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INSECT FAT BODY: ENERGY, METABOLISM, AND REGULATION

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Abstract

The fat body plays major roles in the life of insects. It is a dynamic tissue involved in multiple metabolic functions. One of these functions is to store and release energy in response to the energy demands of the insect. Insects store energy reserves in the form of glycogen and triglycerides in the adipocytes, the main fat body cell. Insect adipocytes can store a great amount of lipid reserves as cytoplasmic lipid droplets. Lipid metabolism is essential for growth and reproduction and provides energy needed during extended nonfeeding periods. This review focuses on energy storage and release and summarizes current understanding of the mechanisms underlying these processes in insects.

INSECT FAT BODY: AN OVERVIEW

The insect fat body plays an essential role in energy storage and utilization. It is the central storage depot for excess nutrients. In addition, it is an organ of great biosynthetic and metabolic activity (77). Fat body cells not only control the synthesis and utilization of energy reserves—fat and glycogen—but also synthesize most of the hemolymph proteins and circulating metabolites. Large amounts of relevant proteins, such as storage proteins used as an amino acid reservoir for morphogenesis, lipophorins responsible for the lipid transport in circulation, or vitellogenins for egg maturation, are secreted by the fat body (74). Most of the insect's intermediary metabolism takes place in this organ, including lipid and carbohydrate metabolism, protein synthesis, and amino acid and nitrogen metabolism. Some metabolic processes are stage specific such as the synthesis and secretion of storage proteins into the hemolymph that occur in the feeding larva or the synthesis of vitellogenin in adult insects.

To perform multiple metabolic functions to fulfill the changing physiological needs of the insect during development, the fat body must be able to integrate signals from other organs. Many of these functions are hormonally regulated, and thus the fat body is the target organ of several hormones (47,107). At the same time, the fat body responds to the metabolic requirements of the organ itself. Therefore, several metabolic processes in the fat body must be tightly coupled to a number of metabolic pathways.

Physiological systems to sense nutrient reserves are expected in all organisms, and in insects nutrient sensing itself appears to be the domain of the fat body (87). Studies of Drosophila melanogaster and, more recently, mosquitoes have shown that the fat body specifically expresses aminoacid transporters that function as nutrient sensors (14,61). The level of nutrient reserves accumulated in the fat body modulates several important aspects of the insect's life such as the rate of insect growth, the timing of metamorphosis, and egg development (87). The fat body coordinates insect growth with metamorphosis or reproduction by storing or releasing components central to these events. For example, the synthesis of vitellogenin in the fat body of Aedes aegypti female mosquitoes is

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transcriptionally upregulated after a blood meal by a mechanism involving a cascade of reactions beginning at the fat body plasma membrane, where specific amino acids present in the hemolymph are sensed by amino acid transporters. This signal activates an evolutionarily conserved nutritional signaling cascade—target of rapamycin pathway that—results in the translation of a specific transcriptional activator of vitellogenin gene expression. As a result, the synthesis of vitellogenin is stimulated, reaching a peak 30 h after the blood meal (94).

In addition to its role related to storage and utilization of nutrients, the fat body is an endocrine organ (65), produces several antimicrobial peptides (44), and participates in detoxification of nitrogen metabolism (74). Clearly, the fat body is a multifunctional organ, as reflected by the transcriptome pattern observed from D. melanogaster and Bombyx mori (32,70).

Whereas many insect tissues have vertebrate analogs, the fat body is an organ unique to insects (77). The fat body is a relatively large organ distributed throughout the insect body, preferentially underneath the integument and surrounding the gut and reproductive organ (36). Unlike the solid structure of the liver, the insect fat body is a loose tissue. Generally, the organ is arranged in thin lobes that are bathed by the hemolymph. This type of organization provides maximal exposure to the hemolymph. Ready access to hemolymph is vital for the organism to adjust appropriately to the changes in the concentration of energy precursors in circulation. This is especially critical under conditions of extreme energy demand such as insect flight, in which the metabolic rate increases 50-to 100-fold (21). Because only small amounts of energy precursors are present in the flight muscle, the energy consumed during flight is provided by circulating energy substrates (trehalose, lipids, and proline), which are replenished by the fat body (21). The fat body arrangement that facilitates close contact between the hemolymph and the fat body cell defines a well-suited system highly adapted to the unique physiology of insects (74).

The fat body is structurally heterogeneous and exhibits regional differentiation that can be distinguished morphologically. Although some functions of the fat body are present all over the tissue, other functions are predominantly localized in certain regions (62,69). The role of the fat body changes at different life stages, at which time it may be drastically altered in its cytological appearance (1).

