Energy Cost of Inflammation in Dairy Cows

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Abstract

Metabolic maladaptation to lactation (ketosis) and heat stress are two economically devastating hurdles to profitability. Heat stress and ketosis affect herds of all sizes and almost every dairy region in the world. The biology of ketosis and heat stress has been studied for almost a half century, but the negative impacts of both are as evident today as they were 30 years ago. Our recent discoveries suggest that endotoxin is the common culprit in both disorders and the intestine appears to be the etiological origin of both metabolic disorders. Endotoxin stimulates the immune system and activated leukocytes switch their metabolism away from oxidative phosphorylation to rely more on aerobic glycolysis. In multiple species, we estimate that immune activation consumes about 1 g glucose/kg BW0.75 or about 2 kg glucose/day in an adult lactating dairy cow. Thus, an activated immune system reprioritizes nutrient partitioning away from the synthesis of economically valuable products.

Introduction

Suboptimal milk yield limits the U.S. dairy industry's productive competitiveness, marginalizes efforts to reduce inputs into food production, and increases animal agriculture's carbon footprint. There are a variety of situations in a cow's production cycle when nutrient utilization is reprioritized from milk synthesis towards agriculturally unproductive purposes. Two well-known examples that markedly reduce milk production are heat stress (**HS**) and the metabolic maladaptation to lactation (i.e., ketosis) following calving. Heat stress negatively impacts a variety of dairy production parameters including milk yield, milk quality and composition, rumen health, growth and reproduction, and is a significant financial burden (~$1 billion/year for dairy the U.S. alone; St. Pierre et al., 2003). Similarly, ketosis is a costly disorder (estimated at ~$300 per case; McArt et al., 2015) and also represents a major obstacle to farm profitability. While the metabolism of ketosis and HS has been studied for more than 40 years, the actual pathologies of both remain poorly understood. Suboptimal feed intake, experienced during both metabolic disorders, is unable to fully explain the decrease in productivity. In other words, the initial insult in the cascade of events ultimately reducing milk synthesis in both HS and ketotic cows has not been identified.

Heat Stress

Many reports indicate the global surface temperature is expected to increase (IPCC, 2007). High ambient temperature, especially when coupled with elevated humidity, imposes severe thermal stress and reduces performance in all agriculturally important species (Baumgard

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and Rhoads, 2011, 2013; Belhadj Slimen et al., 2015). Heat stress interferes with animal comfort and suppresses productive efficiency (Fuquay, 1981; Strong et al., 2015). Furthermore, it is well-known that selecting animals based on productivity increases their metabolic heat production which makes them less heat resistant. In other words, increased production decreases heat tolerance (Brown-Brandl et al., 2004; Spiers et al., 2004). During periods of HS, animals initiate major thermo-regulatory adaptations in order to maintain euthermia. The result of HS is underachievement of an animal's full genetic potential. It has traditionally been assumed that inadequate feed intake caused by the thermal load was responsible for decreased milk production (Fuquay, 1981; West, 2003; Strong et al., 2015). Presumably, reduced feed intake is a survival strategy as digesting and processing nutrients generates heat, especially in ruminants (i.e., thermic effect of feed; Collin et al., 2001; West, 2003). However, reduced feed intake only explains approximately 35 to 50% of the decreased milk yield during environmental-induced hyperthermia (Rhoads et al., 2009; Wheelock et al., 2010; Baumgard et al., 2011). Therefore, HS affects many production parameters either directly (i.e., decreased milk yield, increased mortality) or indirectly (i.e., via decreased feed intake; Collier et al., 2006; Adin et al., 2009; Hansen 2009; Baumgard and Rhoads, 2011, 2013; Mahjoubi et al., 2014). The remaining "direct" effects of HS are explained by the fact that heat-stressed animals exploit novel homeorhetic strategies to direct metabolic and fuel selection priorities independent of nutrient intake or energy balance.

