a control group (procedures included either the removal and/or transplant/implant of adipose tissue); comparator/control, either sham-operated animals or animals with no surgery performed; and for primary outcome measures, BW and BF were required for all included studies. Other outcome variables included FI and circulating biomarkers (e.g., leptin, triglycerides [TG], IL-6, and tumor necrosis factor [TNF]-α). Papers without abstracts, review articles, case study articles, and non-English papers were not considered in this review but were considered for referencing or as other relevant primary research articles as applicable. Dates of papers included anything published prior to January 1, 2017.

Search and selection of studies

Two search databases were used to identify relevant articles, PubMed and Scopus. A combination of the following keywords was used to search for papers: “adipose tissue,” “fat,” “transplantation,” “lipectomy,” “removal,” “graft,” “implantation,” “abdominal fat,” “adipose,” “subcutaneous fat,” “adipocyte,” “body fat,” or “fat pad.” The syntax used in PubMed was as follows: (“Adipose Tissue”[Major] OR fat) AND (“transplantation”[Subheading] OR lipectomy OR removal). The syntax used for the Scopus search was as follows: ((TITLE-ABS_KEY (lipectomy) OR TITLE-ABS-KEY (removal) OR TITLE-ABS-KEY (transplant) OR TITLE-ABS-KEY (graft*) OR TITLE-ABS-KEY (implantation)) AND DOCTYPE (ar OR re) AND PUBYEAR < 2017) and ((TITLE-ABS-KEY (“abdominal fat”) OR TITLE-ABS-KEY (adipose) OR TITLE-ABS-KEY (“subcutaneous fat”) OR TITLE-ABS-KEY (adipocyte) OR TITLE-ABS-KEY (fat) OR TITLE-ABS-KEY (“body fat”) OR TITLE-ABS-KEY (“fat pad”)) AND DOCTYPE (ar OR re) AND PUBYEAR < 2017). Searches were performed on January 13, 2017.

After removing duplicates, a total of 17,478 English-only articles were collected. Of these, 14,909 papers were removed either because they involved the nontarget subject population (26.44%) or because they were not pertinent to the research question (73.56%) (e.g., plastic surgery, cancer drug and/or treatments). The remaining 2,569 papers included small mammal studies that had one or more of the following terms in the title, abstract, and/or keyword list: rat, mice/mouse/murine, rodent, hamster, squirrel, rabbit, and voles. Of these, two authors (ALM, KAK) independently screened and identified articles for full-text review. Full-text articles (n = 119) were reviewed, of which 55 were excluded because they did not report the two required outcome measures (BW and BF) or did not have a control comparison group, bringing the final total to 64 articles. The article selection process is summarized in Figure 1.

Data charting

The major outcome measures included BW, BF, food (energy) intake, and circulating biomarkers. Characteristics of the study design were also documented, including the surgery type (lipectomy, transplant/implant, or both), adipose tissue type (white, brown, or both), control
Obesity Surgical Manipulation of Body Fat in Small Mammals Murillo et al.

Results

Characteristics of studies

Most studies were performed in mice (35%) or rats (35%) (Figure 2B). The duration of the experiments ranged from 1 to 43 weeks post surgery. The adipose tissue depots manipulated, adipose tissue types, and study design factors are summarized (Figure 2A, 2C-2D). The four major outcome measures of interest reported were changes in BW (100%), BF (100%), food (energy) intake (64%), and specific circulating biomarkers (31%). The study design and outcome measures are summarized for each surgery type as follows: lipectomy in Table 1, transplantation in Table 2, and combination of surgeries in Table 3.

Outcome measures are summarized in Figure 3. Age at time of surgery and BF type or amounts manipulated are summarized in Figure 4.

Body weight

Total BW at baseline was either weight matched or nonsignificant between control and experimental groups in all studies. Immediately following surgery, animals with adipose tissue removed via lipectomy had significantly lower BW, whereas animals with adipose tissue implanted via transplantation had significantly higher BW, as would be expected. To investigate the regulation of energetics, we recorded the reported changes in BW in the long term by comparing weight at baseline to weight at termination and recorded our findings as significantly increased, decreased, or no change. Results with multiple control and/or experimental groups that showed either increased, decreased, or no change in BW were recorded as “mixed.” Findings that were considered “inconclusive” referred to cases for which the final BW data were not presented or not comparable (e.g., if studies measured different fat depots that were not comparable from control to experimental groups). Furthermore, the length of studies ranged from 3 to 43 weeks, and between 5% to 80% of BF was manipulated.

Total BW was not statistically significant compared with sham-operated groups at termination after surgical manipulation of WAT or BAT in Osborne-Mendel (8-12), Sprague Dawley (13-17) and Wistar (18-25) rats. Total BW after WAT removal (26) in Zucker rats (lean and obese) was not significant at termination. However, studies reported mixed findings after BAT removal combined with varying housing temperatures where BW was not significantly different (27) or increased (12).

In contrast, another study found that surgical manipulations of WAT and BAT (transplanted or lipectomized) individually decreased BW (28). Both Lister Hooded rats with removed BAT (29) and Long Evans rats with WAT lipectomized or transplanted (30) had increased BW. Therefore, changes in BW in most rat studies in the long term (or at termination) were not significantly different compared with baseline weight, with the exception of a few studies (12,27-30).
Overall, C57BL/6J mice with WAT or BAT removed had inconclusive results (e.g., some subgroups had lipectomized animals with either a lower BW or no significant changes in BW) (31-37). Similarly, C57BL/6J ob/ob mice had no changes in BW (38) or had mixed (39-41) results. Female CBA/J mice with WAT transplanted had decreased BW, but this was likely due to calorie restriction of the stock-fed diet. In summary, studies performed in mice presented mixed conclusions on the effects of BW after surgery.

No significant changes in BW at termination have been reported in studies of various mammals such as Syrian and Siberian hamsters (42-54), Gold-mantled ground squirrels (55,56), New Zealand rabbits (57), prairie voles (45), and Manchester black mice (58). Total BW results in mice of other strains, including C3H Manchester, liver-specific insulin receptor knockout (LIRKO), PPAR-γ, wild-type and db/db, New Zealand, and NIH Swiss with WAT and BAT surgically manipulated, were inconclusive (59-67). Excised BAT in Mongolian gerbils had decreased BW. Hence, hamsters and other small mammals had either no change in BW or were considered inconclusive at termination compared with baseline levels.

In summary, postsurgery BW in lipectomy studies (summarized in Table 1) had no change (n = 38), decreased (n = 2), increased (n = 1), was inconclusive (n = 1), or was mixed (n = 4). Total BW in transplantation studies (summarized in Table 2) had no change (n = 3), increased (n = 1), decreased (n = 1), or was inconclusive (n = 3). Finally, BW in studies with both transplanted and lipectomized adipose tissue (summarized in Table 3) had no change (n = 5), increased (n = 1), decreased (n = 2), or had mixed results (n = 2). These findings are summarized in Figure 3A, illustrating that independent of the surgical method of adipose manipulation, the preponderance of data suggests no change in BW at follow-up measures (details on the effects of transplantation or combined surgeries on changes in total BW can be found in Supporting Information Figure S1A-B).