The basic cell of the fat body is the adipocyte, characterized by the presence of numerous lipid droplets. Triglycerides are the major component of the lipid droplets, and at the end of the feeding period lipid droplets occupy most of the intracellular space along with glycogen and protein granules (36). A less common fat body cell is the urocyte, which is specialized for urate storage. Urocytes have been described in the fat bodies of cockroaches and locusts but are not present in Lepidoptera. In these insects adipocytes themselves acquire the ability to accumulate urate at the end of the larval stage, and the urate contents disappear during development of the adult (137). A third type of fat body cell is the mycetocyte, found in cockroaches, aphids, and some Hemiptera. These cells contain microorganisms living inside vacuoles in permanent symbiosis with the insect (36). Symbionts have been speculated to produce essential components that are not incorporated with the diet (39). In some insects oenocytes can be found distributed among adipocytes. Unlike the fat body, which has a mesodermal origin, oenocytes are derived from the ectoderm. These are specialized cells that can be associated with either epidermal cells or fat body cells whose function is linked with the synthesis of cuticular lipids, proteins, and hydrocarbons (79). A recent study reported that several genes involved in lipid-metabolism functions of the vertebrate liver are expressed in Drosophila oenocytes and may have a role in lipid mobilization during starvation (59).

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The storage function of the fat body is fundamental in the life of holometabolous insects. During the larval feeding stages, energy reserves are accumulated to be used during metamorphosis as well as to provide reserves for the new adult. Insects need to accumulate at least a minimal amount of nutrient storage to survive through metamorphosis (87). In addition, the amount of nutrient stored in larvae has important consequences for the adult life, as smaller size results in reduced fecundity (27). Adult insects that do not feed rely on these reserves to support life and reproduction. On the other hand, insects that feed in the adult stage use dietary supply to improve their energy status, particularly in preparation for reproduction. Egg development involves a substantial mobilization of reserves from the fat body to the ovaries. The importance of fat body reserves carried over from larval stages for oogenesis is seen in the case of anautogenous mosquitoes, in which blood meal–induced activation of the target of rapamycin–signaling pathway and subsequent egg maturation depend on the accumulation of adequate nutritional reserves during larval development (108). In the next sections we focus on the accumulation of fat body energy reserves and their mobilization.

ACCUMULATION OF ENERGY RESERVES: Storage of Nutrients as Glycogen and Triglycerides

Insects have to expend energy constantly, and if they are not feeding, they must live on reserves accumulated in periods of food abundance. Glycogen and triglyceride are the energy reserves in animal cells. Glucose is stored in a polymeric form, glycogen, that can be readily degraded on demand to be used as a glycolytic fuel (114). Fatty acids stored as triglyceride can be used for energy production through β-oxidation (13). Triglyceride is stored in an anhydrous form, whereas glycogen is stored in a bulky hydrated form. Triglycerides also have a higher caloric content per unit of weight than glycogen, and provide a useful source of water upon oxidation, yielding almost two times more metabolic water than glycogen. These considerations have direct implications on energy metabolism of insects (40). Fat reserves are the most important reserve used by insects to meet their energy demand during diapause (60), to provide energy for the developing embryo (146), and to fuel prolonged periods of flight (21).

Storage of fatty acids and glucose is essential in insects for other functions as well. Fatty acids serve as precursors in the synthesis of eicosanoids and pheromones, and they are needed in substantial amounts for the synthesis of phospholipids and waxes (79,112). Likewise, glucose is used for synthesis of chitin, a major cuticle component (79), and for the synthesis of sugar alcohols, which are needed for adaptation to cold (116) or drought (133).

The amount of reserves accumulated in the fat body differs among insect species. However, lipid is always the major component of the fat body, representing more than 50% of the dry weight (52,141). The amount of glycogen is significantly lower than fat and fluctuates considerably based on motor and short-time feeding activity or environmental conditions (1,81,114,121). Glycogen can be almost depleted after metamorphosis, and the new adult regains glycogen stores once feeding begins (81,141).

Glycogen is synthesized from UDP-glucose mainly derived from dietary carbohydrates or amino acids. UDP-glucose can be used for the synthesis of either glycogen or trehalose, the circulating sugar in the hemolymph (120). When fat body trehalose reaches a certain concentration, its synthesis is inhibited and UDP-glucose is used for glycogen synthesis (46).

Lipid is the main fat body component, and more than 90% of the lipid stored is triglyceride (17,30). Triglyceride is synthesized from dietary carbohydrates, fatty acids, or proteins.

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Lipogenesis in the fat body is similar to that of mammalian tissues (17). The direct precursor for triglyceride synthesis is diglyceride, which can be formed from (a) phosphatidic acid produced by the glycerophosphate pathway, (b) the monoacylglycerol pathway, (c) degradation of phospholipids, or (d) deacylation of triglyceride catalyzed by lipases. Formation of triglyceride is accomplished by esterification of diglyceride that is catalyzed by diacylglycerol acyltransferase in a reaction that uses fatty-acyl-CoA (13). Fatty acids are rapidly taken up by the fat body and readily incorporated into triglyceride and, in smaller amounts, into other glycerides and phospholipids (17,111). The amount of fatty acid or acetate incorporated by the fat body is dependent on the developmental stage and feeding status of the insect (17,80,102,143).