Ketosis

The periparturient period is associated with substantial metabolic changes involving normal homeorhetic adaptations to support milk production. Early lactation dairy cattle enter a normal physiological state during which they are unable to consume enough nutrients to meet maintenance and milk production costs and animals typically enter into negative energy balance (**NEB**; Drackley, 1999). During NEB, cows mobilize non-esterified fatty acids (**NEFA**) in order to partition glucose for milk production in a homeorhetic strategy known as the "glucose sparing effect." These NEFA can undergo one of three fates: 1) energy production via complete oxidation through the TCA cycle; 2) partial oxidation to produce ketone bodies (acetone, acetoacetic acid, and β-hydroxybutyric acid [**BHBA**]; and 3) re-esterification to form triglycerides (**TAG**), which are either exported as very low density lipoprotein to deliver fatty acids to extra-hepatic tissue or "stored" in the liver (Ingvartsen, 2006; Ingvartsen and Moyes, 2013; McArt et al., 2013). Mitochondria available oxaloacetate is needed for fatty acid derived acetate to enter the TCA cycle; however, oxaloacetate exits the TCA cycle because it is a key gluconeogenic precursor during NEB and therefore full NEFA oxidation is limited. The ruminant liver has limited ability to export the large amount of NEFA mobilized from adipose tissue during NEB, resulting in hepatic TAG accumulation (Grummer, 1993; Drackley, 1999; Gross et al., 2013). Consequently, ketone body production is a mechanism by which fatty acids can be partially oxidized in the liver and exported into the bloodstream as a water-soluble, transportable form of acetyl units to peripheral tissues. In dairy cattle, ketosis is arbitrarily defined as an excess of circulating ketone bodies and is characterized by decreases in feed intake, milk production, and increased risk of developing other transition period diseases (Chapinal et al., 2012). Epidemiological data indicate about 20% of transitioning dairy cows clinically experience ketosis (BHBA > 3.0 mM; Gillund et al., 2001) while the incidence of subclinical ketosis (>1.2 mM BHBA) is thought to be much higher (> 40%; McArt et al., 2012).

Therefore, ketosis is thought to result from an imbalance in energy demand, excessive adipose tissue mobilization, and increased ketone body production in hepatic tissue (Drackley et al., 2001; Garro et al., 2014).

Heat Stress Etiology

Mechanisms responsible for altered nutrient partitioning during HS are not clear; however, they might be mediated by HS effects on gastrointestinal health and function as we and others have demonstrated HS compromised intestinal barrier function (Lambert et al., 2002; Dokladny et al., 2006; Yang et al., 2007; Pearce et al., 2013; Sanz-Fernandez et al., 2014). During HS, blood flow is diverted from the viscera to the periphery in an attempt to dissipate heat (Lambert et al., 2002), leading to intestinal hypoxia (Hall et al., 1999). Enterocytes are particularly sensitive to hypoxia and nutrient restriction (Rollwagen et al., 2006), resulting in ATP depletion and increased oxidative and nitrosative stress (Hall et al., 2001). This contributes to tight junction dysfunction and gross morphological changes that ultimately reduce intestinal barrier function (Lambert et al., 2002; Pearce et al., 2013). As a result, HS increases the passage of luminal content into portal and systemic blood (Hall et al., 2001; Pearce et al., 2013). Endotoxin, otherwise referred to as lipopolysaccharide (**LPS**), is a glycolipid embedded in the outer membrane of gram-negative bacteria, which is abundant and prolific in luminal content, and is a well-characterized potent immune stimulator in multiple species (Berczi et al., 1966; Giri et al., 1990; Tough et al., 1997). Activation of the immune system occurs when LPS binding protein (**LBP**) initially binds LPS and together with CD14 and TLR4 delivers LPS for removal and detoxification, thus LBP is frequently used as a biomarker for LPS infiltration (Ceciliani et al., 2012). For a detailed description of how livestock and other species detoxify LPS, see our recent review (Mani et al., 2012). Endotoxin infiltration during HS into the bloodstream which was first observed by Graber et al. (1971), is common among heat stroke patients (Leon, 2007), and is thought to play a central role in heat stroke pathophysiology as survival increases when intestinal bacterial load is reduced or when plasma LPS is neutralized (Bynum et al., 1979; Gathiram et al., 1987). It is remarkable how animals suffering from heat stroke or severe endotoxemia share many physiological and metabolic similarities to HS, such as an increase in circulating insulin (Lim et al., 2007). Infusing LPS into the mammary gland increased (~2 fold) circulating insulin in lactating cows (Waldron et al., 2006). In addition, we intravenously infused LPS into growing calves and pigs and demonstrated >10 fold increase in circulating insulin (Rhoads et al., 2009; Kvidera et al., 2016, 2017c). Interestingly, increased insulin occurs prior to increased inflammation and the temporal pattern agrees with our previous in vivo data and a recent in vitro report (Bhat et al., 2014) suggesting LPS stimulates insulin secretion, either directly or via GLP-1 (Kahles et al., 2014). The possibility that LPS increases insulin secretion likely explains the hyperinsulinemia we have repeatedly reported in a variety of heat-stressed agriculture models (Baumgard and Rhoads, 2013). Again, the increase in insulin in both models is energetically difficult to explain as feed intake was severely depressed in both experiments.