**Body fat**

Although surgical manipulation of BW in these studies has focused on adipose tissue, primary outcomes focusing on BW limit the ability to clarify the role of energy partitioning during weight recovery and accurately assess whether fat or fat-free mass is changed in response to the surgical manipulation. To better assess the regulation of energetics in animals, we consider changes in the adipose organ, which consists of white and brown adipocytes in the subcutaneous depots and visceral depots (68-70). WAT has multiple physiological and mechanical functions, such as energy storage, whereas the main function of BAT is for cold-induced thermogenesis or heat generation. To assess the effects of surgeries in the included studies on changes in BF, the remaining fat pads were measured using the following three approaches: (1) surgically removing and weighing them after animal termination, (2) noninvasive measures such as nuclear magnetic resonance or dual-energy x-ray absorptiometry scans, and (3) a combination of invasive and noninvasive methods.
| Reference                  | Animal                | ATb | Agec | Sex | Total N | Control/ treatment | Factord | Timea | Cagef | BW | BF | FI | CB |
|---------------------------|-----------------------|-----|------|-----|---------|-------------------|---------|-------|-------|----|----|----|----|
| Faust et al. (1977) (17)  | Osborne-Mendel       | WAT | 3    | NR  | 31      | 2/2               | D       | 4 or 28 | NR   | -  | -  |    |    |
| Faust et al. (1977) (10)  | Sprague Dawley       | 3-8 | M    | 72  | 3/3     | D                 | 22      | NR    | -    | -  | -  |    |    |
| Schemmel et al. (1971) (8)| Osborne-Mendel       | 4   | M    | 38  | 4/4     | D                 | 32      | S     | -    | -  | -  |    |    |
| Liszka et al. (1998) (26) | Obese Zucker         | 6   | F    | 36  | 1/1     | G                 | 43      | S     | -    | -  | x  |    |    |
| Taylor et al. (1973) (18) | Wistar Zucker        | 6-8 | M    | 54  | 3/3     | E                 | 16      | S     | -    | x  |    |    |    |
| Coelho et al. (2009) (24) | Wistar Zucker        | 8   | M    | 60  | 2/2     | E                 | 12      | S     | -    | -  | -  |    |    |
| Dettloff-Pokora et al. (2015) (25)| Wistar | 12 | M    | 16  | 1/1 | None | 13 | S | - | ↓ | x | - | o | |
| Bueno et al. (2005) (22) | Wistar Zucker | 13 | M    | 8   | 1/3   | C                 | 1 or 4 | NR | ↓ - | x | - | o | |
| Habilante et al. (2010) (23)| Wistar | 13 | M    | 40  | 2/2   | E                 | 5       | NR | -    | x  | -  |    |    |
| Bueno et al. (2011) (21) | Wistar Zucker | 13 | M    | 72  | 1/1   | D                 | 1 or 4 | S  | -    | x  | -  | o  | |
| Larson and Anderson (1978) (16)| Sprague Dawley | 15 | M    | 28  | 1/1 | None | 13 | S | - | - |    |    |    |
| Kral (1976) (15)         | Sprague Dawley       | 15-16 | M   | 20  | 1/1 | None | 6-12 | S | - | - |    |    |    |
| Borst et al. (2005) (13) | Sprague Dawley       | 16  | M    | 16  | 1/1   | None | 4       | NR | -    | x  | -  | o  | |
| Faust et al. (1979) (9)  | Sprague Dawley       | 16  | M    | 21  | 1/3   | D                 | 24      | NR | -    | -  |    |    |    |
| Michel and Cabanac (1999) (20)| Wistar | 52 | M    | 19  | 1/1 | None | 6     | S | - | ↑ |    |    |    |    |
| Bailey and Anderson (1980) (14)| Sprague Dawley | NR | M    | 95  | 1/4  | None | 8      | S | - | - |    |    |    |    |
| Hausman et al. (2004) (19)| Sprague Dawley | NR | M    | 74  | 1/1  | None | 16     | S | - | - |    |    |    |    |
| Stern et al. (1984) (27) | Obese Zucker         | 4   | F    | 29  | 2/2   | T,G               | 9       | S     | -/-  | -/† | -/† | -/- | |
| Horwitz et al. (1985) (12)| Lean and Obese Zucker; | 4-7 | F    | 18 to 30 | 1 to 2 | T,G | 7 to 10 | S | -/-  | -/† | -/† | -/† | -/- | |
| Moore et al. (1985) (11) | Osborne-Mendel       | 5   | F    | 18  | 1/1   | None | 9       | S | - | ↓ | ↓ |    |    |    |
| Stephens et al. (1981) (29) | Lister Hooded     | 10  | M    | 24  | 2/2   | D                 | 6.4     | M | ↑ | ↑ | ↑ |    |    |
| Mice                     |                       |     |      |     |        |                   |         |       |     |    |    |    |    |
| Harris et al. (2002) (39) | C57/BL/6J            | 5   | M    | 60  | 2/2   | G                 | 8-21    | M | z | - |    |    | o  |
| Booth et al. (2016) (61) | FKO-gamma            | 12  | M    | 28  | 2/2   | G                 | 13      | S | - | ↓ | - | o  | |
| Mulder et al. (2016) (33)| C57/BL/6J            | 12  | M    | 72  | 3/3   | D                 | 6-24    | NR | x | - | - | o  | |
| Chlouverakis and Hojnicki (1974) (38)| Ob/Ob | 16 | F    | 11  | 1/1 | G     | 7.4      | NR | - | - |    |    |    |    |
| Cox-York et al. (2015) (31)| C57/BL/6          | NR  | M    | 80  | 4/4   | D                 | 5 or 13 | S | - | x | - | o  | |
| Connolly and Carnie (1982) (59)| Manchester   | 8-12 | M    | 45  | 2/1   | D                 | 3.1     | M | - | ↑ | ↑ |    | |
| Darcy et al. (2016) (62)| df/df              | 12  | M    | 40  | 1/3   | G                 | 8       | S | - | x |    |    | |
| Connolly et al. (1982) (58)| Manchester       | 6-7 | M    | 24  | 1/1   | T                 | 3       | M | - | ↑ |    |    | |
| Emanuelli et al. (2014) (60)| LIRKO         | 7   | M    | NR  | 1/3   | D,G               | 7       | NR | z | - | ↑ | o  | |
| Reference | Animal | ATb | Agec | Sex | Total N | Control/treatment | Factord | Timee | Cagef | BW | BF | FI | CB |
|-----------|--------|-----|------|-----|---------|------------------|---------|-------|-------|-----|----|----|----|
| Demas and Sakaria (2005) | Siberian | WAT | 8 | F | 40 | 2/2 | C | 27 | S | - | - | o |
| Youngstrom and Bartness (1998) | Siberian | WAT | 8-12 | M | 175 | 4/4 | P | 12 | S | - | x | - |
| Mauer and Bartness (1997) | Siberian | WAT | 10-12 | M | 50 to 93 | 2/3 | None | 12 | S | - | - | - |
| Hamilton and Wade (1988) | Syrian | WAT | 12 | F | 36-54 | 2/2 | D | 12 or | S | - | - | - |
| Shi and Bartness (2005) | Siberian | WAT | 12 | M | 60 | 2/4 | C | 12 | S | - | - | - |
| Mauer and Bartness (1997) | Siberian | WAT | 12 | M | 22 | 1/1 | None | 12 | S | - | - | - |
| Shi et al. (2004) | Siberian | WAT | 12-16 | M | 40 | 1/1 | None | 3 or 6 | S | - | x | - |
| Dailey and Bartness (2008) | Siberian | WAT | 14 | M | 36 | 3/8 | E | 12 | S | - | ↓ | - | o |
| Mauer and Bartness (1995) | Siberian | WAT | NR | M | 84 | 4/4 | C | 8 | S | - | - | - |
| Mauer and Bartness (1997) | Siberian | WAT | 10-12 | M | 25 | 2/2 | D,P | 12 | NR | -/ | x/x | ↓/ |
| Weber et al. (2000) | Syrian | WAT | NR | F | 28 | 2/1 | D | 12 | S | - | ↑ | - | o |
| Reyne et al. (1983) | New Zealand | WAT | 24-144 | M | 33 | 4/2 | A | 12 | S | - | - | - |
| Dark et al. (1985) | Gold-mantled | WAT | 12-16 | M | 21 | 1/1 | None | 13 | S | - | - | - |
| Forger et al. (1988) | Gold-mantled | WAT | 98 | F | 22 | 1/1 | None | 7 | S | - | - | - |
| Demas et al. (2003) | Prairie voles, Siberian hamsters | WAT | 8 | M | 36 to 54 | 1/2 | C | 12 | NR | - | x | - |
| Yang et al. (2012) | Mongolian gerbil | WAT | 24 to 28 | M | 40 | 2/2 | T | 3 | S | ↓ | - | - |