The conversion of carbohydrates, a major component of the insect diet, to lipid in the fat body is well documented (17,27,64,66,131). The capacity of the fat body for lipogenesis from glucose is much higher than that for glycogen synthesis, which explains the higher content of lipid compared to glycogen in the insect fat body. In female A. aegypti 50% of glucose incorporated with the diet is used for the synthesis of lipids, and 35% is used for glycogen synthesis (140). A study of the incorporation of glucose in the last instar larval fat body of the silkworm showed that lipogenesis predominates in the first half of the stage, whereas glycogen synthesis becomes more active at the late stage (66). Lipid stores remain stable during the remainder of larval life and are carried over into pupae and pharate adults. However, much of the glycogen serves as an energy source during the postfeeding larval period, and the rest is preserved to be utilized in pupae and adults. A similar pattern in the utilization of energy reserves is reported for crickets during the final nymphal instar and the molt to the adult (1). Therefore, although both triglyceride and glycogen are predominant reserves stored in the fat body during the last larval period, their fates are rather different.

Rediscovery of the Lipid Droplets

Intracellular storage of triglyceride occurs in specialized cytoplasmic compartments called lipid droplets. Almost all tissues can synthesize and store triglyceride in small lipid droplets, but adipocytes are specialized cells for lipid storage. Growing evidence shows that lipid droplets are not just a passive reservoir of lipids but in fact are dynamic organelles serving a central role in fat and energy metabolism (91). A lipid droplet consists of a core of neutral lipids (triglyceride and cholesterol esters) surrounded by a monolayer of phospholipid and cholesterol, into which specific proteins are embedded or peripherally associated (24,26).

During times of energy demand, the organism accesses triglyceride stores via the coordinated action of lipases (lipolysis). Given the low solubility of triglyceride in phospholipids, the surface of the lipid droplet represents a barrier to the lipases that must access triglyceride molecules. This is one of the reasons lipid droplets play a major role in the regulation of lipolysis. The lipid droplet surface has to be perturbed in order to initiate the lipolytic event. The molecular mechanism underlying the process by which the lipase gains access to the substrate—triglyceride in the core of a lipid droplet particle—is unknown. This process seems to be controlled by evolutionarily conserved proteins from the PAT family, which is a group of proteins that share sequence similarity and localize to lipid droplets (24,26). In vertebrates PAT proteins localize tolipid droplets either constitutively (perilipin and adipocytes differentiation-related protein) or in response to lipogenic and/or lipolytic stimuli (TI47, S3-12, and OXPAT, a PAT protein associated with oxidative metabolism) (26). Perilipin is the best characterized lipid droplet protein. It is a critical regulator of lipolysis in vertebrate adipocytes and, depending on its phosphorylation level, it can prevent or stimulate triglyceride hydrolysis (26).

Insect genomes encode two PAT proteins, Lsd1 and Lsd2 (24,56). The overall sequence similarity of lipid droplet storage (Lsd) proteins with the vertebrate family members is very

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low (56). However, the information available on Lsd1 and Lsd2 shows significant evidence in support of major roles for these proteins in insect lipid metabolism. Both proteins associate with lipids and share sequence similarities in the N-terminal regions (8). Lsd2 seems to be involved in promoting lipid accumulation, whereas Lsd1 is involved in activation of lipolysis. Lsd2 is expressed during all developmental stages and is required for normal storage of triglyceride in the fly (119). Overexpression and deletion of Lsd2 in Drosophila lead to an increase and a reduction of the triglyceride content, respectively (56,119). The lack of Lsd2 is also associated with a decrease in the lipid content of the embryo, suggesting that it is important for the transference of lipids to the developing oocyte (135). Lsd2 is found in fat body, ovaries (43,135), and wing imaginal discs (43), but it is particularly abundant in ovaries.

In contrast to the apparent function of Lsd2, which would act as a barrier to lipases, studies carried out in Manduca sexta have suggested that Lsd1 plays a major role in the activation of lipolysis (6,99). Like perilipin in vertebrates, Lsd1 is the major phosphoprotein of the lipid droplets after hormone stimulation of lipolysis (99). Phosphorylation of Lsd1 is responsible for most of the lipolytic response elicited by adipokinetic hormone (AKH) in M. sexta. These studies (6,99) provided a clear indication that lipid droplets represent an active subcellular compartment in insects. M. sexta Lsd1 localizes exclusively in the lipid droplets and is found exclusively in the fat body of the adult stage (5). Lsd1 is undetected in feeding larva and its abundance progressively increases as the insect develops from nonfeeding larva to adult.

In addition to their functional differences, Lsd1 and Lsd2 are distinguished by their physical properties. Lsd1 is only soluble in aqueous media when bound to a lipid surface or in the presence of chaotropes and detergents. However, Lsd2 adopts a compact structure and is soluble in aqueous media in the absence of detergents (8). Based on these properties, Lsd1 is expected to be found associated only with lipid structures, whereas Lsd2 can also be found in the cytosol.