Transition Period Inflammation

Recently, the concept that LPS impacts normal nutrient partitioning and potentially contributes to metabolic maladaptation to lactation has started to receive attention. Although LPS itself has not been the primary causative focus, general inflammation has been the topic of numerous investigations. Increased

inflammatory markers following parturition have been reported in cows (Ametaj et al., 2005; Humblet et al., 2006; Bertoni et al., 2008; Mullins et al., 2012). Presumably, the inflammatory state following calving disrupts normal nutrient partitioning and is detrimental to productivity (Loor et al., 2005; Bertoni et al., 2008), and this assumption was recently reinforced when TNFα infusion decreased productivity (albeit without overt changes in metabolism; Yuan et al., 2013; Martel et al., 2014). Additionally, in late-lactation cows, injecting TNFα increased (>100%) liver TAG content without a change in circulating NEFA (Bradford et al., 2009). Our recent data demonstrates increased inflammatory markers in cows diagnosed with ketosis only and no other health disorders. In comparison with healthy controls, ketotic cows had increased circulating LPS prior to calving and post-partum acute phase proteins, such as LPS-binding protein, serum amyloid A, and haptoglobin, were also increased (Figure 1; Abuajamieh et al., 2016).

Endotoxin can originate from a variety of locations, and obvious sources in transition dairy cows include the uterus (metritis), mammary gland (mastitis), and the gastrointestinal tract (Mani et al., 2012). However, we believe intestinal permeability may be a prime contributor to inflammation in the transition dairy cow. Post-calving, dairy cows undergo a dietary shift from a high-forage to a high concentrate ration, and these grains can be rapidly fermented at a rate exceeding removal of volatile fatty acids, resulting in depressed ruminal pH (Owens et al., 1998). Consequently, rumen acidosis may be induced and this can compromise the gastrointestinal tract barrier (Khafipour et al., 2009). In order to further investigate the effects of intestinal permeability on production and inflammation, we intentionally induced intestinal permeability in mid-lactation dairy cows using a gamma secretase inhibitor (**GSI**),