*aOutcome results labeled as follows: no change (-), increase (↑), decrease (↓), omitted (o), mixed results (z), and not comparable or inconclusive (x), and articles with multiple experiments separated with "/." Entry left blank if study did not record outcome for body weight (BW), body fat (BF), food intake (FI), and circulating biomarkers (CB).
bAT, adipose tissue. White adipose tissue denoted WAT, brown adipose tissue denoted BAT, and both indicates that WAT and BAT were both manipulated in study.
cAge at time of surgery in weeks.
dFactors included in study design abbreviated as follows: C, chemical injection; D diet; G, genotype/genetic; E, exercise trained; T, temperature; A, age; and P, photoperiod.
eDuration of study post surgery in weeks.
fHousing of animal post surgery: S, single housed; M, multiple animals per cage.
NR, not reported.
TABLE 2 Summary of transplantation studies (n = 8)

| Reference | Study design | Animal | AT<sup>a</sup> | Sex | Total N | Control/treatment | Factor<sup>d</sup> | Time<sup>e</sup> | Cage<sup>f</sup> | BW | BF | FI | CB |
|-----------|--------------|--------|----------------|-----|---------|-------------------|------------------|-------------|-------------|-----|-----|----|----|
| Harris (2015) | (32) C57BL/6/J 6 M | NR | NR | NR/NR | D | 3-17 | NR | - | - | o | | |
| Hocking et al. (2015) | | | | | | | | | | | | | |
| Guo et al. (2009) | (64) Lepr db/db 8 M, F | 16 | 0/2 | G,A | 12 | NR | x | x | | | | | |
| Ashwell and Meade (1978) | (63) New Zealand Obese 8-52 M, F | 22 | 0/5 | A | 4-16 | NR | x | x | | | | | |
| Ashwell and Meade (1980) | | | | | | | | | | | | | |
| Ashwell and Meade (1981) | (41) CBA/J 6 F | NR | 1/1 | D,C | 9 | NR | | | | | | | |
| Gunawardana and Piston (2012) | | | | | | | | | | | | | |
| Rytka et al. (2011) | (73) C57BL6/J 6 M | 10-20 | 1/1 | None | 5 | NR | | | | | | | |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | |

<sup>a</sup>Outcome results labeled as follows: no change (-), increase (↑), decrease (↓), omitted (o), and not comparable or inconclusive (x). Entry left blank if study did not record following outcomes: body weight (BW), body fat (BF), food intake (FI), and circulating biomarkers (CB).

<sup>b</sup>AT, adipose tissue. White adipose tissue denoted WAT, and brown adipose tissue denoted BAT.

<sup>c</sup>Age at time of surgery in weeks.

<sup>d</sup>Factors included in study design are abbreviated as follows: C, chemical injection; D, diet; G, genotype/genetic; and A, age.

<sup>e</sup>Duration of study post surgery in weeks.

<sup>f</sup>Housing of animal post surgery.

NR, not reported.

Total BF at baseline was similar and nonsignificant between control and experimental groups within studies. Animals with adipose tissue removed via lipectomy had less total BF immediately following surgery. In contrast, animals with adipose tissue implanted via transplantation had increased total BF. The compensation of BF following surgery was supported in animals that regained fat equivalent to the control groups over 3 to 43 weeks after surgery. The amount of adipose tissue manipulation varied across species and by procedure. Though it is difficult to comprehensively and accurately quantify the adipose depots, we summarize the information reported by the authors. In rats, a range of 1% to 80% of WAT and/or 20% to 25% of BAT was lipectomized. A narrower range of adipose tissue in mice was lipectomized (20% to 30% of WAT or BAT). Lipectomized WAT ranged from 5% to 40% and 70% to 80% in hamsters and rabbits, respectively. In transplantation studies of mice, the amount of implanted fat is restricted based on space, and approximately 4 to 6 g of fat were implanted into animals. Generally, this occurred if remaining fat pads adapted to the fat deficit through storing energy in remaining depots to regain lost weight in fat. In this section, the long-term changes in total BF were recorded as either significantly increased, decreased, or not changed based on results reporting differences in BF from baseline to termination. Studies with multiple control and/or experimental groups were recorded as “mixed” if the groups showed a combination of increased, decreased, and/or no change in BF. Results were considered “inconclusive” if the final BF data were not presented or not comparable (e.g., if studies measured different fat pads and were not comparable between groups). All studies reported BF and are summarized in Table 1.

Osborne-Mendel rats with either WAT or BAT removed did not have statistically significant changes in BF at termination, ranging from 22 to 32 weeks post surgery (8-10), except at 9 weeks, when total BF remained significantly decreased (11,12,27). Sprague Dawley rats with WAT and BAT removed yielded no significant differences in BF post surgery at 4 to 28 weeks (14-17). Zucker lean fatty rats with lipectomized BAT had either no change in BF (27), increased BF (12), or were inconclusive (47). Wistar rats that underwent WAT removal or WAT and BAT transplantation had total BF that was significantly decreased (25,28), increased (20), or not changed (19,24) or the findings were inconclusive (18,21-23,25). Gold-mantled ground squirrels with WAT and BAT removed had no significant changes in BF post surgery (55,56). In contrast, results varied for Syrian and Siberian hamsters, in which some had no change (42,44,46,50,51,53,54,71), were increased (43,52,53), were decreased (48), or were inconclusive (percent BF was not reported) (45,47,49). Surgical manipulations of WAT and BAT in mice led to decreased BF in experimental animals (36,37,41,61), whereas other studies reported inconclusive results or no observed changes (31-35,38,39,60,62-67,72,73). BAT removal resulted in increased BW at termination in Manchester mice (58). In other animals, BF after WAT lipectomy had no change in rabbits (57) or in Mongolian gerbils (74), and the data were inconclusive in prairie voles (45). Lastly, transplanted WAT yielded higher levels of BF in rats (30) and mice (40) at termination.

