Review

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Review

Lipid Metabolism in Relation to Carbohydrate Metabolism

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Abstract: Carbohydrates and lipids integrate into a complex metabolic network that is essential to maintain homeostasis. In insects, as in most metazoans, dietary carbohydrates are taken up as monosaccharides whose excess is toxic, even at relatively low concentrations. To cope with this toxicity, monosaccharides are stored either as glycogen or neutral lipids, the latter constituting a quasi-unlimited energy store. Breakdown of these stores in response to energy demand depends on insect species and on several physiological parameters. In this chapter, we review the multiple metabolic pathways and strategies linking carbohydrates and lipids that insects utilize to respond to nutrient availability, food scarcity or physiological activities.

Keywords: monosaccharides; glycolysis; lipogenesis; triacylglycerol; midgut; fat body; oenocytes; muscles; haemolymph; homeostasis

9.1. Introduction

Insects colonize a huge variety of ecological niches on Earth. Despite a great diversity of diets, their food always comprises carbohydrate biomolecules. Carbohydrates are organic compounds containing carbon, oxygen and hydrogen atoms, most frequently with a 2:1 hydrogen-oxygen ratio. They are divided into three main classes ranging from monosaccharide and disaccharide simple sugars (*e.g.* glucose, maltose) to complex polymers (*e.g.* glycogen, starch) and glycoconjugates (*e.g.* glycolipids) (Chandel, 2022). The proportion of each class of dietary carbohydrates depends on the insect feeding source. Since carbohydrates are commonly taken up by enterocytes as monosaccharides, dietary oligosaccharides, polysaccharides and glycoconjugates, they require enzymatic hydrolysis in the midgut (Terra and Ferreira, 2012; Chapman et al., 2013; Sahaka et al., 2020). In insects, the major monosaccharides resulting from enzymatic digestion in the gut lumen are glucose, fructose and galactose; whereas trehalose is the most abundant circulating sugar in the haemolymph (Wyatt and Kale, 1957). Trehalose is a nonreductive disaccharide linking two glucose units in a 1,1-glycosidic bound, which impedes the reductive toxicity of glucose (Mattila and Hietakangas, 2017).

Monosaccharides and their metabolic byproducts are toxic compounds, even at low concentrations (Rabbani and Thornalley, 2013). To prevent this toxicity once taken up into animal cells, glucose is catabolized through glycolysis to produce energy or stored as glycogen granules. However, the capacity for glycogen storage is limited, so that additional storage strategies have been selected throughout evolution to provide energy resources in case of food scarcity (Steele, 1982). Lipogenesis leading to the production of triacylglycerols (TAGs) is directly connected to carbohydrate catabolism through a metabolic axis comprising successively glycolysis, tricarboxylic acid (TCA) cycle and fatty acid (FA) synthesis. TAG storage in lipid droplets is, to a certain extent, unlimited, making it the essential strategy for energy storage (Brookheart et al., 2009; Patel and Abate, 2013). In contrast, glycolipids do not constitute an energy storage form; they are mainly found at the extracellular membrane layer, playing critical roles in numerous cellular functions (Nishihara, 2020). Cholesterol is critical for membrane fluidity and steroid hormone synthesis. Cholesterol biogenesis requires the condensation of two farnesylpyrophosphate units. Insects lack the enzymes for

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farnesylpyrophosphate condensation to sterol synthesis (Zhang et al., 2019). Therefore, cholesterol is not connected to carbohydrate metabolism and must be dietary provided (Clark and Block, 1959).

Lipid catabolism is not expected to reverse to carbohydrate biogenesis; thus, the carbohydrate to lipid metabolic axis is considered unidirectional. The fate of glucose to energy production or to glycogen/TAG storage is tightly controlled, involving the Mondo/Mlx transcription factor that responds to glucose metabolites, thereby regulating several metabolic routes, including FA synthesis (Mattila and Hietakangas, 2017; Richards et al., 2017; Havula and Hietakangas, 2018). In this chapter, we will focus on the physiological links that connect the carbohydrate to lipid metabolism at the whole insect body level. To this end, we will first summarize the metabolic routes from dietary carbohydrates to lipid synthesis and storage. Next, we will describe the roles of the various organs in these processes. Finally, we will discuss the relevance of this vectorial metabolic axis in maintaining energy homeostasis.

9.2. The Metabolic Network Linking Carbohydrates to Lipids

9.2.1. Monosaccharide Fates

Monosaccharides do not accumulate in the intracellular compartment. They are either stored as glycogen or metabolized through catabolic pathways, including glycolysis or the pentose-phosphate pathway (Figure 1).

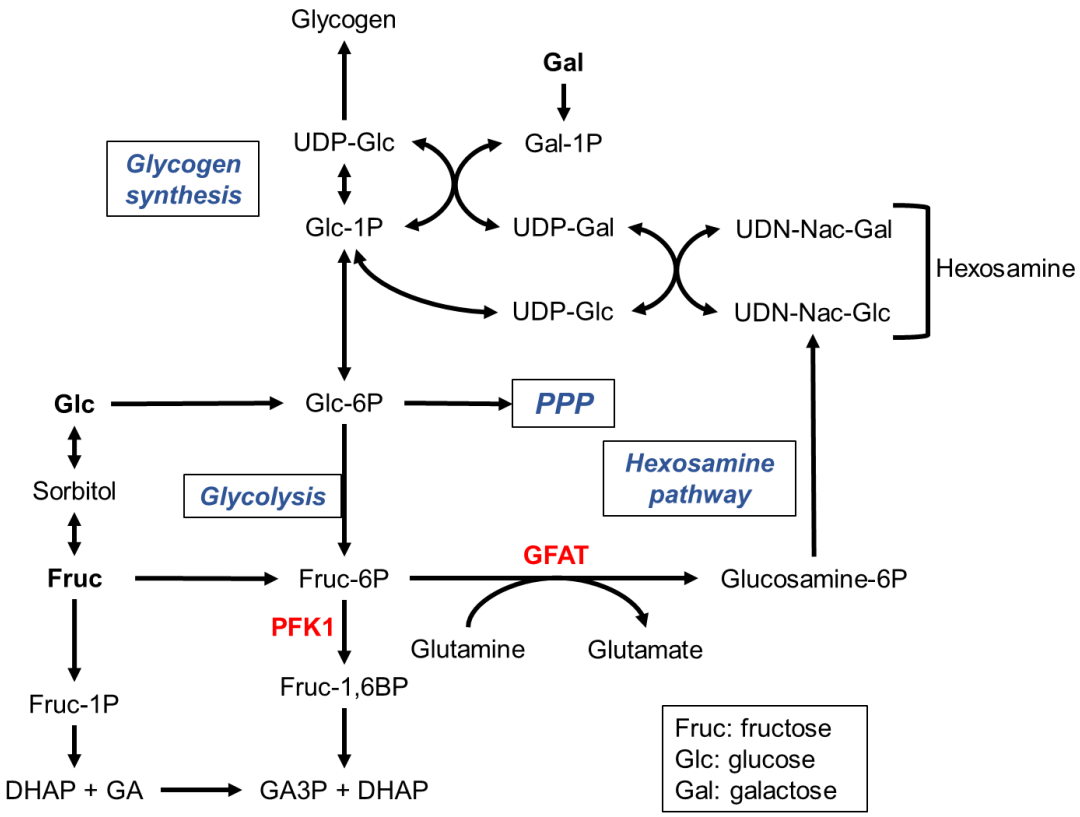

Figure 1. **Monosaccharide fates**. Glucose, fructose and galactose are the main monosaccharides taken by enterocytes after hydrolysis of dietary carbohydrates. Glucose is metabolized to glycogen or glycolysis. Fructose can enter glycolysis at various steps. Galactose enters this metabolic network as galactose-1P. Glycolytic intermediates may be used by the pentose phosphate pathway (PPP) or the hexosamine pathway.