In addition to Lsd1 and Lsd2, several other lipid droplet proteins could have roles in the regulation of triglyceride accumulation and hydrolysis. The roles of Lsd1 and Lsd2 in lipid metabolism and the fact that most lipid-droplet-associated proteins identified—more than a hundred—in Drosophila larval adipocytes are involved in cellular metabolism (22) highlight the involvement of lipid droplets in insect metabolism. The study of the function of the lipid droplet proteins will provide new insights into the mechanisms of lipid deposition and mobilization.

Atypical Lipid Storage in Insects

Fat body adipocytes are cells with great plasticity, able to store large amounts of triglycerides (36). Accumulation of lipids by diapausing insects is well documented (40). Extreme lipid deposition can cause fat body hypertrophy, and this is a mechanism that enhances overwintering survival in Culex pipiens females (25,88). Males do not enter diapause and do not survive the winter. Prior to diapause adult females accumulate twice the lipid reserves of their nondiapausing counterparts (25,88). Fat body lipid accumulation is built entirely by feeding on plant juices rich in carbohydrates. These individuals feed more frequently prior to diapause than nondiapausing females (103). Diapausing females do not take blood meals, and the molecular machinery to digest the blood meal is not present (25,103). Consistent with the elevated level of lipogenesis that results in fat body hypertrophy, an increase in the level of expression of fatty acid synthase has been shown (103).

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On the other hand, several parasitoid species in Hymenoptera and Diptera are unable to store lipid reserves as adults. Although these species feed on sugar-rich diets, they cannot convert excess carbohydrate into lipids. The physiological mechanism underlying this unique condition is unknown (132).

MOBILIZATION OF CARBOHYDRATE RESERVES

Glycogen is mobilized for use by other tissues, mostly in the form of trehalose (120). The utilization of glycogen depends on the activity of glycogen phosphorylase, which provides glucosyl residues for trehalose synthesis (114,120). Fat body phosphorylase activity increases during larval development. An increase in activity prior to pupation is linked to the need for energy and glucose for chitin synthesis. Likewise, pupal-adult development is marked by high phosphorylase activity. Different insects exhibit different patterns of phosphorylase activity during the pupal period. In some insects the increase in phosphorylase activity is observed at the beginning of the period, whereas in others phosphorylase activity increases toward the end of the pupal stage (114).

The secretion of trehalose by adipocytes involves a membrane transporter. The identification and characterization of the first insect trehalose transporter has been recently reported (75). The nature and mechanism of function of fat body trehalose transporters is unknown for most insects.

Apart from the use of trehalose for maintenance of energy metabolism during fasting or nonfeeding periods (see review in Reference 120), trehalose is a substrate for insect flight in general. Long-term flyers, such as locusts (125) and mosquitoes, subjected to several hours of flight (72,73) start flying using trehalose and after some time switch to lipids. Short-term flyers such as the cockroach Periplaneta americana (41) use mostly trehalose. On the other hand, the Colorado potato beetle (Leptinotarsa decemlineata), which oxidizes proline to fuel flight, also needs a concomitant utilization of glucose to produce pyruvate and to allow the proline-alanine cycle to occur (48). A particular group of insects is represented by the bees, which exclusively utilize carbohydrates to power flight (117). These insects support flight by using sugars stored in the crop rather than reserves from the fat body.

Glycogen is also mobilized for the production of trehalose and sugar alcohols under stressing conditions of temperature (116) and drought (133). These osmolytes play essentially the same roles as trehalose, preventing cellular damage under conditions of low temperature and during diapause (37). Studies of several insects have shown that cold acclimation leads to an increase in body contents of trehalose and glucose (93,128). These changes are supported by a rapid decrease in glycogen (55).

Glycogen is also found in eggs, and it is synthesized in the ovary from glucose, which is imported from the hemolymph after hydrolysis of trehalose (71,138). In B. mori glycogen accumulation in the developing ovary is under the control of diapause hormone. However, the role of diapause hormone on the activity of glycogen phosphorylase has not been investigated.

MOBILIZATION OF LIPID RESERVES

Fatty acids stored in the lipid droplets of the fat body are mobilized for a number of purposes, including the provision of energy to flight muscles, in the form of diglyceride, trehalose, or proline; the provision of lipids to the ovaries; and the overall maintenance of the metabolic activity of other tissues, including the fat body. The first required step of fatty acid mobilization consists in the action of fat body triglyceride lipases to catalyze the hydrolysis of the triglyceride molecules contained in the lipid droplets. Two lipases that are

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expressed in the fat body have been identified so far: insect adipose triglyceride lipase (ATGL), or Brummer lipase (57), and triglyceride lipase (TGL) (6,11). TGL is the main lipase in M. sexta. This is the only insect lipase that has been purified (11) and characterized (6,7,97–99). TGL is the homolog of Drosophila CG8552, whose function was proved by expression of the Drosophila protein in insect cell lines (6). TGL shares significant sequence similarity with vertebrate phospholipases from the phosphatidic acid phospholipase A1(PA-PLA1) family (6), but it shows no homology to the main triglyceride hydrolases of vertebrate adipocytes, hormone-sensitive lipase (HSL) and ATGL. TGL is well conserved among insects (6). In addition to its main triglyceride and diglyceride hydrolase activities, TGL has a significant phospholipase A1 activity (6).