Several studies have reported on the potential anatomical location-specific effects of specific adipose depots. No significant differences in adipose regrowth based on the location of excised fat pads were observed in PPAR-γ knockout mice (61), Sprague Dawley rats (13,14), C57BL/6J mice (31,33), wild-type or ob/ob mice (39), Wistar rats (19,23), Osborne-Mendel rats (8), and Gold-mantled ground squirrels (55), which was consistent with other studies (16,17).
# TABLE 3 Summary of studies with both lipectomy and transplantation (n=10)

| Reference                  | Animal       | ATb | Agec | Sex | Total N | Control/treatment | Factord | Timee | Cagef | BW | BF | FI | CB |
|----------------------------|--------------|-----|------|-----|---------|------------------|---------|-------|-------|----|----|----|----|
| Mice                       |              |     |      |     |         |                  |         |       |       |    |    |    |    |
| Rooks et al. (2004) (66)   | Sprague Dawley WAT | 5 to 6 | M     | 50-54 | 1/2     | None        | 2 or 5   | S     |       | -  | -  | -  | o  |
| Ishikawa et al. (2006) (67)| BALB/c       | 6   | M    | 21   | 1/2     | G           | 10       | NR    |       | -  | x  | -  | 0  |
| Foster et al. (2013) (35)  | C57BL/6      | 7   | M    | 18-28 | 1-2/2   | D           | 5-6      | S     |       | -/-| x/-| -/-| 0  |
| Tran et al. (2008) (34)    | C57BL/6      | 12  | M    | 35   | 1/4     | G           | 12       | NR    |       | z  | z  | -  | 0  |
| Foster et al. (2011) (36)  | C57BL/6      | NR  | M    | 18-40 | 1/2-4   | None        | 8        | NR    |       | -/-| -/-| -/-| -  |
| Liu et al. (2015) (37)     | C57BL/6 BAT  | 6   | M    | 18 to 20 | 1/1   | None  | 13     | S     | ↓    | ↓  | ↓  | -  | o  |
| Hamsters                   |              |     |      |     |         |                  |         |       |       |    |    |    |    |
| Lacy and Bartness (2004) (53)| Siberian WAT | 9-12 | M    | 21-54 | 1/2-3   | None        | 12 or 13 | NR   | -/-/-| -/-/↑ | -/↑/-| -  |
| Lacy and Bartness (2005) (52)| Siberian WAT | 9-12 | M    | 65-88 | 1-2/4-6 | None        | 12       | S     | ↓   | ↑  | -  | -  | 0  |
| Rats                       |              |     |      |     |         |                  |         |       |       |    |    |    |    |
| Torres-Villabos et al. (2016) (28)| Wistar WAT | 21  | F    | 39   | 2/4     | D           | 26       | S     | ↓   | ↓  | -  | -  | -  |
| Foster et al. (2010) (30)  | Long Evans   | 28  | F    | 20   | 2/2     | None        | 8        | S     | ↑   | ↑  | -  | -  | o  |

*aOutcome results labeled as follows: no change (-), increase (↑), decrease (↓), omitted (x), mixed results (z), and not comparable or inconclusive (o), and articles with multiple experiments separated with ‘/’. Entry left blank if study did not record outcomes for body weight (BW), body fat (BF), food intake (FI), and circulating biomarkers (CB).

*bAT, adipose tissue. White adipose tissue denoted WAT, and brown adipose tissue denoted BAT.

dFactors included in study design are abbreviated as follows: D, diet; and G, genotype/genetic.

eDuration of study post surgery in weeks.

fHousing of animal post surgery: S, single housed.

NR, not reported.
In summary, BF at termination in lipectomy studies (summarized in Table 1) had no change \((n = 23)\), increased \((n = 5)\), decreased \((n = 4)\), were inconclusive \((n = 12)\), or were mixed \((n = 2)\) when comparing total BF measures at baseline to termination. For transplantation studies (summarized in Table 2), no changes \((n = 3)\), increases \((n = 1)\), decreases \((n = 1)\), or inconclusive \((n = 3)\) changes in BF were observed when comparing BF levels at baseline to termination (details on the effects of transplantation or combined surgeries on total BF can be found in Supporting Information Figure S1A-B). Lastly, BF in studies with both transplanted and lipectomized fat (summarized in Table 3) had no change \((n = 1)\), was inconclusive \((n = 1)\), increased \((n = 2)\), decreased \((n = 2)\), or had mixed results \((n = 4)\) at termination compared with baseline levels (summarized in Figure 3A).
Food intake
It is well understood that adipose tissue produces and releases leptin, which has a major role in regulating energy intake and expenditure (25). Thus, surgical manipulation of total body adiposity might alter circulating leptin and other adipose-derived hormone levels, contributing to acute and/or chronic changes in energy intake. To better understand the role of energy intake due to altered total BF after surgery, this section summarizes findings on energy consumption, which we refer to as FI and was reported in 41 (64%) studies (8,11-15,17,19,21-25,27-31,33-35,37,42,47-49,51-61,66,71,74). Energy intake before termination was compared with baseline levels and described as either increased, decreased, or no observed change. Sham-operated or experimental groups had lower FI within the first 24 hours following surgery, likely because of the stress of the procedure and effects of anesthesia. The observed FI was similar among sham-operated and experimental groups fed chow diets in mice (33,58,61) and higher in HFD-fed groups (29,59). C57BL/6J mice with WAT transplanted had lower FI compared with the control group (40). No differences in FI were observed based on lipoectomy in Osborne-Mendel rats (8), male Wistar rats (19,21,25), and Lister hooded rats (29). In male Sprague Dawley rats, one study demonstrated no differences in FI (15). In another study, FI was temporarily suppressed following lipoectomy and returned to baseline by 4 weeks of recovery (14). Lean and obese Zucker rats demonstrated no significant differences in FI in sham-operated versus lipoctomized animals, but FI was greater in obese rats compared with lean rats (27). No significant differences in FI based on lipoectomy in adult Siberian hamsters (50,54), Syrian hamsters (42), and Mongolian gerbils (74) were observed.

In lipoectomy studies (n = 33), there was either no change (n = 27), increases (n = 3), decreases (n = 1), or mixed results (n = 2) of energy intake at the end of the study compared with baseline measures. FI reported in studies with both lipoectomy and transplantation (n = 8) observed no changes (n = 6) or mixed results (n = 2) of energy intake when comparing final measures with baseline levels (details on the effects of transplantation or combined surgeries on overall FI can be found in Supporting Information Figure S1B). Thus, FI overall was not significantly impacted by surgical manipulations of BF after animals recovered from the surgery. Instead, FI appeared to be influenced by the availability and palatability of HFD in two of the three studies, in which significantly higher energy intake was observed in mice fed a HFD (29,59).