a compound that specifically inhibits crypt stem cell differentiation into enterocytes via disrupting Notch signaling (van Es et al., 2005). We anticipated feed intake of GSI administered cows would decrease, so we pair-fed controls in order to eliminate the confounding effect of dissimilar feed intake. In agreement with characteristics of leaky gut, treatment with GSI decreased feed intake and altered jejunum morphology (shortened crypt depth, decreased villus height, and decreased villus height to crypt depth ratio). Furthermore, circulating insulin and LBP increased in GSI cows relative to controls. Interestingly, circulating serum amyloid A and haptoglobin of pair-fed controls increased similarly to GSI treated cows, indicating inflammation was occurring in both treatments (Kvidera et al., 2017b). This is not surprising, as pair-fed controls were receiving ~20% of their ad libitum intake and decreased feed intake has been shown to increase intestinal permeability in feed restricted rodents and humans (Rodriguez et al., 1996; Welsh et al., 1998) and we have also observed this in pigs (Pearce et al., 2013; Sanz-Fernandez et al., 2014). Recently, we confirmed the detrimental effects of feed restriction in mid-lactation cows by demonstrating a linear increase in circulating acute phase proteins and endotoxin with increasing severity of feed restriction. Furthermore, cows fed 40% of ad libitum intake had shortened ileum villous height and crypt depth, indicating reduced intestinal health (Kvidera et al., 2017d). In summary, inflammation is present during the transition period and likely contributes to changes in whole-animal energetics.

Metabolism of Inflammation

LPS-induced inflammation has an energetic cost which redirects nutrients away from anabolic processes that support milk and muscle synthesis (see review by Johnson, 1997, 1998, Figures 2,3,4) and thus compromises

productivity. Upon activation, immune cells become obligate glucose utilizers via a metabolic shift from oxidative phosphorylation to aerobic glycolysis, a process known as the Warburg effect. This metabolic shift allows for rapid ATP production and synthesis of important intermediates which support proliferation and production of reactive oxygen species (Calder et al., 2007; Palsson-McDermott and O'Neill, 2013). In an effort to facilitate glucose uptake, immune cells become more insulin sensitive and increase expression of GLUT3 and GLUT4 transporters (Maratou et al., 2007; O'Boyle et al., 2012), whereas peripheral tissues become insulin resistant (Maitra et al., 2000; Poggi et al., 2007; Liang et al., 2013). Furthermore, metabolic adjustments including hyperglycemia or hypoglycemia (depending upon the stage and severity of infection), increased circulating insulin and glucagon, skeletal muscle catabolism, and subsequent nitrogen loss (Wannemacher et al., 1980), and hypertriglyceridemia (Filkins, 1978; Wannemacher et al., 1980; Lanza-Jacoby et al., 1998; McGuinness, 2005) occur. Interestingly, despite hypertriglyceridemia, circulating BHBA often decreases following LPS administration (Waldron et al., 2003a,b; Graugnard et al., 2013; Kvidera et al., 2017a). The mechanism of LPS-induced decreases in BHBA has not been fully elucidated, but may be explained by increased ketone oxidation by peripheral tissues (Zarrin et al., 2014). In addition to changes in circulating metabolites, LPS has been shown to increase liver lipid accumulation both directly through changes in lipid oxidation and transport enzymes and indirectly through increases in circulating NEFA (Bradford et al., 2009). Collectively, these metabolic alterations are presumably employed to ensure adequate glucose delivery to activated leukocytes.

Adequately fueling immune cells is a critical component in successfully mounting an effective immune response (MacIver et al., 2008). Improving glucose availability can increase longevity and function of activated leukocytes (Sagone et al., 1974; Furukawa et al., 2000; Healy et al., 2002; Garcia et al., 2015). Thus, mitigation strategies which may help divert glucose towards immune cells have the potential to improve function. Interestingly, Lee et al., (2000), observed increased glucose uptake and improved macrophage function with chromium supplementation, likely due to chromium's role in improving insulin sensitivity. We have also demonstrated increased circulating neutrophils in both pigs (Mayorga et al., 2016) and cows (Horst et al., 2018) with chromium supplementation.