Brummer lipase, or insect ATGL, was identified in Drosophila (57). Insect ATGL belongs to the calcium-independent phospholipase A2 (iPLA2) family, which includes three closely related vertebrate lipases: ATGL, iPLA2-ε, and iPLA2-η (68). These are phospholipases that also display lipase and transacylase activity. A study using genetic approaches suggested that ATGL plays an important role in the metabolism of energy in Drosophila. The loss of ATGL caused accumulation of triglyceride and therefore fat flies, whereas its overexpression rendered lean flies (57). Triglyceride mobilization was not impaired in ATGL-null mutants, which consumed over 70% of stored triglyceride under starvation (57), suggesting that ATGL is not a limiting enzyme in the mobilization of lipids in Drosophila.

Utilization of Lipids

This section presents a revision of the studies showing mobilization and/or utilization of lipids for direct support of flight and for the synthesis of trehalose and proline, as well as during starvation, embryogenesis, and the immune response.

Flight—Direct utilization of fat reserves to support flight is in general required in long-term flying insects (20). Studies using half-thorax preparations of Locusta migratoria showed the ability of electrically stimulated flight muscles to metabolize lipids and carbohydrates (104). However, demonstrating the preference for lipid oxidation, oxidation of carbohydrates was highly inhibited in the presence of lipophorin (54). Mobilization of fat body lipids during flight has been shown in many insects (20,31,48,72,145). Fat body lipids are commonly secreted into the hemolymph as diacylglycerol, which is transported to the tissues by the insect lipoprotein, lipophorin (110,126). The utilization of lipids in insects has been reviewed on several occasions (2,20,30,40). As indicated in the following paragraph, an indirect utilization of lipids to fuel flight is present in some insects whose flight muscles use proline as the main energy substrate.

Synthesis of trehalose and proline—The synthesis of trehalose in the fat body is an energy-dependent process. Studies in two cockroach species (83,136) have shown that synthesis and release of trehalose is coupled to fatty acid oxidation. In fact, inhibition of β-oxidation prevents AKH-induced release of trehalose (83). These studies suggest that at least in some insects trehalose synthesis is dependent on fatty acid mobilization and oxidation.

Proline is an abundant substrate found in the hemolymph of most insect species. It is synthesized in the fat body from acetyl-CoA and alanine and then released into the hemolymph (29). Studies based on two insect species, the tsetse fly, Glossina morsitans, and the Colorado potato beetle, Leptinotarsa decemlineata, that use proline as the main fuel to power flight indicate that the synthesis of proline requires fatty acid mobilization (29,48). The exceptional ability of these insects to use proline resides in the properties of their muscle mitochondria, which have the enzymes required to oxidize proline as well as a low capability to oxidize fatty acids and pyruvate (48,53). Utilization of proline during flight is

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accompanied by an increase in the concentration of alanine in hemolymph (48). Alanine is reused for the synthesis of proline in the fat body and is considered a shuttle for the transport of acetate units from the fat body to muscles. Several studies have shown that fatty acids stored in the fat body provide the acetate units required for proline synthesis (16,29,134). Furthermore, flight and AKH promote a parallel increase in lipase activity and proline synthesis in beetles (16), and extracts of corpora cardiaca induce both lipolysis and proline synthesis in tsetse fly fat body (101). The hemolymph lipids also increase during flight in the Colorado potato beetle. Overall, the studies of insects whose flight muscles have a high selectivity for proline oxidation indicate that the mobilization of triglyceride depots is central and tightly linked to the use of proline.

Starvation—Starvation is another condition in which lipid mobilization is observed. For instance, starvation of L. migratoria is characterized by a threefold increase in hemolymph lipid concentration due to a prominent elevation of diglycerides (20). A similar situation is observed in M. sexta, in which starvation induces a twofold increase in hemolymph lipid concentration (141). Unlike flight-induced lipid mobilization, the increase of hemolymph diglyceride during starvation is independent of AKH. The signal that promotes activation of lipolysis during starvation remains unknown. However, in both insects, injection of trehalose reduces the lipid concentration in hemolymph, implying that an inverse relationship exists between the hemolymph concentration of lipid and trehalose (10,20). Trehalose has an inhibitory effect on the lipolytic activity of the fat body as judged by the decrease of M. sexta fat body lipase activity (10) and the production of diglyceride by the locust fat body (82). The mechanism underlying this process is unknown, but an in vitro study (82) suggests a direct effect of trehalose on the rate of lipolysis.