Circulating biomarkers
The effects of the surgical removal of adipose tissue on changes in adipokines, cytokines, and other circulating biomarkers that the adipose organ may produce or secrete have been reviewed in adipokines, cytokines, and other circulating biomarkers that the adipose organ may produce or secrete have been reviewed in adipose tissue and sera of animals undergoing obesity-related procedures and effects of anesthesia. The observed FI was similar among sham-operated and experimental groups fed chow diets in mice (33,58,61) and higher in HFD-fed groups (29,59). C57BL/6J mice with WAT transplanted had lower FI compared with the control group (40). No differences in FI were observed based on lipoectomy in Osborne-Mendel rats (8), male Wistar rats (19,21,25), and Lister hooded rats (29). In male Sprague Dawley rats, one study demonstrated no differences in FI (15). In another study, FI was temporarily suppressed following lipoectomy and returned to baseline by 4 weeks of recovery (14). Lean and obese Zucker rats demonstrated no significant differences in FI in sham-operated versus lipoctomized animals, but FI was greater in obese rats compared with lean rats (27). No significant differences in FI based on lipoectomy in adult Siberian hamsters (50,54), Syrian hamsters (42), and Mongolian gerbils (74) were observed.

In lipoectomy studies (n = 33), there was either no change (n = 27), increases (n = 3), decreases (n = 1), or mixed results (n = 2) of energy intake at the end of the study compared with baseline measures. FI reported in studies with both lipoectomy and transplantation (n = 8) observed no changes (n = 6) or mixed results (n = 2) of energy intake when comparing final measures with baseline levels (details on the effects of transplantation or combined surgeries on overall FI can be found in Supporting Information Figure S1B). Thus, FI overall was not significantly impacted by surgical manipulations of BF after animals recovered from the surgery. Instead, FI appeared to be influenced by the availability and palatability of HFD in two of the three studies, in which significantly higher energy intake was observed in mice fed a HFD (29,59).

Genetic, environmental, developmental, and behavioral factors
As noted previously, the maintenance of energy balance requires the complex integration of information regarding energy stores, energy expenditure, and energy intake. These regulatory responses do not occur in isolation and are proposed to be sensitive to interactive effects of multiple factors (e.g., genetic mutations, metabolic response to environmental conditions, etc.). Several other factors were evaluated in 43 (67%) studies (in addition to surgery) relating to energetics and BF regulation (summarized in Figure 2D and Tables 1–3). The effects of genotype, strains, or genetic factors were explored in 18% of included studies. Other factors examined were age (4%), injection of external chemical agents (10%), diet (24%), exercise (6%), photoperiod (3%), and temperature (6%). Each of these experimental factors are summarized here.

Genotype. Several studies have assessed changes in BW and BF based on genotype to determine whether adipose compartment characteristics, such as the regulation of differentiation and accumulation of new adipocytes, differ based on animal strains or genetic factors (34,38,61,72). These characteristics were reported for 13 (18%) of the included studies (27,38). Comparisons were made between male C57BL/6J ob/ob and either wild-type mice (39), their lean littersmates (72), or mice with green fluorescent protein as a transgene on the beta-actin promoter (34). Additionally, female obese Zucker rats and lean rats (12,26,27,34,39,60-62,64,65,67,72), female ob/ob mice (38), male LIRKO mice (60), male PPAR-γ knockout transgenic mice and homozygous LoxP control mice (61), male dwarf homozygous mice (62), male and female wild-type and db/db mice (65), and male athymic mice of the BALB/c strain (67) were evaluated. Most studies showed nonsignificant changes in BW, BF, or FI following surgery compared with the control groups. However, BW, BF, and FI increased after surgery in female Zucker rats (12,27).

Age. Few studies (n = 3, 4%) included age as a factor in the experimental design, in which surgeries were performed for more than one age group to determine if final BW and/or BF was influenced by age at the time of surgery (57,63,64). The proliferation and regeneration of BF is no longer at its peak once small mammals reach adulthood (69). The small mammals’ ages of “maturity” we considered are as follows: 3 to 6 months for mice, 7 months for rats, 6 months for rabbits, 3 months for gerbils, 4 to 6 months for hamsters, 11 to 12 months for squirls, and 3 to 4 months for prairie voles. It is not clear to what extent the age of the animal affects BF compensation following surgical alterations of fat. New Zealand rabbits ranging from 24 to 144 weeks old which underwent lipoectomy of WAT had no significant changes in BW, BF, or FI (57). Male and female mice (New Zealand obese Lepr db/db, and Lepr wild type) aged 8 to 52 weeks that had fat transplants did not report
BW, BF, and FI, and thus the effects of age in these studies (63,64) were inconclusive. Age at time of surgery and BF manipulations are summarized in Figure 4.

Chemical injections. Compensation of BW and BF after surgical manipulation of fat combined with injections of external chemical agents were reported in 7 (10%) of the studies (22,41,44-46,51,72) and may give insight into the metabolic effects of surgery when combined with chemical agents. Siberian hamsters and prairie voles injected with the antigen keyhole limpet haemocyanin post surgery had nonsignificant changes in BW and BF (44-46,51). BW was significantly decreased in both lipectomized control and treated with monosodium glutamate (22). Male C57BL/6J ob/ob mice and their lean littermate mice with WAT transplanted and injected with gold-thioglycoside post surgery had inconclusive changes in BW and BF because statistical comparisons were not performed (72). Gold-thioglycoside-injected female CBA/J mice with WAT transplanted had decreased BW and BF, but this was due to calorie restriction of the stock-fed diet (41).

Diet. The effects of dietary factors on BW and BF compensation and FI behavior was observed in 17 (24%) studies included in this review (8-10,17,21,28,29,31-33,35,41-43,54,59,60). Groups of animals such as rats, mice, or hamsters were fed ad libitum chow diets or alternative ad libitum diets post surgery. Alternative diets given to animals were defined in the literature as follows: (1) HFD, consisting of 45% to 60% energy from fat (8-10,21,28,32,33,35,43,60); (2) high-carbohydrate diet, with 28%, 14%, and 58% energy from protein, fat, and carbohydrate, respectively (28); (3) HFD-Western, with 45% energy from fat (31); (4) cafeteria diet, such as “various energy dense human foods” (29,59); or (5) low-fat diet, with 13%, 65%, and 22% of kilocalories from fat, carbohydrate, and protein, respectively (42,43). The wide range of macronutrient composition in the diets reported makes comparisons across studies difficult.