Glycogen is a polymer of glucose units linked by $\alpha(1\rightarrow4)$ bonds, forming chains branched by $\alpha(1\rightarrow6)$ bonds (Adeva-Andany et al., 2016a; Chandel, 2022). Glycogen synthesis comprises the intermediates glucose-1-phosphate (glucose-1P) and UDP-glucose, and sequentially requires phosphoglucomutase, UDP-glucose phosphorylase, glycogen synthase and a branching enzyme

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(Figure 1). Breakdown of glycogen is catalyzed in the cytoplasm by glycogen phosphorylase and a debranching enzyme, and in lysosome by an acid α-glucosidase (Roach et al., 2012; Adeva-Andany et al., 2016a; Chandel, 2022).

Glycolysis first proceeds in a preparatory phase that consumes two ATP units, leading to the formation of the trioses glyceraldehyde-3phosphate (GA3P) and dihydroxyacetone-phosphate (DHAP) (Figure 1). In the glycolysis payoff phase, each GA3P unit is oxidized to pyruvate, yielding one NADH and two ATP molecules.

The pentose-phosphate pathway (PPP) (Figure 1) comprises a first oxidative phase, where glucose-6P is oxidized to produce NADPH and ribose-5P and a second non-oxidative phase that regenerates a pool of glucose-6P (Horecker, 2002).

Fructose can be converted to glucose through the intermediate sorbitol (Figure 1) (Krause and Wegner, 2020). A few studies reveal that sorbitol plays a role in immune response, in learning and in the seasonal physiological turnover of overwintering insects (Yang et al., 2019; Sano et al., 2022; Weiglein et al., 2019; Mustard et al., 2018; Drahun et al., 2023). Nonetheless, the relevance of sorbitol in the fructose to glucose conversion to feed glycolysis has been sparsely evaluated in insects. To enter glycolysis (Figure 1), fructose is phosphorylated either by a hexokinase to fructose-6P or by a ketohexokinase to fructose-1P (Johnson et al., 2020). The former enters glycolysis, whereas the latter is cleaved in DAHP and glyceraldehyde (GA), which is phosphorylated to GA3P by a triose kinase (Figure 1). Phosphorylation of fructose-6P to fructose-1,6-bisphosphate by PFK1 is the rate-limiting step of glucose consumption through glycolysis (Mor et al., 2011). The fructose-1P pathway bypasses this key regulatory step and thus enhances lipogenesis, thereby, favoring obesity and metabolic syndrome in human patients (Krause and Wegner, 2020).

The Leloir pathway is the main galactose metabolic pathway leading to the formation of UDP-galactose and glucose-1P, thereby i) contributing to glycogen synthesis, ii) entering glycolysis or iii) initiating the hexosamine pathway required for glycoproteins and glycolipids biosynthesis (Adeva-Andany et al., 2016a; Daenzer and Fridovich-Keil, 2017) (Figure 1). Nonetheless, the glycolytic metabolism of galactose is slower compared to that of glucose and fructose (Chandel, 2022).

The hexosamine pathway (Figure 1) starts with the rate-limiting step catalyzed by glutamine fructose 6-P amidotransferase (GFAT) to finally results in the production of UDP-N-acetylglucosamine (Chandel, 2022). The UDP-galactose epimerase (GALE) catalyzes the reversible interconversion of UDP-galactose to UDP-glucose, but also of UDP-N-acetylglucosamine to N-acetylgalactosamine, all these sugar derivatives being potential substrates for lipid glycosylation (Daenzer and Fridovich-Keil, 2017).

Trehalose synthesis results from the condensation of glucose-6-phosphate and UDP-glucose to trehalose-6-phosphate catalyzed by trehalose phosphate synthase and its dephosphorylation by trehalose phosphatase (Thompson, 2003).

9.2.2. Glycolytic Products and Byproducts

The payoff phase of glycolysis results in the production of one NADH and two ATP molecules through the conversion of each GA3P unit into pyruvate (Figure 2). In the cytoplasm, the reversible conversion of one pyruvate to one lactate molecule is catalyzed by the lactate dehydrogenase (LDH), which concurrently oxidizes one NADH coenzyme to NAD+. In the mitochondria, the oxidation of pyruvate to acetyl-CoA by the pyruvate dehydrogenase enzymatic complex is coupled to the reduction of NAD+ to NADH. Acetyl-CoA reacts with oxaloacetate to form citrate, thereby initiating the TCA cycle. Citrate oxidation to oxaloacetate proceeds through seven enzymatic reactions coupled to the formation of one FAD and three NADH units. Regeneration of these coenzymes by the respiratory chains at the mitochondrial inner membrane yields high amounts of ATP (Towarnicki and Ballard, 2020).

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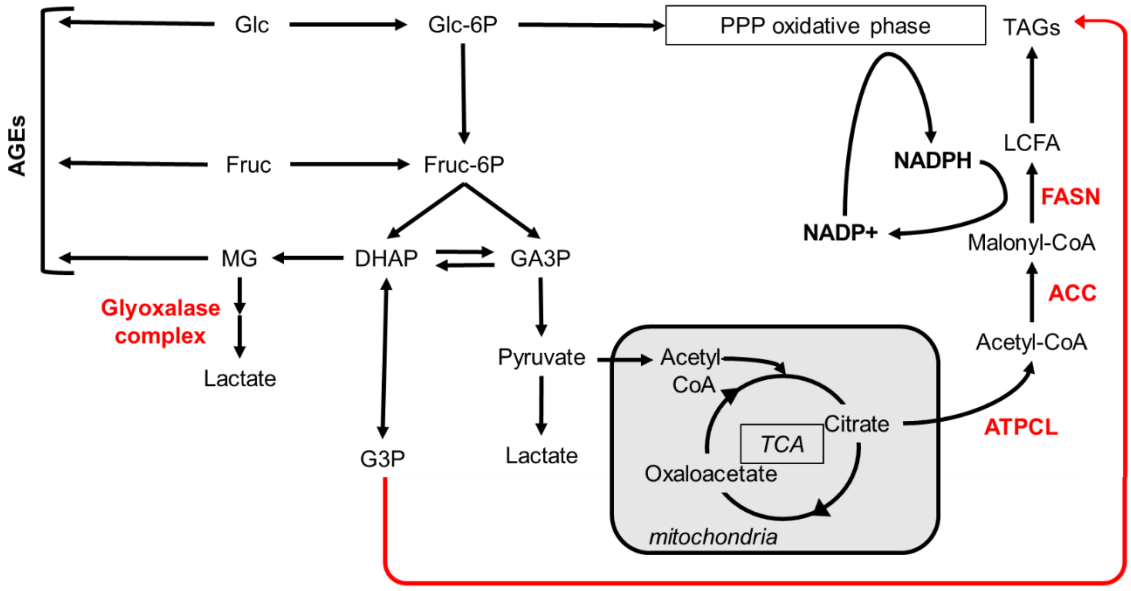

Figure 2. **Connecting glycolysis to lipogenesis**. The final glycolytic product pyruvate is either fermented to lactate or oxidized to acetyl-CoA in the mitochondria. Excess of citrate is transferred back to the cytoplasm and used for FA synthesis. The NADPH required for this FA synthesis may be produced by the PPP oxidative phase. Glucose, fructose and trioses phosphate may lead to α-oxoaldehydes that react with amine groups to form AGEs. The toxicity of methylglyoxal (MG) can be neutralized by the glyoxalase complex. G3P is required for TAG synthesis through the Kennedy pathway.