Embryogenesis—Lipids comprise 30–40% of the dry weight of insect oocytes (27,122,127), and they are the main source of energy for the developing embryo (20,127). During their maturation, insect oocytes increase their lipid content several fold in a short period, usually one or two days. Although oocytes are able to synthesize fatty acids de novo, this contribution does not account for more than 1% of the egg lipid content. The vast majority of the lipid accumulated in oocytes originates in the fat body and is transported to the ovaries by lipophorin (144,146). The accumulation of lipid in the ovaries is concomitant to a massive reduction in the lipid content of the fat body (81,144). Consistent with the significance of lipophorin in oogenesis, expression of apolipoprotein genes (118) and lipoprotein receptors increases during vitellogenesis (33,35). Ovaries take up some of the lipids by receptor-mediated endocytosis of the lipoprotein particle. This mechanism is evident in the appearance of the protein components of lipophorin inside the growing oocytes (118,146). The contribution of this mechanism to the total uptake of lipid by ovaries is not clear. Studies of M. sexta suggest that this mechanism only contributes 5% of the lipids taken up by ovaries. It seems that most of the lipid is taken up by an extracellular mechanism that requires hydrolysis of diglyceride and subsequent uptake of the fatty acids produced (146). The lipid content of vitellogenin is much lower than that of lipophorin. However, given the large amount of vitellogenin that is taken up by developing oocytes, its contribution to the lipid content of oocytes may be significant. Like lipophorin, vitellogenin is produced in the fat body, secreted into the hemolymph, and taken up by developing oocytes by vitellogenin-receptor-mediated endocytosis (123).

Immune response—Lipids are also mobilized to the hemolymph in response to immune challenge (34,38,90). A study of mosquito-parasite interactions (Plasmodium falciparum and Anopheles gambiae) confirmed that infected field mosquitoes present an increased transcriptional level of lipophorin proteins (84). The nature of the signals that trigger mobilization of lipids during infections and the fate of the mobilized lipids are not known.

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Lipids could be used as an energy source and/or for membrane biogenesis in the sites of infection or in hemocytes.

HORMONAL REGULATION OF FAT BODY ENERGY MOBILIZATION

The mobilization of fat body energy reserves is essentially regulated by AKH (49), which is produced by the corpora cardiaca (51). The most widely recognized action of the AKH family of peptides is their stimulation of the fat body to convert stored glycogen and triglyceride into hemolymph trehalose and diglyceride, respectively. In some insects AKH also stimulates the synthesis of proline (48,50,51). Supporting a role of AKH in glycogen mobilization, ablation of AKH-producing cells in Drosophila promotes a decrease in trehalose levels in both larvae and adults (67,76,78). AKH receptors from D. melanogaster and B. mori have been identified (113). They are related to the mammalian gonadotropin-releasing hormone receptor. Additional evidence in support of a role of AKH in energy metabolism was provided by a study on Drosophila showing that deletion mutants of the AKH receptor accumulate more body fat than do controls (58).

The mode of action of AKH for various insect species has been investigated and previously reviewed (47,49,51,124). The effects of AKH in M. sexta depend on the developmental stage. AKH mobilizes glycogen through the activation of glycogen phosphorylase during the larval stages and promotes a lipolytic response in the adult (2). The lipolytic response induced by AKH in M. sexta involves a rapid increase in Ca2+ influx and an increase in the intracellular concentration of cAMP, which leads to the activation of cAMP-dependent protein kinase A (PKA) (3). Whether these two pathways are activated simultaneously by the AKH receptor or are the result of a cascade effect remains to be determined.

Mobilization of energy reserves is also involved in the acute stress response of insects. This response is controlled by the neurohormone octopamine, the invertebrate counterpart of noradrenaline (106). The action of octopamine is mediated by G-protein-coupled receptors that are coupled to either an increase or a decrease of the intracellular level of cAMP, or to the generation of intracellular calcium signals (42). Octopamine stimulates lipid mobilization in several insects (45,92,109). In M. sexta it stimulates glycogen phosphorylase in the larval stage (86), but the response is moderate compared with that elicited by AKH.

Large amounts of energy are needed to support flight. The release of hormones during flight has been studied best in locusts and an integrated relationship between octopamine and AKH during flight has been shown. The increase of hemolymph diglyceride has a biphasic pattern, with aplateau between 10 and 20 min of flight. During the first few minutes of flight octopamine is released, inducing the first release of diglyceride from the fat body. The subsequent, more prolonged phase of lipid elevation is produced by the release of AKHs, whose titers increase sharply after 15 min of flight (92). Some studies suggest that octopamine elicits the secretion of AKH by the corpora cardiaca during flight (92). However, incubation of corpora cardiaca with octopamine failed to induce AKH secretion (95). The release of AKH could be triggered by the decrease in hemolymph trehalose that occurs soon after the initiation of flight (21). In Drosophila a decrease in extracellular trehalose concentration stimulated the secretion of AKH from the corpora cardiaca (76). In agreement with this observation, a previous study showed that trehalose and glucose inhibit the release of AKH from adipokinetic cells (96). The available information suggests that the levels of hemolymph trehalose and/or glucose play a direct role in the secretion of AKH by the corpora cardiaca.