Energetic Cost of Immune Activation

The energetic cost of immunoactivation is substantial, but the ubiquitous nature of the immune system makes quantifying the energetic demand difficult. Therefore, our group recently employed a series of LPS-euglycemic clamps to quantify the energetic cost of an activated immune system. Using this model, we estimated approximately 1 kg of glucose is used by the immune system during a 12 hour period in lactating dairy cows. Interestingly, on a metabolic body weight basis, the amount of glucose utilized by LPS-activated immune system in lactating cows, growing steers, and growing pigs were 0.64, 1.0, and 1.1 g glucose/kg $BW^{0.75}$/h, respectively; Kvidera et al., 2016, 2017 a,c). Increased immune system glucose utilization occurs simultaneously with infection-induced decreased feed intake; this coupling of enhanced nutrient requirements with hypophagia obviously decrease the amount of nutrients available for the synthesis of valuable products (milk, meat, fetus, and wool).

We and others have now demonstrated that both HS and ketotic animals have

increased circulating markers of endotoxin and inflammation. We believe that the circulating LPS in both maladies originates from the intestine and thus both likely have an activated immune system. This activated systemic immune response reprioritizes the hierarchy of glucose utilization, and milk synthesis is consequently deemphasized.

Conclusion

Altogether, our studies suggest that ketosis and HS may share the same etiology (i.e., decreased gut integrity) as indicated by altered intestinal morphology and increased plasma inflammatory biomarkers. This inflammation can redirect resources normally used for growth, milk production, and reproduction toward agriculturally unproductive purposes. More research is still needed to understand the mechanisms and consequences of intestinal permeability and associated inflammation in order to provide foundational information for developing strategies aimed at maintaining productivity during HS and the transition period.