The lactate resulting from anaerobic fermentation in muscles is secreted and can be taken up by other tissues. For instance, in the mammalian liver, lactate from muscles is converted by LDH to pyruvate that is carboxylated to oxaloacetate by pyruvate carboxylase to fuel gluconeogenesis (Adeva-Andany et al., 2016b). To initiate gluconeogenesis, the conversion of oxaloacetate to phosphoenolpyruvate by the phosphoenolpyruvate carboxykinase (PEPCK) bypasses the irreversible phosphoenolpyruvate to pyruvate final reaction of glycolysis. When initiated from TCA cycle intermediates, gluconeogenesis depletes oxaloacetate, which must be compensated by anaplerotic reactions. Anaplerosis is commonly considered to depend on amino acid metabolism, in particular via transaminase-catalyzed reactions that convert aspartate to oxaloacetate and glutamate to α-ketoglutarate (Brooks, 1987; Inigo et al., 2021).

The trioses DHAP and GA3P can be interconverted by the triose phosphate isomerase (Figure 2). GA3P will fuel glycolysis, whereas DHAP can be reduced to G3P (glycerol 3-phosphate) that is used for TAG biogenesis through the Kennedy pathway (Coleman and Mashek, 2011; Ko et al., 2020). In addition, DHAP and GA3P may spontaneously be oxidized to methylglyoxal (MG), which is an α-oxoaldehyde that strongly reacts with the amine groups of proteins, DNA or nucleotides to form advanced-glycation-end-products (AGEs). Several studies support the notion that AGEs —in particular, glycated proteins that become resistant to proteasome degradation— are responsible for the toxic effects of sugars (Annandale et al., 2021). Nonetheless, to prevent this toxicity, MG can be metabolized to lactate by the glyoxalase system composed of the glyoxalase 1 (Glo1) and glyoxalase 2 enzymes (Thornalley, 1993) (Figure 2).

9.2.3. Lipid Metabolism

Excess of citrate from the TCA cycle is transferred back to the cytoplasm, where it is converted to oxaloacetate and acetyl-CoA; the latter is used for FA synthesis that proceeds in two main enzymatic steps (Figure 2). First, Acetyl-CoA-Carboxylase (ACC) catalyzes the carboxylation of acetyl-CoA into malonyl-CoA that is the rate-limiting step for FA synthesis (Barber et al., 2005). Next, fatty acid synthase (FASN) sequentially incorporates malonyl-CoA units to one acetyl-CoA primer to produce long chain fatty acids (LCFAs) (Smith et al., 2003; Maier et al., 2010). The biochemical

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reactions catalyzed by FASN require two NADPH coenzymes for incorporation of each malonyl-CoA unit (Figure 2). The NADPH may be synthesized through i) the pentose phosphate pathway, ii) the reduction of malate or iii) the one-carbon metabolism (Fan et al., 2014).

Newly synthesized LCFA are used for the synthesis of phospholipids or stored as TAGs in lipid droplets (Coleman and Mashek, 2011; Ko et al., 2020) (Figure 3). Synthesis of TAGs that may proceed through three distinct pathways, as well as phospholipid biogenesis are described in chapter 6. In the context of energy demand, the breakdown of TAGs releases LCFAs used for mitochondrial β-oxidation. The resulting acetyl-CoA either feeds the TCA cycle or is converted to ketone bodies that efflux into the circulatory system or the insect haemolymph to sustain the energy demand of other organs (Bailey and Horne, 1972; Huang et al., 2019). Nonetheless, this catabolic route does not happen in the context of FA synthesis, since malonyl-CoA produced by ACC inhibits the CPT-1 mediated transfer of LCFAs into the mitochondria (Saggerson, 2008). Importantly, β-oxidation of even-chain LCFA cannot fuel gluconeogenesis but rather fosters anaplerotic reactions to increase the oxaloacetate pool required to metabolize the resulting high amounts of acetyl-CoA. Even in the case of β-oxidation of odd-chain LCFA, whose final product propionyl-CoA can be converted into succinyl-CoA (Inigo et al., 2021; Fogle et al., 2019), the need in oxaloacetate substrates to metabolize acetyl-CoA impedes gluconeogenesis. Therefore, the metabolic vectorial axis from carbohydrate catabolism to lipid synthesis via the propionyl-CoA resulting from odd-chain LCFA oxidation is unlikely to reverse to carbohydrate biosynthesis.

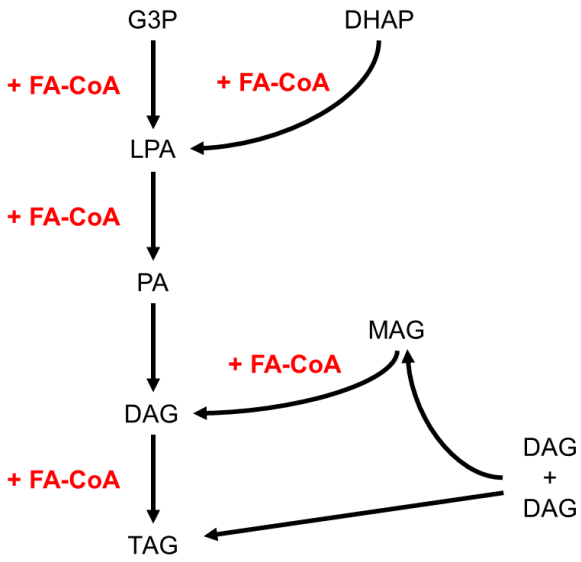

Figure 3. **TAG synthesis pathways**. This synthesis may originate from G3P (Kennedy pathway), DHAP, MAG or transacylation of DAGs. Note that newly synthesized FAs are always required.

Glycolipids are cell membrane components acting in signaling. Their synthesis is catalyzed by glycosyltransferases that covalently attach sugar moieties to the hydroxyl group of either a glycerolipid or a sphingolipid backbone. Glycolipid synthesis takes place at the Golgi apparatus, so that glycolipids are presented at the cell surface exposing their sugar moiety in the extracellular milieu (Nishihara, 2020).