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Mechanism of Activation of Glycogenolysis

The mobilization of glycogen is dependent on the activity of glycogen phosphorylase, which catalyzes degradation of glycogen to glucose-1-phosphate. This is converted into glucose-6-phosphate, which is utilized, together with UDP-glucose, in the synthesis of trehalose (46) or, alternatively, enters glycolysis. AKH stimulates the activation of glycogen phosphorylase in the fat body via phosphorylation of the protein that converts the b form, which is active only in the presence of AMP, to the a form, which is active by itself. The b form is activated by AMP, whereas it is inhibited by ADP, ATP, and glucose (9,129). In M. sexta fat body the a form is not inhibited by ATP (9). This means the fat body is able to convert glycogen into trehalose in response to metabolic demands of other tissues, even when the energy charge of the fat body is high. In contrast, all forms of phosphorylase from Manduca flight muscle are inhibited by near-physiological concentrations of ATP (28), showing a clear difference in the regulation of phosphorylase between these two tissues. Because the fat body is the principal biosynthetic tissue of the insect, its energy charge is expected to be high during most periods of development. For example, in starved M. sexta larvae the energy charge in the fat body increased in parallel to glycogen phosphorylase activity. Consequently, the mobilization of fat body glycogen reserves is mostly achieved by phosphorylase a, which is regulated not by the energy charge, but hormonally via phosphorylation. Phosphorylase b is unlikely to be active under the physiological conditions of the fat body.

To drive the utilization of glucose-6-phosphate for the synthesis of trehalose, glycolysis must be switched off. Evidence suggesting that corpora cardiaca have an inhibitory effect of glycolysis has been shown in the fat body (115) and flight muscle (105). Inhibition of glycolysis is achieved by lowering the concentration of fructose-2,6-biphosphate (F-2,6-P2), the major allosteric regulator of phosphofructokinase, a key regulatory enzyme of glycolysis (19,130). In cockroach fat body AKH induces a marked decrease in the concentration of F-2,6-P2, resulting in a 90% decrease in phosphofructokinase activity (18).

An interesting observation is that the level of F-2,6-P2 in the fat body correlates with the level of glucose in the hemolymph (85). This has been observed in Manduca larvae at the beginning of fasting. In these insects the level of trehalose is relatively constant even during fasting (142). However, a rapid, approximately fivefold decrease in the hemolymph level of glucose is observed in the first 30 min of fasting. The decrease in hemolymph glucose concentration is important because it correlates with the level of F-2,6-P2 in the fat body (85). The correlation between hemolymph glucose and the level of the major regulator of glycolysis shows that hemolymph glucose is an indicator of the status of carbohydrate metabolism in the fat body. In addition, it shows a direct role for glucose in controlling carbohydrate metabolism in the fat body.

With regard to the mechanism of glycogen mobilization due to cold adaptation, low-temperature-triggered activation of glycogen breakdown for polyol synthesis results from an increase in PKA activity (100) and phosphorylation-mediated activation of glycogen phosphorylase (63). In addition to these changes, an increase in the activity of several enzymes involved in the synthesis of polyols has been described to occur in the fall (89).

Mechanism of Activation of Lipolysis

The mobilization of triglyceride stores during flight is controlled by AKH (47,124), which increases the rate of triglyceride hydrolysis and promotes a concomitant release of diacylglycerol into the hemolymph. Increases in lipase activity of fat body homogenates after initiation of flight or AKH injection have been observed in several insects (12,15,16). AKH induces a fourfold increase in PKA activity of M. sexta fat body in a matter of 2–5 min. Therefore, PKA-mediated protein phosphorylation is considered a major factor in the

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activation of lipolysis. TGL is phosphorylated by PKA in vitro (11). However, in vitro studies using PKA and TGL, both purified from M. sexta fat body (11,97), showed that PKA-catalyzed phosphorylation of TGL does not affect the TGL activity against lipid droplets (99). In fact, TGL is constitutively phosphorylated in vivo, and its phosphorylation levelis unchanged by AKH (98). Surprisingly, TGL activity was 2.4-fold higher when assayed against lipid droplets isolated from AKH-stimulated fat bodies, suggesting an effect of AKH on the lipid droplets (99). Time course studies of AKH-induced changes in the phosphorylation of lipid droplet proteins identified Lsd1 as a major PKA target (99), and showed a correlation between TGL activity and the phosphorylation of Lsd1. Subsequent studies using purified Lsd1 reconstituted in lipid droplet-like particles suggested a direct effect of PKA phosphorylation of Lsd1 on the activity of TGL (7). Most of the lipolytic (70%) response induced by AKH is accounted for by the changes induced in the lipid droplets. Changes in the cytosol, where TGL localizes, are responsible for 30% of the lipolytic response. Therefore, the lipolytic action of AKH is basically defined by its effect on the activity of the lipid droplets through the phosphorylation of Lsd1.