Studies of HFD-fed Osborne-Mendel rats (10), Sprague Dawley rats (17), C57BL/6 mice (33), and LIRKO mice (60) reported increased BW, BF, or FI compared with groups fed standard chow diets. Other HFD studies of Osborne-Mendel rats (8,9), Wistar rats (21), C57BL/6 (31), cafeteria-fed Lister hooded rats (29) and C3H Manchester mice (59)

### Table 4

| Reference | Study design | Surgery type | Animal | ATb | Factorc | Circulating biomarkersa |
|-----------|-------------|--------------|--------|-----|---------|-------------------------|
| Lipectomy |            |              |        |     |         | TG  | Leptin | IL-6 | TNF-α |
| Borst et al. (2005) | Transplantation | Rats | Sprague Dawley | WAT | G     | ↑   |        |      | -     |
| Bueno et al. (2005) | Transplantation | Wistar | C     | ↑   |         |      |        |      | -     |
| Bueno et al. (2011) | Transplantation | Wistar | None | ↓   |         |      |        |      | -     |
| Dettlaff-Pokora et al. (2015) | Transplantation | Mice | C57BL/6/J | WAT | D,G   |      |        |      | -     |
| Harris et al. (2002) | Transplantation | Mice | C57BL/6J | WAT | G     | ↑   |        |      |        |
| Emanuelli et al. (2014) | Transplantation | Mice | LIRKO | WAT | G     | ↑   |        |      |        |
| Cox-York et al. (2015) | Transplantation | Mice | C57BL/6 | D    | ↑↑   |      |        |      | -     |
| Booth et al. (2016) | Transplantation | Mice | FKO-gamma | G    | -     | ↓   |        |      | -     |
| Mulder et al. (2016) | Transplantation | Mice | C57BL/6/J | D    | ↓    |      |        |      | -     |
| Weber et al. (2000) | Transplantation | Hamsters | Syrian | WAT | D    | ↑   |        |      | -     |
| Demas and Sakaria (2005) | Transplantation | Hamsters | Prairie voles, Siberian hamsters | C     | ↑     |      |        |      | -     |
| Dailey and Bartness (2008) | Transplantation | Mice | Syrian | WAT | D    | ↑   |        |      | -     |
| Harris (2015) | Transplantation | Mice | db/db | WAT | G     | ↑   |        |      | -     |
| Hocking et al. (2015) | Both | C57BL6/J | D    | ↑↑   | ↑    | ↑    |        |      |      |
| Rooks et al. (2004) | Transplantation | Mice | Sprague Dawley | WAT | None | z   |        |      | -     |
| Tran et al. (2008) | Transplantation | Mice | C57BL/6 | G    | ↓    | ↑    |        |      |      |
| Foster et al. (2010) | Transplantation | Mice | Long Evans | None | -    | ↑    |        |      |      |
| Foster et al. (2013) | Transplantation | Mice | C57BL/6 | None | ↑    | ↑    |        |      |      |
| Liu et al. (2015) | Transplantation | Mice | C57BL/6 | BAT | None | ↓    | ↓    |        |      |
| Lacy and Bartness (2005) | Transplantation | Hamsters | Syrian | WAT | None | -   |        |      | -     |

**Note:**
- Circulating biomarkers at final time point labeled as follows: no change (-), increase (↑), decrease (↓), or mixed results (z).
- AT, adipose tissue. White adipose tissue denoted WAT, and brown adipose tissue denoted BAT.
- Factors included in the study design are abbreviated as follows: C, chemical injection; D, diet; G, genotype/genetic; and E, exercise trained.
reported increased BF and FI following the diet and surgery compared with chow-fed animals and increased BW only in Stephens et al. (29). Similarly, an HFD led to increased BW and FI in C57BL/6 mice following WAT being removed (35) or transplanted (32) compared with controls. In contrast, male Wistar rats that underwent BAT and WAT lipectomy or transplantation and were fed either a HFD or high-carbohydrate diet had decreased BW and BF (28). Other studies of Syrian hamsters with WAT removed observed increased BW, BF, and FI on a HFD compared with a low-fat diet, independent of surgery type (42, 43). Female CBA/J mice with WAT transplanted had decreased BW and BF, but this was due to calorie restriction of the stock-fed diet (used as an alternative to chow diet) (41), in which animals were allowed 2.2 g/day or 3.3 g/day of the stock diet. Siberian hamsters with lipectomized WAT had decreased BW after surgery with a restricted diet, approximately 65% less food than ad libitum animals (54). One out of seventeen studies had designed or reported methods that would support reporting of diet and group interactions in statistical analyses (29).

**Exercise.** The effects of exercise training were summarized for 4 (6%) of the studies included in the review (18, 23, 24, 48). Female Wistar rats aged 8 weeks (24) or 13 weeks (23) had WAT removed, and after 1 week, were exercise trained by continuous swimming for 15 to 30 minutes/day. Water tanks ranged between 32°C and 36°C (23) or 28°C and 32°C (24), and animals had weights attached to the tail equivalent to 5% of the animal’s BW. Changes in BW, BF, and FI at termination were mostly not significantly different. Female Wistar rats aged 6 to 8 weeks with WAT removed that were exercise trained on a motor-driven treadmill (Collins Co., Braintree, Massachusetts) for 16 weeks post surgery had no significant changes in BW or BF compared with control groups (18). However, exercise-trained male Siberian hamsters with WAT removed had decreased BF but no significant changes in BW or FI (48). None of the studies tested for interactions between exercise program and group.

**Photoperiod and temperature.** Changes in energy balance could be modified by altering the animal’s exposure to photoperiods and housing temperatures, and some species may be more sensitive to these change than others (12, 27, 49). Here, 2 (3%) and 4 (6%) of studies incorporated photoperiod- (49, 54) or temperature-related (12, 27, 59, 74) factors in the study design, respectively. Siberian hamsters aged 8 to 12 weeks with WAT removed in conjunction with photoperiod treatment (e.g., long day vs. short day) had no significant changes in BW and FI and inconclusive results for BF (49). Another study of lipectomized Siberian hamsters exposed to long day (control and lipectomized) had greater BW compared with short-day animals (control and lipectomized) (54). Lean and obese Zucker rats aged 4 to 7 weeks with BAT removed housed in 25°C conditions had differing results for BW (increased or not significant), BF (increased, decreased, or not significant), and FI (decreased or not significant) (12, 27). Manchester black mice with removed BAT housed in 4°C for 24 hours did not change BW or BF (58). Furthermore, Mongolian gerbils with removed BAT had decreased BW, BF, and leptin and increased FI in cold environmental settings (74).

**Conclusion**

The body’s ability to respond to biological triggers to regulate BF and remain within a set point (or range) by altering FI (energy) or energy expenditure have been studied through lipectomy models. In particular, the hypothalamus has been hypothesized to be responsible for the hormonal, metabolic, and behavioral factors triggered by various input and output signals that act to passively or actively regulate total BF content and is discussed in a prior review published in 2001 (75). Though lipectomy models offer some insight into how lipid (energy) stores and body composition are regulated, the input and output signals are not well defined. This scoping review summarized what has been reported to date about the regulation of energetics and BF after adipose tissue was surgically manipulated in small mammals. Using two search databases (PubMed and Scopus), a total of 64 studies were identified based on the eligibility and inclusion and exclusion criteria. Out of 64 studies we have identified, 35 studies have been published since a prior review was published in 2001 (75), indicating a continued degree of research interest in this topic. Most studies examined lipectomy (72%) and manipulated fat in mice (35%) or rats (35%). It was found that most animals were able to recover weight equivalent to their baseline level within weeks or months after the surgery (most experiments ranged from 3 to 43 weeks) and with a range of 5% to 80% of BF manipulated (reported in 40 studies).