9.3. Major Organs Implicated

9.3.1. Digestive Tract

The type of dietary carbohydrates directly depends on the insect feeding source (Table 1) (Patrick et al., 2013). Given that monosaccharides are the main form of sugar absorbed by the enterocytes, dietary oligosaccharides, polysaccharides and glycoconjugates require enzymatic hydrolysis of glycosylic bonds in the midgut lumen prior to intestinal uptake. A number of carbohydrase activities have been identified in the salivary glands and in the midgut of several phytophagous bugs,

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suggesting that carbohydrate hydrolysis starts upon food ingestion (Hori, 1975) or prior to it, as reported for external digestion of starch in *Drosophila melanogaster* (Haj-Ahmad and Hickey, 1982; Boer and Hickey, 1986; Szyszka and Galizia, 2018). Insect enterocytes synthesize amylases that hydrolyze starch and glycogen, and maltases that hydrolyze maltose (Benkel and Hickey, 1986; Terra and Ferreira, 1994; Zinke et al., 2002; Mattila et al., 2015; Pimentel et al., 2018). Conversely, cellulose and pectin digestion relies in most species on enzymes synthesized by enteric microorganisms (Watanabe and Tokuda, 2010; Ransom-Jones et al., 2012; Calderon-Cortes et al., 2012). Release of sugar moieties from glycolipids involves specific hydrolases secreted by the enterocytes, as reported for the folivorous lepidopteran *Epiphyas postvittana* and *Helicoverpa armigera* (Christeller et al., 2011; Sahaka et al., 2020). The origin of a given carbohydrate hydrolase cannot, however, be formally assigned to the genome of either the enterocyte or the microbiota, but varies depending on the insect species. For instance, cellulases and/or pectinases have been reported as encoded by the genome of the termite *Reticulitermes speratus*, the hemipteran *Lygus lineolaris* and the coleopteran *Phaedon cochleariae*, *Tribolium castaneum*, and *Sphenophorus levis* (Watanabe et al., 1998; Girard and Jouanin, 1999; Allen and Mertens, 2008; Willis et al., 2011; Evangelista et al., 2015).

Table 1. Dietary carbohydrates of insects.

Carbohydrate	**Type**	**Main dietary source**
Glucose	monosaccharide $C_6H_{12}O_6$	universal
Fructose	monosaccharide $C_6H_{12}O_6$	fruits
Galactose	monosaccharide $C_6H_{12}O_6$	milk, honey, plant galactolipids
Sucrose	1 glucose + 1 fructose	plant roots, fruits and sap
Maltose	2 glucose	germinating seeds
Trehalose	2 glucose	insect haemolymph
Cellobiose	2 glucose	cellulose digestion
Raffinose	1 galactose + 1 glucose + 1 fructose	plant seeds
Melezitose	2 glucose + 1 fructose	plant sap, honey
Glycogen	branched glucose polymer	animal stores
Starch	branched glucose polymer	plant stores
Inulin	branched fructose polymer	plant stores
Cellulose	linear glucose polymer	plant cell walls
Hemicellulose	branched monosaccharide polymer	plant cell walls
Pectin	galacturonic acid polymer	plant cell walls
Glycolipid	monosaccharide + diacylglycerol	cell membranes
Galactolipid	galactose + diacylglycerol	thylakoid membranes

The physiology of aphids soaking up an unbalanced diet from plant phloem, containing high amounts of carbohydrates —mostly sucrose— with low amino acid and lipid levels, illustrates the tight metabolic link between carbohydrates and lipids through a unidirectional axis. It has been shown in the sap exclusive feeder *Acyrthosiphon pisum* that most of the dietary sucrose is used for lipid synthesis, mostly neutral lipids (Febvay et al., 1992). Consequently, TAGs are in high levels in the fat

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body but also in cornicle secretion that contains as well high amounts of sugars (Rahbe et al., 1994). Their midgut symbionts are essential for their growth and their reproductive functions. However, antibiotic-induced depletion of their intestinal symbionts affects amino acid and glycogen synthesis but conversely increases lipid levels (Febvay et al., 1999; Lv et al., 2018), suggesting that these symbionts are required for amino acid but not lipid metabolism. The respective contributions of midgut and fat body cells in this lipogenic process in aphids have not been addressed to date.

Sugar transporters are members of the solute carrier proteins, including the major facilitators GLUT/SLC2, the sodium-driven glucose symporters SGLTs/SLC5 and the plant-specific SWEET/SLC50 (Deng and Yan, 2016). In mammalian enterocytes, glucose uptake proceeds through SGLT1 located at the brush border, whereas passive reversible export at the basal membrane mainly depends on GLUT2 for glucose and galactose and on GLUT5 for fructose (Wright et al., 2007; Gonzalez and Betts, 2019; Taskinen et al., 2019). In insects, the midgut is the main organ where monosaccharide absorption takes place, although this may also occur at the epidermis of endophagous parasitoids as reported for the larvae of the wasp *Aphidius ervi* (Caccia et al., 2005). Genomic analyses led to the identification of sugar transporters in several insect species (Kikuta et al., 2015; Moreira et al., 2017; Govindaraj et al., 2016; Pimentel et al., 2018; Wang and Wang, 2020). Utilization of chemical inhibitors revealed a powerful approach to confirm sugar transporter specificity. In this way, expression of a potential hexose transporter (NIHT1) has been reported in the midgut of the hemipteran *Nilaparvata lugens* that feeds on sucrose-enriched phloem sap (Price et al., 2007). NIHT1 expression in vesicles mediates glucose but not fructose transport. This transport is inhibited by cytochalasin B, suggesting that NIHT1 is a functional GLUT2 homologue. Homologues of GLUTs and SGLTs have been found in the anterior midgut of *Dysdercus peruvianus* (Bifano et al., 2010). In this hemipteran, glucose transport is activated by K2SO4 and inhibited by the GLUT inhibitor phloretin and by the SGLT inhibitor phlorizin, supporting that GLUT- and SGLT-like functions are conserved in insects. In *D. melanogaster*, the soluble carrier dSLC5A5 has been shown to be the *bona fide* SGLT1 homologue required for apical endocytosis into the enterocytes (Li et al., 2021). Expression of a trehalose transporter (TreT) has been found in the midgut of *Anopheles gambiae* and *Musca domestica* (Liu et al., 2013; Pimentel et al., 2018). However, given the high luminal trehalase levels (Becker et al., 1996) TreT is unlikely fulfilling the uptake of dietary trehalose, but rather buffering haemolymph trehalose levels to maintain homeostasis.

In mammals, the classical view is that nutrients taken up from the intestinal lumen are directly routed to the liver, which is the major site of intermediary metabolism. In insect midgut cells, monosaccharides resulting from carbohydrate hydrolysis can either efflux into the haemolymph or be converted to FAs via neolipogenesis as reported in *Pieris brassicae* and *D. melanogaster* (Turunen, 1993; Kokki et al., 2021). In the enterocytes, FAs are transiently esterified to TAGs and stored as lipid droplets, from where they are progressively exported in the form of diacylglycerol (DAG) loaded lipoproteins through the haemolymph to the requiring organs (Ford and Van Heusden, 1994; Pennington and Wells, 2002; Grillo et al., 2003; Palm et al., 2012; Heier and Kuhnlein, 2018).

9.3.2. Fat Body and Oenocytes

Fat body cells are in tight contact with oenocytes in a number of insect species. The fat body is an insect organ that combines hepatic and adipose functions related to energy homeostasis, nutrient storage and detoxification (Arrese and Soulages, 2010; Li et al., 2019). In contrast, the oenocytes fulfil catabolic hepatic-like functions related to starvation (Gutierrez et al., 2007; Moraes and Montagne, 2021; Huang et al., 2022). So far, investigations of the lipid anabolic pathways in the oenocytes of *D. melanogaster* did not reveal hepatic-like functions; instead, oenocytes produce FAs required to sustain the production of cuticular hydrocarbons (Wicker-Thomas et al., 2015; Storelli et al., 2019; Montagne and Wicker-Thomas, 2020; Blomquist and Ginzel, 2021; Huang et al., 2022) and to maintain tracheal watertightness (Parvy et al., 2012).