Lsd1 is poorly expressed in the feeding larvae, but it is highly expressed in adipocytes from nonfeeding adult insects (5). Coincidentally, adult M. sexta is characterized by its great capacity to mobilize lipid stores (2). The pattern of expression of Lsd1 reaffirms its role as a regulator of lipolysis and could explain why AKH does not induce lipid mobilization in larvae (5). Lsd1 is a protein conserved among insects and these studies show that its function is similar to perilipin A from mammalian lipid droplets (24).

Part of the lipolytic response induced by AKH is due to changes that occur in the cytosol, including the activation of TGL (98). As mentioned above, AKH-induced activation of the cytosolic TG-lipase activity has been reported in several insects including moth (10), beetle (16), and locust (15). This mechanism of activation, which is independent of the phosphorylation state of TGL, remains to be elucidated. The primary structure of TGL suggests the presence of two structural domains, the WWE domain located in the N-terminal region, and the DDHD domain, located in the C-terminal region (6). These domains could play a role in the regulation of TGL activity by interacting with other proteins. This type of regulation could be relevant to the control of the basal lipolytic activity, or AKH-independent activity. The regulation of basal lipolysis is expected to be more relevant in the feeding stages. The high level of lipolysis observed in starved adult can be significantly reversed by increasing the level of trehalose in circulation. High levels of trehalose lower the TG-lipase activity of cytosol and the concentration of lipids in the hemolymph (10). As in mammals, basal lipolysis could be also regulated by other lipases, such as ATGL (139). In Drosophila, insect ATGL has been associated with most of the basal lipolysis and only partially with AKH-induced lipolysis (58). The regulation of insect ATGL activity could be controlled by its level of expression and probably by other mechanisms. Mammalian ATGL activity is modulated by the protein CGI-58 (comparative genome identification-58). Because the Drosophila genome contains a CGI-58 homolog gene, it has been suggested that insect ATGL could also be regulated by interaction with CGI-58 (58).

The presence of multiple conserved phosphorylation sites in both TGL and Lsd1 anticipates complex mechanisms of regulation of TGL activity. Given the central role of lipolysis in energy metabolism, the regulation of lipolysis by multiple hormonal or metabolic signals is expected. These regulatory pathways remain to be elucidated.

CONCLUDING REMARKS

New information indicates that several aspects of the deposition and mobilization of triglycerides in insects are accomplished by evolutionarily conserved mechanisms. In many

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ways, the study of fat metabolism is less complex in insects than in vertebrates, suggesting that insects will provide an advantage for the advancement of our understanding of fundamental aspects of fat metabolism. Drosophila is being used as a model system for research on the molecular analysis of human diseases such as obesity (23). Those studies are based on genetic manipulation and are directed to discover new regulators of lipid metabolism. A complete understanding of the basic mechanisms of lipid mobilization will facilitate the interpretation of studies based on genetic approaches. Expanding our knowledge of the mechanism of energy metabolism in insects is essential not only for a better understanding of insect biochemistry and physiology, but also because the information could contribute to answering questions relevant to human health.

SUMMARY POINTS

1. The fat body plays a major role in intermediary metabolism and it is the central storage depot of nutrients and energy reserves. The storage function of the fat body is essential to the life of holometabolous insects, which must accumulate at least a minimal amount of nutrients in the larval stages to survive during periods of starvation and metamorphosis. Fat body reserves carried over from the larval stage are also crucial for oogenesis.
2. Fat body energy reserves are mobilized in response to the energy demands of other tissues. At the same time, the fat body responds to the metabolic requirements of the organ itself. Therefore, the mobilization of energy stores must be tightly coupled to a number of metabolic pathways.
3. Lipids always represent the major component of the fat body and the main source of metabolic fuel. Triglycerides, the major lipid form, are stored in the core of the lipid droplets surrounded by phospholipids and a coat of proteins. Lipid droplets are dynamic organelles whose metabolic activity is dependent on the protein components. Several of these proteins are involved in the regulation of triglyceride storage and mobilization.
4. The lipolytic machinery identified so far in insects includes two lipases, TGL and Brummer lipase, and two evolutionarily conserved lipid droplet proteins, Lsd1 and Lsd2. The lipolytic action of AKH is triggered by phosphorylation of Lsd1, which activates TGL. In contrast, the activity of Brummer lipase seems to be independent of AKH. Other mechanisms and proteins could also modulate the rate of triglyceride mobilization under basal and/or stimulated metabolic conditions.
5. Current information indicates that insects share with mammals and other organisms several aspects of the mechanisms of deposition and mobilization of triglycerides. This information validates the use of insect models to investigate basic questions related to the processes of lipid storage and mobilization. The discovery of new regulators of lipid metabolism could be facilitated in insect models, which offer technical advantages related to their size, short life span, and the ease of genetic manipulation. The fruit fly model offers particularly powerful genetic techniques that could be useful to define the roles of putative regulators of lipid homeostasis.

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