To better understand the energy and body-composition regulation, more studies are needed in different contexts, such as age and genetic factors, yet many of these animal studies included in this review do not translate easily to human and clinical applications. For example, among the included studies, decreased FI (energy) after lipectomy was observed, but there was no significant difference in intake over time for chow-fed animals. In contrast, HFD led to greater postsurgery BF or BW, likely because of the palatability and energy-density of foods. To elucidate the homeostatic processes underlying energetics and BW regulation, IL-6 and TNF-α levels reportedly increased after surgery, whereas changes in TG and leptin levels either increased or decreased based on adipose tissue, diet, and genotype variations. The effect of body temperature, hunger, and exercise were not well documented. Hence, more studies are needed because many reported in this review were of limited contribution because of inadequate mechanistic data, small number of studies in female animals, or a lack of statistical tests reported.

Our present findings suggest that the surgical manipulation of BF, specifically lipectomy as a single intervention, does not have consistent, long-term effects on reducing BW or BF; implying that biological feedback mechanisms act to resist long-term changes of BW or BF. In recent decades, the mathematical modeling of BW, composition, and energetics has advanced substantially and is the key complement to the data we summarize in this scoping review. For example, previous work by Thomas et al. (76, 77) and Hall et al. (78-80) combined energy balance modeling with experimental data to study the regulation of body composition and energetics. That is, mechanistic experiments combined with modeling approaches may be useful for understanding the underlying biological feedback mechanisms that act to resist long-term changes in BW post lipectomy. Though developing a model to capture the factors involved in regulating changes in energetics and body composition is not simple, the predictions produced by these models can be tested against experimental data to better elucidate the sensory or effector functions that act to regulate BW or BF. For example, if we have a mathematical model that allows predictions of a vector of variables, denoted \( Y \), as a function of an input vector of variables, denoted \( x \), and a vector of parameters, denoted \( \theta \), we could, in the most generic terms, represent the predicted values of \( Y \), denoted \( \hat{Y} = f(x, \theta) \). If we have two competing models, such as Models 1 and 2, that make alternative
predictions given the same input values of x, then we can represent this as: \( \hat{y} = f_1(x, \beta_1) \) for Model 1 versus \( \hat{y} = f_2(x, \beta_2) \) for Model 2. To the extent that the two models make different predictions, they offer the opportunity to test two competing theories as discussed by Meehl (81) in his classic paper on theory testing and making point predictions. Moreover, once existing mathematical models are extended or elaborated to make point predictions for responses of behavior anatomy, or physiology after surgical perturbations of body energy storage, then the literature we have reviewed here could be utilized to potentially test the fit of those competing theories.

Several methodological gaps in the included studies limit the ability to address the set point or settling point theories. To build on this body of work, mechanistic experimental studies and data on key variables influencing the regulation of energetics and BF or BW are needed. While leptin signaling regulated BW and/or sensing in a negative-feedback system, Jansson et al. (82) identified osteocytes as a regulator of fat mass homeostasis independent of leptin (or “gravitostal”), which could be further studied. Recent technologies such as gene knockdowns, knockouts, and tissue-specific genetic manipulations may add knowledge of fat regeneration, and selection of individual mutants within specific pathways proposed to mediate the energetic homeostasis could be considered. Measures on adipose tissue (e.g., cell size/number), energy balance (e.g., energy expenditure/intake, testing at thermoneutral conditions), and hormones (see Table 4) incorporated into models allow for the assessment of long-term changes in BW or BF after adipectomy.

In summary, findings of this review combined with mathematical models allow us to test hypotheses about BW and BF regulation and to inform the designs of studies to more rigorously test such hypotheses going forward.

Acknowledgments

The authors would like to acknowledge Dr. Jeffrey Albert, Dr. Amit Hagar, Dr. Barry Levin, Dr. Diana Thomas, Dr. Kevin Hall, and the anonymous reviewer(s) for their helpful feedback and suggestions on the contents in this manuscript. They would also like to thank Anne Lovell for her help with designing the animal drawings.