The fat body accumulates high amounts of TAGs in the form of lipid droplets, which may involve import of dietary lipids or neolipogenesis. Whether the fat body is solely a storage organ or also contributes to intermediary metabolism has been addressed in a number of studies.

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Incorporation of dietary radiolabeled lipids in the fat fraction of the fat body of the lepidopteran *P. brassicae* and of the cockroach *Periplaneta americana* has been reported (Turunen, 1975; Turunen and Kastari, 1979; Chino and Downer, 1979). Conversely, the fat body of the locusts *Schistocerca gregaria* and *Locusta migratoria* has been shown to perform intermediary metabolisms, including TCA cycle, respiration and fatty acid synthesis and to incorporate radiolabeled elements from glucose and amino acids into TAG-containing lipid droplets (Clements, 1959; Tietz, 1961; Hines and Smith, 1963). These studies indicate that acyl groups of the TAG stores may have different origins (Coleman, 2019; Olzmann and Carvalho, 2019; Heier et al., 2021). TAG synthesis through the Kennedy pathway begins with the acylation of a glycerol-3-phosphate backbone in mitochondria or endoplasmic reticulum (ER), whereas the dihydroxyacetone-phosphate (DHAP) pathway begins with DHAP acylation in the peroxisome. Both pathways result in the production of lysophosphatidic acid, which after two acylation reactions in the ER leads successively to phosphatidic acid, DAG and TAG. Acylation of monoacylglycerol (MAG) in the ER is a third pathway for TAG biogenesis. A fourth pathway, which also takes place in the ER, is the transacylation of two DAG units that results in the formation of one TAG and one MAG molecules; the latter may follow the MAG pathway to TAG. In sum, any of these pathways requires additional FA units (Figure 3). The TAG biogenesis pathway that takes place in the fat body has been sparsely addressed and likely depends on the insect species and/or its specific diet type (Kastari and Turunen, 1977). For instance, in *Rhodnius prolixus*, the Kennedy pathway has been shown to be the only pathway for TAG synthesis (Alves-Bezerra and Gondim, 2012). Nonetheless, given that in most species DAGs but not TAGs are transferred from the midgut to the fat body through the haemolymph, FA synthesis must operate in the fat body to sustain TAG biogenesis. Consistently, in *D. melanogaster*, fat body knockdown of ACC or FASN results in an almost complete depletion of overall TAGs and of fat body lipid droplets (Parvy et al., 2012; Garrido et al., 2015) and incorporation of high amounts of radiolabeled dietary glucose has been reported in total lipids (Musselman et al., 2013).

Glycogen has been reported to accumulate in the fat body of several insect species, including *S. gregaria*, *Bombyx mori*, *P.american*, *Culex pipiens* and *D. melanogaster* (Clements, 1959; Inagaki and Yamashita, 1986; Veenstra, 1989; King et al., 2020; Garrido et al., 2015; Yamada et al., 2018; Yamada et al., 2019). The fat body also synthesizes and accumulates trehalose and is considered to be the only organ where this synthesis takes place (Thompson, 2003; Mattila and Hietakangas, 2017). High levels of trehalose synthesis and the expression of trehalose-6-phosphate synthase have been reported in the fat body of *B. mori*, *L. migratoria* and *Mythimna separata* (Murphy and Wyatt, 1965; Agbanyo and Taylor, 1986; Yang et al., 2023). In *D. melanogaster*, starvation-induced glycogen breakdown of fat body stores is crucial to maintain homeostasis of circulating trehalose (Yamada et al., 2018).

In the context of starvation, TAGs are hydrolyzed in glycerol and FAs to feed β–oxidation, which ends up with the formation of acetyl-CoA units. Acetyl-CoA may feed the TCA cycle or generate ketone bodies, which are transferred to the requiring organs (Bailey and Horne, 1972). Studies in *D. melanogaster* suggest that the oenocytes perform β–oxidation upon fasting, as do mammalian hepatocytes that accumulate lipid droplets after the remobilization of adipocyte lipid stores. Likewise, fasting or genetically-provoked breakdown of fat body TAGs induces lipid droplet accumulation in the oenocytes (Gutierrez et al., 2007). Congruently, enzymes responsible for ketone body formation are highly expressed in the oenocytes of *D. melanogaster* (Huang et al., 2019). Oenocyte-ablated *D. melanogaster* larvae are almost unable to burn their TAG stores in the context of fasting, which might suggest that the oenocyte are the only organs to perform FA β–oxidation (Gutierrez et al., 2007). Nonetheless, since the oenocytes produce a FA required for the watertightness of the tracheal system, oenocyte-ablated *D. melanogaster* larvae are in anoxic condition, and thereby cannot perform FA β–oxidation (Parvy et al., 2012). Of note, FA consumption through β–oxidation has been reported in the flight muscles of a number of lepidopteran and orthopteran species (see below). Therefore, it is unlikely that the oenocytes are the only organs able to perform FA β–oxidation in the context of starvation and the respective contributions of the fat body and of the muscles remain to be precisely established.

9.3.3. Muscles

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Muscles are necessary for locomotion dispersion in the environment (skeletal muscles) or for internal physiological functions (peristalsis of intestinal visceral muscles; heart activity). The metabolic pathway to provide energy depends on the species and on the muscle type. Metabolism of visceral muscles has been sparsely studied in insects. In *D. melanogaster* a study focusing on the energy sensor AMP-activated protein kinase (AMPK) revealed that it is essential for intestinal peristalsis and that its mutation impaired nutrient absorption and glucose incorporation in glycogen and neutral lipids (Bland et al., 2010). Conversely, muscle metabolism has been extensively studied in insect skeletal flight muscles, which are the most energy demanding per tissue weight (Wegener, 1996). The immediate on/off state transition at flight onset requires a rapid and efficient production of energy, which is considered to rely on carbohydrate consumption through glycolysis (Auerswald and G, 1995; Canavoso et al., 2003; Suarez et al., 2005; Zhang et al., 2011; Gaviraghi et al., 2019). However, proline oxidation by the proline dehydrogenase at the mitochondrial respiratory chains is proposed to be a sparker metabolite at flight onset in several insect species (Bursell, 1981; Auerswald and G, 1995; Gade and Auerswald, 2002; Soares et al., 2015; Gaviraghi et al., 2019; Stec et al., 2021).

Glucose may originate from muscle glycogen stores, whose breakdown is catalyzed by the debranching enzyme AGL and by the glycogen phosphorylase that releases glucose-1P units (Childress and Sacktor, 1970; Wegener, 1996; Yamada et al., 2018). Glycogen storage and glycogen phosphorylase have been described in the muscles of numerous insect species (Childress et al., 1970; Downer and Matthews, 1976; Turturro and Shafiq, 1979; Steele, 1982; Lorenz, 2007; Zhang et al., 2011; Garrido et al., 2015; Yamada et al., 2019). Remobilization of glycogen from the fat body resulting in the synthesis of trehalose, which is transported through the haemolymph is the other major source of glycolytic substrate in muscles after trehalose uptake and Trehalase hydrolysis to glucose (Kanamori et al., 2010; Thompson, 2003; Murphy and Wyatt, 1965; Agbanyo and Taylor, 1986; Shukla et al., 2015; Mattila and Hietakangas, 2017; Yang et al., 2023). Consistently, glycogen phosphorylase has been reported in the fat body of several insect species including *D. melanogaster* and the cockroaches *Nauphoeta cinerea* and *P.americana* (Steele, 1982; Gade, 1991; Yamada et al., 2018; Yamada et al., 2019).

Glucose consumption through glycolysis produces at the payoff phase a pool of reduced NADH that can be regenerated to NAD+ in the anaerobic reduction of pyruvate to lactate (Figure 4). Slower working skeletal muscles(e.g. leg muscles) may oxidize NADH to NAD+ by pyruvate to lactate, as described in the jumping muscles of *Schistocerca americana* (Kirkton and Tyler, 2021). Conversely, the high glycolytic rate of flight muscles would produce dramatic amounts of lactate that might be toxic. To cope with this deleterious effect, flight muscles consume pyruvate through the TCA cycle, resulting in the lack of NAD+ to sustain the payoff phase of glycolysis (Figure 4). The fastest metabolic pathway to regenerate the pool of NAD+ proceeds through the G3P shuttle (Mracek et al., 2013; Gaviraghi et al., 2019). G3P is produced from DHAP reduction oxidizing NADH to NAD+. While G3P is a precursor for TAG synthesis through the Kennedy pathway in fat body cells, in muscles, it is regenerated at the mitochondrial inner membrane to DHAP by reducing the FAD coenzyme, which subsequently results in ATP production by the respiratory chains. Therefore, the G3P shuttle in flight muscle cells reduces the cytosolic pool of G3P, which would have been used for TAG or phospholipid synthesis in other tissues. Interestingly, a study on the bumblebee *Bombus terrestris*, which can fly at low ambient temperatures, suggests that the G3P shuttle plays a thermogenic role in pre-warming flight muscles (Masson et al., 2017).

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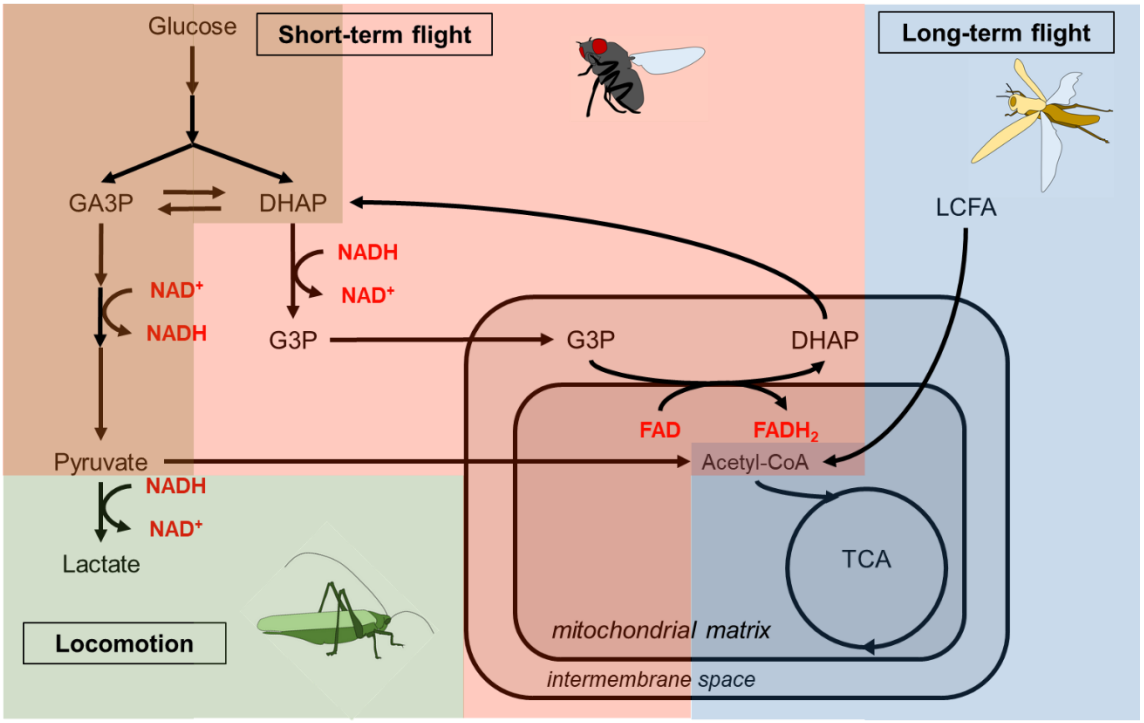

Figure 4. Metabolism of insect flight muscles. Glucose consumption in flight muscles follows the aerobic glycolytic pathway **through** mitochondrial respiration; regeneration of the cytoplasmic NAD+ cofactor proceeds through the G3P shuttle. Energy production through anaerobic glycolysis yields high amounts of lactate that is toxic in flight muscles, but is used in locomotion muscles. Long-term flight usually consumes TAG stores through FA β-oxidation.

The production of energy for flight muscles relies on carbohydrates for short-term and medium-term flights in several insect species (Beenakkers, 1969), but may also depend on lipid consumption (Li et al., 2023), as reported for *Manduca sexta*, *L. migratoria* and *Gryllus bimaculatus* (Ziegler and Schulz, 1986; van der Horst et al., 1993; Lorenz, 2007) (Table 2). Given that neutral lipids represent an enormous energy store, consumption of remobilized lipids represents an advantage for the long-term flight of non-feeding adult insects (Anand and Lorenz, 2008). In *L. migratoria*, carbohydrate is the predominant energy source during the first 30 minutes of flight, while lipid remobilization from fat body stores in the form of circulating DAGs progressively increases to become the major energy source for the following 30 minutes of flight (Jutsum and Goldsworthy, 1976). In *Panstrongylus megistus*, haemolymph carbohydrates and muscle glycogen progressively drop during 45 minutes flight, while fat body glycogen slightly decreases, suggesting that the latter do not sustain energy flight. In contrast, between 15 and 45 minutes of flight, lipid stores from muscles and fat body strongly decrease, while those in the haemolymph increase, indicating that lipids become the predominant energy source during extended flight duration (Canavoso et al., 2003).

Table 2. Metabolites for flight muscles in various insect species.