© 2019 The Obesity Society

References

1. Müller MJ, Bosy-Westphal A, Heymsfield SB. Is there evidence for a set point that regulates human body weight? F1000 Med Rep 2010;2:59. doi:10.3410/M2.59
2. Speakman JA, Levitsky DA, Allison DB, et al. Set points, settling points and some alternative models: theoretical options to understand how genes and environments combine to regulate body adiposity. Dis Model Mech 2011;4:733-745.
3. Kennedy GC. The hypothalamic control of food intake in rats. Proc R Soc Lond Biol Sci 1990;137:535-549.
4. Liebelt RA, Ichinoe S, Nicholson N. Regulatory influences of adipose tissue on food intake and body weight. Ann N Y Acad Sci 1965;131:559-582.
5. Enzi G, Tremolada C, Baritussio A. Body weight increase, food intake and glucose tolerance in lipoatectomized rats. J Physiol Sci 1998;102:1122-1127.
6. Bailey JW, Anderson DB. Rate of fat compensation and growth efficiency of lipoatectomized Sprague Dawley rats. J Nutr 1980;110:1785-1792.
7. Kral JG. Surgical reduction of adipose tissue in the male Sprague Dawley rat. Am J Physiol 1976;231:1090-1096.
8. Larson KA, Anderson DB. The effects of lipoatectomy on remaining adipose tissue depots in the Sprague Dawley rat. Growth 1978;42:469-477.
9. Faust IM, Johnson PR, Hirsch J. Adipose tissue regeneration in adult rats. Proc Exp Biol Med 1979;161:111-114.
10. Faust IM, Johnson PR, Hirsch J. Surgical removal of adipose tissue alters feeding behavior and the development of obesity in rats. Science 1977;197:393-396.
11. Moore BJ, Inokuchi T, Stern JS, Horwitz BA. Complete adipose lipoatectomy leads to increased fat deposition in Obese-Menderan rats. Am J Physiol 1985;240(2 Pt 2):R231-R235.
12. Horwitz BA, Inokuchi T, Moore BJ, Stern JS. The effect of brown fat removal on the development of obesity in Zucker and Obese-Menderan rats. Int J Obes 1985;9(suppl 2):43-48.
13. Toros SE, Conover CF, Bagby GJ. Association of resistin with visceral fat and muscle insulin resistance. Cytokine 2005;32:39-44.
14. Bailey JW, Anderson DB. Rate of fat compensation and growth efficiency of lipooatectomized Sprague Dawley rats. J Nutr 1980;110:1785-1792.
15. Michel C, Cabanac M. Lipoatectomy, body weight, and body weight set point in rats. Physiol Behav 1999;66:473-479.
16. Bueno AA, Habibante CA, Oyama LM, Estadela D, Ribeiro EB, Oller do Nascimento CM. White adipose tissue net growth after partial lipoatectomy in high fat diet induced obese Wistar rats. J Physiol Sci 2011;61:55-63.
17. Bueno AA, Estadela D, Habibante CA, et al. Lipid metabolism of monosodium glutamate obese rats after partial removal of adipose tissue. Physiol Rev 2005;54:57-65.
18. Habibante CA, Oyama LM, Bueno AA, et al. Exercise training in rats impairs the remnescence of white adipose tissue after partial lipoatectomy. Eur J Appl Physiol 2010;109:371-377.
19. Coelho DF, Gualano B, Artioli GG, et al. Exercise training attenuates lipoatectomy-induced impaired glucose tolerance in rats. Endocr Regul 2009;43:107-116.
20. Dettafl-Pokora A, Sledzinski T, Swierczynski J. Up-regulation of orexigenic and down-regulation of anorexigenic neuropeptide gene expression in rat hypothalamus after partial lipoatectomy. J Appl Biomed 2015;13:105-112.
21. Lissika TG, Dellon LA, Im M, Angel MF, Plotnick L. Effect of lipoatectomy on growth and development of hyperinsulinemia and hyperlipidemia in the Zucker rat. Plast Reconstr Surg 1998;102:1122-1127.
22. Stern JS, Inokuchi T, Castonguay TW. Scapular brown fat removal enhances development of adiposity in cold-exposed obese Zucker rats. Am J Physiol 1984;246:E918-E926.
23. Torres-Villalobos G, Hamden-Perez N, Diaz-Villalobos A, et al. Autologous subcutaneous adipose tissue transplants improve adipose tissue metabolism and reduce insulin resistance and fatty liver in diet-induced obese rats. Physiol Rep 2016;4:LPR.12390-12390.
24. Stephens DN, Nash SC, Proffitt C. Dietary obesity in adult and weaning rats following removal of interscapular brown adipose tissue. Pflugers Arch 1981;392:7-12.
25. Foster MT, Shi H, Seeley RJ, Woods SC. Transplantation or removal of intra-abdominal adipose tissue prevents age-induced glucose insensitivity. Physiol Behav 2010;101:282-288.
26. Cox-York K, Wei Y, Wang D, Pagliassotti MJ, Foster MT. Lower body adipose tissue removal decreases glucose tolerance and insulin sensitivity in mice with exposure to high fat diet. Adipocyte 2015:32-43.
27. Hocking SL, Stewart RL, Brandon AE, et al. Subcutaneous fat transplantation alleviates diet-induced glucose intolerance and inflammation in mice. Diabetologia 2015;58:1587-1600.
28. Mulder P, Morrison MC, Wielinga PY, van Duyvenvoorde W, Kooistra T. Kleemann R. Surgical removal of inflamed epididymal white adipose tissue attenuates the development of non-alcoholic steatohepatitis in obesity. Int J Obes (Lond) 2016;40:675-684.
29. Tran TT, Yamamoto Y, Gesta S, Kahn CR. Beneficial effects of subcutaneous fat transplantation on metabolism. Cell Metab 2008;9:410-420.
30. Foster MT, Sofic S, Caldwell J, Kohli R, deKloet AD, Seeley RJ. Subcutaneous adipose tissue transplantation in diet-induced obese mice attenuates metabolic dysregulation while removal exacerbates it. Physiol Rep 2013;1:e00015. doi:10.1136/physrep.2012.00015.
31. Foster MT, Shi H, Sofic S, Kohli R, Seeley RJ, Woods SC. Transplantation of non-visceral fat to the visceral cavity improves glucose tolerance in mice: investigation of hepatic lipids and insulin sensitivity. Diabetologia 2011;54:2890-2899.
32. Liu X, Wang S, You Y, et al. Brown adipose tissue transplantation reverses obesity in Ob/Ob mice. Endocrinology 2015;156:2461-2469.
33. Chlouerakis C, Hopcinski D. Lipoatectomy in obese hyperglycemic mice (obob). Metabolism 1974;23:133-137.
34. Harris RBS, Hausman DB, Bartness TJ. Compensation for partial lipoatectomy in mice with genetic alterations of leptin and its receptor subtypes. Am J Physiol Regul Integr Comp Physiol 2002;283:R1-10.
35. Gunawardana SC, Piston DW. Reversal of type 1 diabetes in mice by brown adipose tissue transplantation. Diabetes 2012;61:674-682.
36. Ashwell M, Meade CJ. Obesity: can some fat cells enlarge while others are shrinking? Lipids 1991;26:475-478.
37. Hamilton JM, Wade GN. Lipoatectomy does not impair fattening induced by short photoperiods or high-fat diets in female Syrian hamsters. Physiol Behav 1988;43:85-92.
60. Emanuelli B, Vienberg SG, Smyth G, et al. Interplay between FGF21 and insulin

59. Connolly E, Carnie JA. Responses to cafeteria feeding in mice after the removal of

58. Connolly E, Morrisey RD, Carnie JA. The effect of interscapular brown adipose tissue

57. Reyne Y, Nougues J, Vezinhet A. Adipose tissue regeneration in 6-month-old and

56. Forger NG, Dark J, Stern JS, Wade GN, Zucker I. Lipectomy influences white adipose

55. Dark J, Forger NG, Stern JS, Zucker I. Recovery of lipid mass after removal of adipose

54. Mauer MM, Bartness TJ. Short-day-like body weight changes do not prevent fat pad

53. Lacy EL, Bartness TJ. Autologous fat transplants influence compensatory white adi-

52. Weber RV, Buckley MC, Fried SK, Krat JG. Subcutaneous lipomectomy causes a metabolic syndrome in hamsters. Am J Physiol Regul Integr Comp Physiol 2000;279:R936-R943.

51. Demas GE, Sakaria S. Leptin regulates energetic tradeoffs between body fat and hu-

50. Demas GE, Drazen DL, Nelson RJ. Reductions in total body fat decrease humoral immunity. Proc Biol Sci 2005;272:1845-1850.

49. Shi H, Bartness TJ. White adipose tissue sympathetic nerve denervation mimics lipomectomy-induced compensatory increases in adiposity. Am J Physiol Regul Integr Comp Physiol 2005;289:R514-R520.

48. Dailey ME, Bartness TJ. Fat pad-specific effects of lipectomy on foraging, food hoard-

47. Shi H, Bowers RR, Bartness TJ. Norepinephrine turnover in brown and white adipose

46. Shi H, Bartness TJ. White adipose tissue sensory nerve denervation mimics lipectomy-

45. Mauer MM, Harris RB, Bartness TJ. The regulation of total body fat: lessons learned

44. Darcy J, McFadden S, Fang Y, et al. Brown adipose tissue function is enhanced in long-lived, male ames dwarf mice. Endocrinology 2016;157:4744-4753.

43. Weber RV, Buckley MC, Fried SK, Krat JG. Subcutaneous lipomectomy causes a metabolic syndrome in hamsters. Am J Physiol Regul Integr Comp Physiol 2000;279:R936-R943.

42. Demas GE, Sakaria S. Leptin regulates energetic tradeoffs between body fat and hu-

41. Demas GE, Drazen DL, Nelson RJ. Reductions in total body fat decrease humoral immunity. Proc Biol Sci 2005;272:1845-1850.

40. Shi H, Bartness TJ. White adipose tissue sympathetic nerve denervation mimics lipomectomy-induced compensatory increases in adiposity. Am J Physiol Regul Integr Comp Physiol 2005;289:R514-R520.

39. Shu H, Bowers RR, Bartness TJ. Noradrenaline turnover in brown and white adipose

38. Dailey ME, Bartness TJ. Fat pad-specific effects of lipectomy on foraging, food hoard-

37. Reyne Y, Nougues J, Vezinhet A. Adipose tissue regeneration in 6-month-old and

36. Demas GE, Drazen DL, Nelson RJ. Reductions in total body fat decrease humoral immunity. Proc Biol Sci 2003;270:905-911.