Insect species	Flight muscle metabolism requirements	Reference
A. aegypti	proline, pyruvate and G3P	(Gaviraghi et al., 2019)
A. gambia	AKH-I dependent haemolymph trehalose	(Kaufmann and Brown, 2008)
Bombus impatiens	proline at flight onset shift to carbohydrate	(Stec et al., 2021)
B. terrestris	G3P shuttle to pre-warm flight muscle	(Masson et al., 2017)

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D. melanogaster	Glycolytic metabolites AKH-dependent lipid metabolism Peroxisome-dependent lipid metabolism Carbohydrate	(Eanes et al., 2006) (Katewa et al., 2012) (Faust et al., 2014) (Zhao et al., 2020)
Decapotoma lunata	Haemolymph carbohydrate	(Auerswald and G, 1995)
G. molesta	Carbohydrate	(Su et al., 2022)
G. firmus	Fat body glycogen, haemolymph trehalose	(Zhang et al., 2011)
L. migratoria	Trehalose and lipids Lipids, high FABP levels in flight muscles	(Robinson and Goldsworthy, 1977) (van der Horst et al., 1993)
M. sexta	Haemolymph lipids FA oxidation shifts to glycolysis with aging	(Ziegler and Schulz, 1986) (Wone et al., 2018)
Pachnoda sinuata	Proline and haemolymph carbohydrates	(Auerswald et al., 1998)
P. megistus	Carbohydrate first, shift to lipids	(Canavoso et al., 2003)
P.americana	Glycogen High expression of glycogen phosphorylase	(Downer and Matthews, 1976) (Steele, 1982)
R. prolixus	Lipids	(Braz et al., 2023)
S. gregaria	Carbohydrate first, shift to lipids	(Rajapakse et al., 2019)
Orchid bees	Carbohydrate	(Suarez et al., 2005)

Studies to identify the mechanism of store remobilization to provide energy to flight muscles revealed the key role of neuropeptides (Li et al., 2023), including the functional glucagon homologue adipokinetic hormone (AKH). AKHs are small peptides synthesized in the corpora cardiaca and transferred through the haemolymph to the fat body, where they bind their cognate G-protein-coupled receptors (Gade and Auerswald, 2003; Gade, 2009). AKH-dependent remobilization is not store specific. In *L. migratoria*, AKH controls the remobilization of lipid and carbohydrate stores from the fat body to feed flight muscle activity (Robinson and Goldsworthy, 1977). In *M. sexta*, AKH controls lipid mobilization to sustain adult flight, but glycogen phosphorylase in starving larvae (Ziegler et al., 1990). In *D. melanogaster*, AKH deficiency results in lipid consumption defects and obese flies, which surprisingly are not flight deficient, although this study assayed only the immediate flying performance, but not long-term flying ability (Galikova et al., 2015). In *A. gambia* injection of a synthetic AKH increases flight performances and haemolymph carbohydrate but not lipids levels (Kaufmann and Brown, 2008). In several beetle species that use proline to pre-warm flight muscles but also for flight, AKH controls haemolymph proline levels (Gade and Auerswald, 2002). Likely because of its role in remobilizing fat body stores, a number of studies focused on the fat body AKH receptor, although it has been detected in a number of distinct cell types (Galikova and Klepsatel, 2023). In *R. prolixus*, the AKH receptor is highly expressed in fat body and flight muscles, and its knockdown results in lipid accumulation in both organs (Alves-Bezerra et al., 2016). In sum, the insulin/glucagon balance to control homeostatic storage and remobilization of carbohydrates and lipids is tightly conserved in insects (Chowanski et al., 2021) (see also chapter 6).

9.4. Integration of Carbohydrate/Lipid Metabolism at the Body Level

9.4.1. Carbohydrate and Lipid Homeostasis

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Systemic regulators of metabolic homeostasis conserved throughout evolution have been identified in insects. In feeding state, dietary sugar and amino acids act through the fat body to trigger insulin-like peptide (ILP) secretion from neurosecretory cells, which in turn mediate several aspects of body growth and metabolic homeostatic response, in particular sugar storage in the form of glycogen and TAGs (Wu and Brown, 2006; Toprak, 2020; Chowanski et al., 2021). Conversely, in case of high energy demand, neuropeptides such as AKH, AKH/Corazonin-related peptide and octopamine stimulate store breakdown to maintain homeostasis (Oguri and Steele, 2003; Roeder, 2005; Michitsch and Steele, 2008; Zhou et al., 2018; Toprak, 2020; Galikova and Klepsatel, 2023). Neutral lipids are always the major components of fat body stores. However, the TAG/glycogen storage ratio as well as their consumption depends on the insect species and on several parameters, including behavior, physiological status, aging and energy level requirement (Lorenz and Anand, 2004; Anand and Lorenz, 2008; Wang et al., 2016). This section focuses on the relationships between carbohydrate and lipid metabolism per se, whereas the mechanisms of endocrine regulation of lipid metabolism are extensively documented in other chapters.

A number of insect-based studies emphasize the metabolic links between carbohydrates and lipids. As mentioned above, this metabolic link is nicely illustrated by the phloem exclusive feeder *A. pisum*, producing lipids in excess that accumulate in fat body but also in cornicle secretions (Febvay et al., 1992; Rahbe et al., 1994). In *R. prolixus*, it has been shown that deficiency in insulin receptor signaling strongly drops TAG synthesis in the fat body after blood meal (Silva-Oliveira et al., 2021). In *Blattella germanica*, high sucrose diet increases the expression of ACC ─the rate-limiting enzyme of fatty acid synthesis─, while ACC-knockdown decreases TAG and cuticular hydrocarbons levels, and increases circulating sugar and glycogen storage (Pei et al., 2023). It has been shown in *P. americana* that FAs stimulate trehalose synthesis in isolated FB cells and that trehalose efflux into the haemolymph depends on arachidonic acid-derived metabolites (Ali et al., 1998; Ali and Steele, 1997). Furthermore, a co-dependence in lipid and glycogen synthesis has been reported in *C. pipiens* where inhibition of either results in decreased biogenesis of both glycogen and TAGs (Olademehin et al., 2020). In *Aedes aegypti* females, where lipid stores are mobilized for egg production, a constant carbohydrate dietary source is required to sustain the accomplishment of the gonotrophic cycles (Briegel et al., 2002; Zhou et al., 2004). In *Grapholita molesta*, while flight muscle energy relies on carbohydrate consumption, lipid stores constitute the main energy source in starvation condition(s) (Su et al., 2022). The flying morph of *Gryllus firmus* female consumes carbohydrates for flight, while TAG consumption is likely related to reproductive behavior in the non-flying reproductive morph (Zhang et al., 2011). A metabolic-based conflict between flight ability and egg production has been reported in several insect species. For instance, in *G. bimaculatus* adult females, carbohydrate and lipid stores are directed to egg production, while flight muscles are concurrently hydrolyzed (Lorenz, 2007). A screening-based study in *D. melanogaster* identified sirtuin 1 as a gene whose mutation results in fat accumulation but improved survival on a feeding media depleted in amino acid but supplemented with sugar (Reis et al., 2010). Another study investigating the relationship between dietary sugar and fat storage revealed that fructose was a more potent obesity-inducer than glucose (Rovenko et al., 2015). This effect likely results from the fructose-1P glycolytic route (§9.2.1), which bypasses the PFK1 rate-limiting reaction of glycolysis (Mor et al., 2011; Krause and Wegner, 2020). Dietary sugar excesses are harmful in humans but also in insects. In *D. melanogaster*, high sugar diet (HSD) has been shown to provoke fat accumulation in the cardiac tube and heart dysfunction, which in part depends on hexosamine metabolism (Na et al., 2013). These studies strengthen the notion that carbohydrate and lipid metabolisms are inseparable processes to maintain homeostasis and might suggest that high amounts of dietary glucose are directly routed to TAG storage through the glycolytic/TCA/Lipogenic axis. However, a *D. melanogaster* study indicates that under chronic HSD, mitochondrial acetyl-coA could be recycled through an anaplerotic/gluconeogenic pathway before being re-metabolized and incorporated into TAGs (Musselman et al., 2013). Further, a study focusing on muscle ACC in *D. melanogaster* supports that life-span extension upon diet restriction depends on a recycling loop of fat synthesis/oxidation (Katewa et al., 2012). In sum, the carbohydrate/lipid

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connection does not obligatory follow a unique direct axis but likely integrates within a complex metabolic network.

9.4.2. Sugar Diet and Type 2 Diabetic-Like Syndrome in D. melanogaster

The *D. melanogaster* model has been of powerful help in investigating the harmful effect of HSD. The Target of rapamycin (TOR) signaling network plays a critical role in metabolic-related diseases (Saxton and Sabatini, 2017; Moraes and Montagne, 2021). TOR is present in two distinct complexes, TORC1 and TORC2, which operate via two parallel branches in *D. melanogaster* (Radimerski et al., 2002). TORC1 integrates nutrient availability through the tumor suppressor TSC and the small GTPase Rheb, while TORC2 resides in the insulin signaling branch that includes the tumor suppressor PTEN and the kinase AKT. The metabolism of *D. melanogaster* larvae over-activating either the TORC1 or the insulin response branch exhibits a significant decrease in overall glycogen and trehalose levels (Devilliers et al., 2021). Nonetheless, insulin- but not TORC1-induced cell-autonomous overgrowth is significantly decreased by glycolysis or FA synthesis defect, suggesting that alternative metabolic strategies operate for TORC1- but not insulin-dependent growth (Devilliers et al., 2021). In mammals, mTOR-dependent metabolic regulations are in part mediated by the NAD^+-dependent deacetylases Sirtuins, as shown for SIRT4 (Csibi et al., 2013). In *D. melanogaster*, mutation of *Sirt4* results in shorter lifespan and increased TAG stores; these mutants are sensitive to starvation and weakly consume their carbohydrate and lipid upon fating (Wood et al., 2018). In *D. melanogaster*, while amino acid controls the production of ilp2 (Colombani et al., 2003), circulating sugar promotes selective release of Dilp3 from insulin producing cells (Kim and Neufeld, 2015).

To characterize the genomic response to dietary sugar, a microarray analysis identified the sucrose-induced transcription factor encoded by *sugarbabe* and showed that it can repress genes required for dietary lipid absorption and fat breakdown (Zinke et al., 2002). Further studies revealed that HSD fed larvae decrease food intake, were hyperglycemic and developmentally delayed compared to larvae fed control diet. HSD-fed larvae accumulate more TAGs, express higher ILPs both at mRNA and protein levels and exhibit decreased insulin response (Musselman et al., 2011; Pasco and Leopold, 2012; Musselman et al., 2013). In addition, larvae fed chronic HSD up-regulate genes of glycolysis, lipogenesis and trehalose synthesis, but also of gluconeogenesis and FA β-oxidation. Interestingly, obesity, ketogenesis, insulin resistance and increased gluconeogenesis are typical hallmarks of type 2 diabetes (Hatting et al., 2018). Congruent with a type 2 diabetic-like syndrome (Back and Kaufman, 2012), genes involved in endoplasmic reticulum and oxidative stresses are also misregulated in larvae fed chronic HSD (Musselman et al., 2013).

The E-box transcription factor Mondo ─homologue to the mammalian carbohydrate responsive element binding protein (ChREBP)─ is up-regulated in HSD fed larvae (Musselman et al., 2011). In mammals, ChREBP activity is stimulated by glycolytic metabolites to direct glucose usage (Richards et al., 2017; Havula and Hietakangas, 2018). In *D. melanogaster*, *Mondo* knockdown as well as mutation of its partner encoded by *Mlx*, result in high sugar sensibility and in the down-regulation of glycolytic and lipogenic genes in the fat body (Havula et al., 2013; Musselman et al., 2013). Consequently, Mondo and Mlx deficient larvae exhibited an increase in haemolymph sugar and a decrease in TAG and phospholipid levels. Finally, it has been shown that in response to dietary sugar, the Mondo/Mlx complex stimulates glycolysis and lipogenesis but also the pentose phosphate pathway amino acid biosynthesis, while repressing glucose intake and gluconeogenesis (Bartok et al., 2015; Mattila et al., 2015). These regulatory processes in part depend on Sugarbabe and on the TGF-β/Activin ligand Dawdle, either of them being metabolic regulators. On one hand, Dawdle has been shown to control the expression of carbohydrases and lipases in the enterocytes (Chng et al., 2014) and *Dawdle* mutant larvae exhibit elevated haemolymph sugars, TAG and glycogen stores (Ghosh and O'Connor, 2014). On the other hand, over-expressing Sugarbabe in insulin producing cells represses ilp3 expression, which in turn results in overall elevated TAG levels (Varghese et al., 2010). Finally, Sugarbabe has been shown to reside within an ERK7/TOR/PWP1 signaling axis to control fat body adiposity, where ERK7 is an anti-anabolic atypical MAP kinase and PWP1 a chromatin binding protein (Hasygar et

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al., 2021). Taken together these studies demonstrate that Mondo and TOR signaling integrate in a complex network to regulate lipid metabolism in response to carbohydrate load.

9.4.3. Sugar Toxicity and Lipogenesis

The metabolic links between obesity and carbohydrate support the notion that lipogenesis protects against excess dietary sugar. This lipogenic-dependent protection is strongly supported by the phenotype induced by the mutation in the *FASN1* gene that encodes the ubiquitous FASN enzyme in *D. melanogaster* (Garrido et al., 2015). These mutants are early larval lethal but can be rescued by an appropriate mixture of dietary lipids. These rescued mutants decrease their food intake and TAG stores and increase their glycogen stores and haemolymph trehalose, but fail to survive on sucrose-supplemented media. Surprisingly, this sensitivity to dietary sugar also operates at the cell-autonomous level, since *FASN1* mutant clones in the fat body are strongly reduced in size in HSD- but not standard- fed larvae (Garrido et al., 2015; Devilliers et al., 2021). An increase in AGEs (§ 9.2.2) is directly associated with high levels of circulating sugar in type 2 diabetic patients and is responsible for the harmful effects (Liu et al., 2023). Methylglyoxal that formed spontaneously from the glycolytic trioses phosphate GA3P and DHAP (Figure 2) is a very active glycation reagent, which is detoxified by the glyoxalase complex (Rabbani and Thornalley, 2012). Genetic interaction between *FASN1* mutation and *glyoxalase1* knockdown in *D. melanogaster* revealed that the toxic effect of sugar also depends on α-oxoaldehyde reagents, both at the organismal and cell-autonomous levels (Garrido et al., 2015). In addition, mutants for *glyoxalase 1* —encoding the first enzyme of the glyoxalase complex— are hyperglycemic, insulin resistant and exhibit elevated methylglyoxal levels and FASN1 activity (Moraru et al., 2018).

In conclusion, a critical function of lipogenesis is to protect against excesses of dietary carbohydrates. At first glance it may be surprising that the basic enzymatic pathway of FA synthesis is conserved throughout evolution suggesting that TAG synthesis is more important than the essential-FA metabolites for animal life. Therefore, it is tempting to surmise that the protection against dietary carbohydrates is more critical than the essential FA requirement. Evolution is canalized by environmental constraints. To survive to alternation of food availability and scarcity episodes, metabolic pathways have been selected in a way that carbohydrates, which are abundant but extremely toxic, can be stored in high amounts in the form of neutral lipids. Excess of food may induce metabolic syndrome and insulin resistance, in part because of lipotoxicity. However, the strong gene conservation of the glycolytic/TCA/lipogenic axis suggests that lipotoxicity is not as harmful as glucotoxicity.

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