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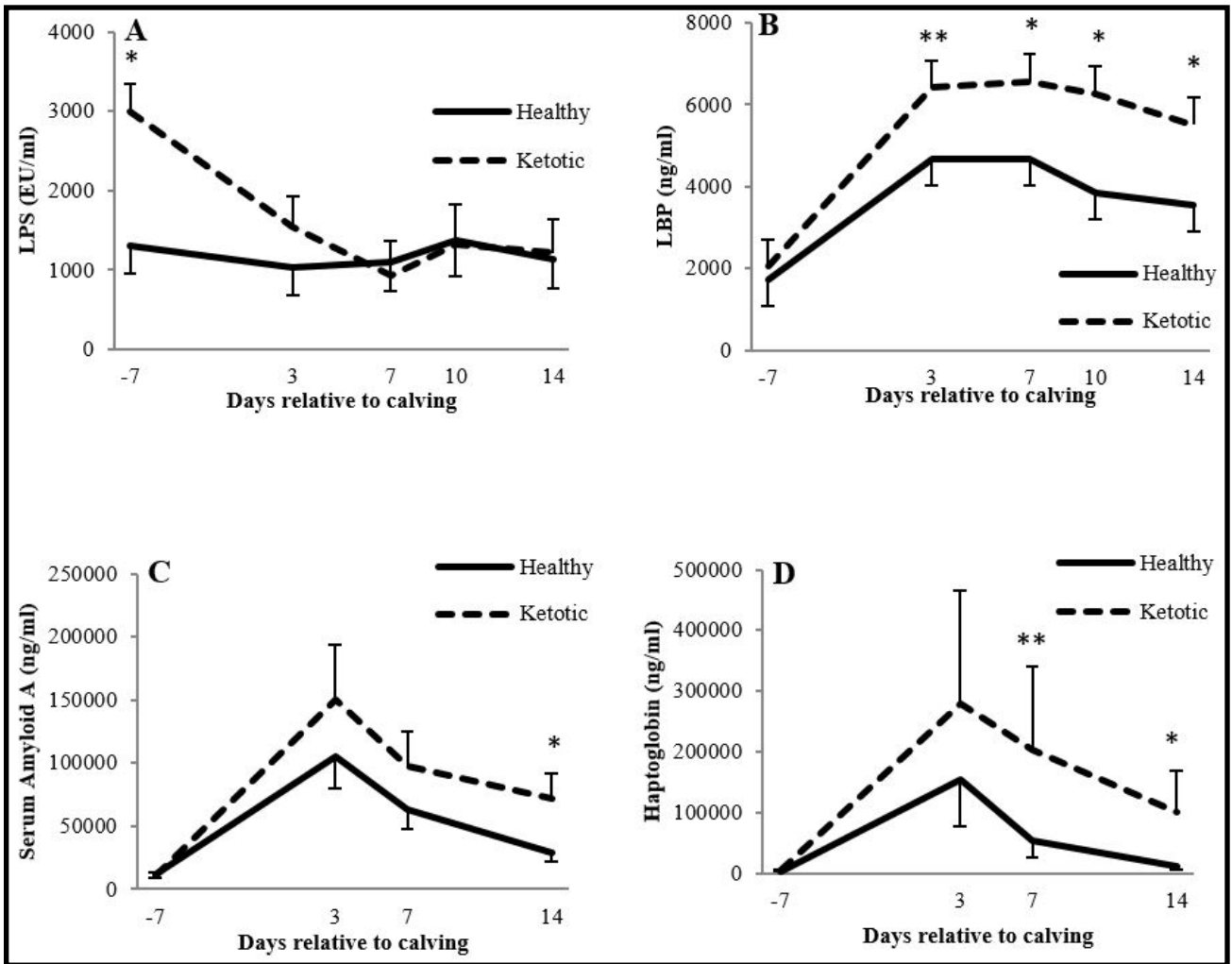
Figure 1. Markers of inflammation in healthy (solid line) and ketotic (dashed line) transition cows (LPS = lipopolysaccharide and LBP = LPS binding protein; Abuajamieh et al., 2016).
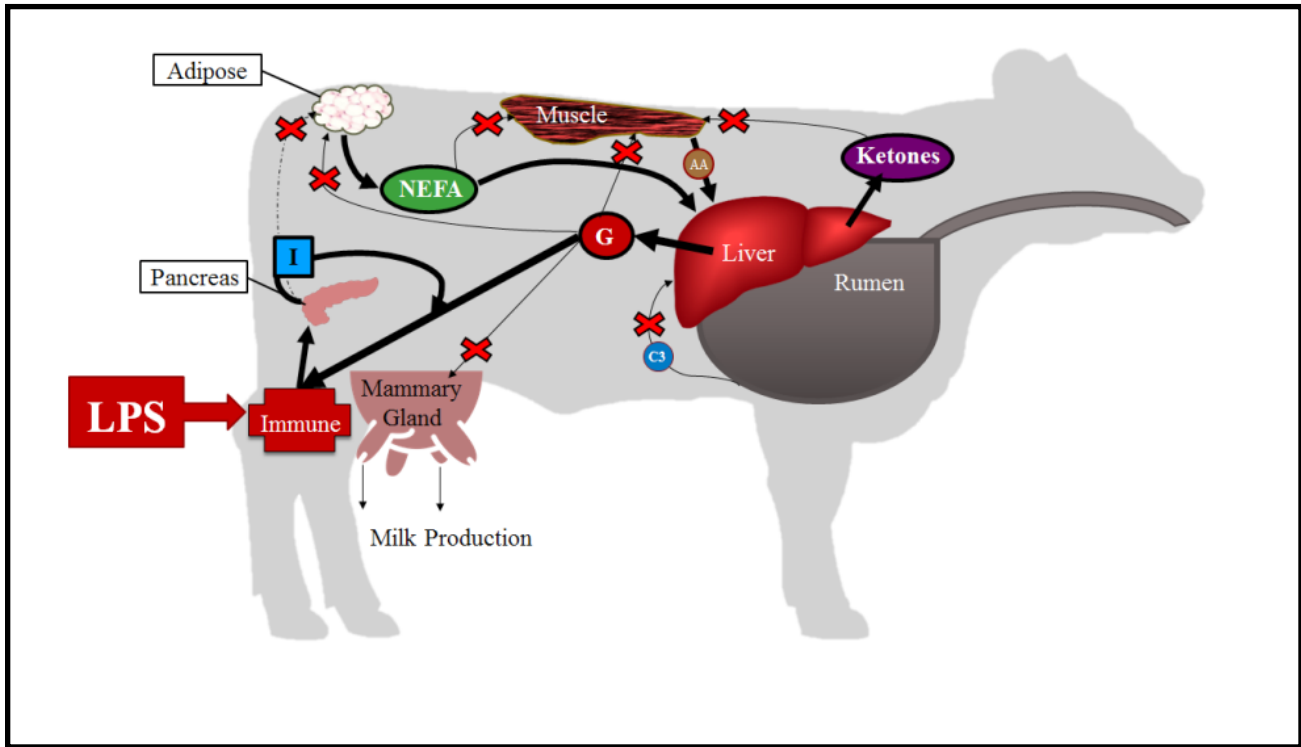
Figure 2. Lipopolysaccharide (LPS) induced alterations in glucose metabolism and insulin sensitivity.
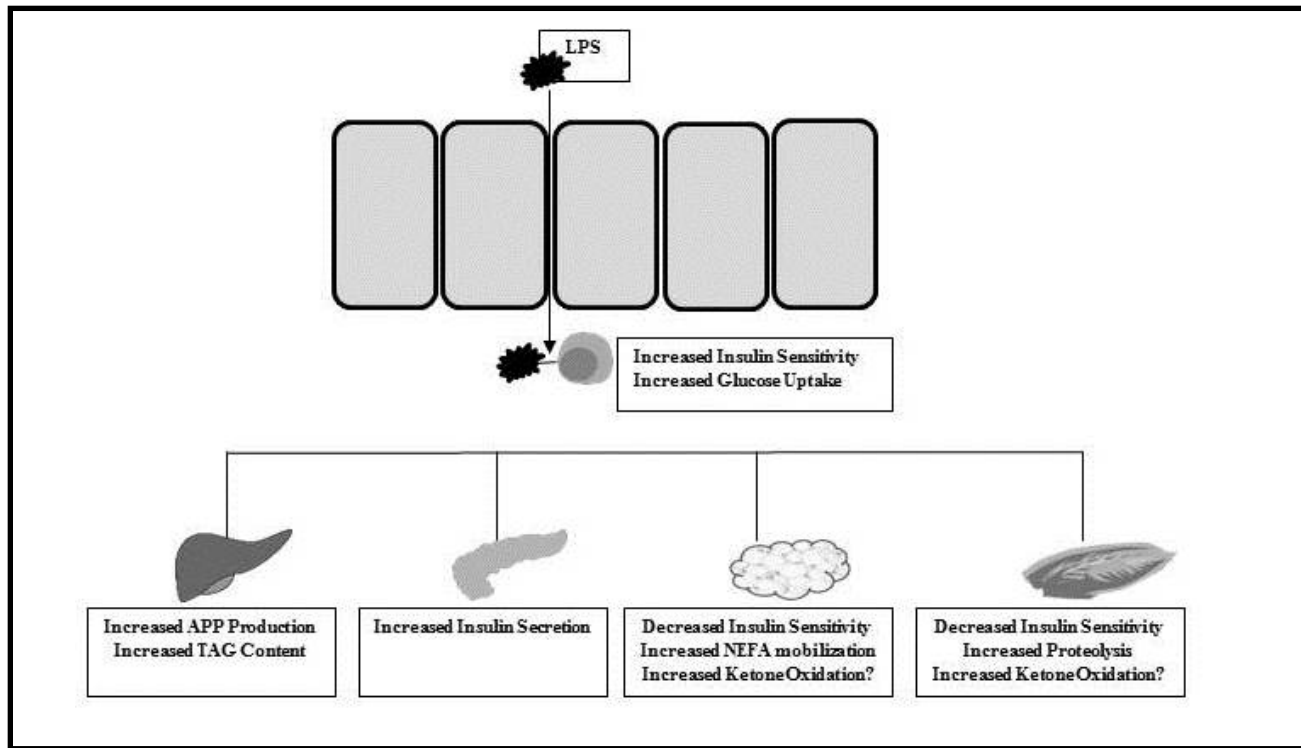

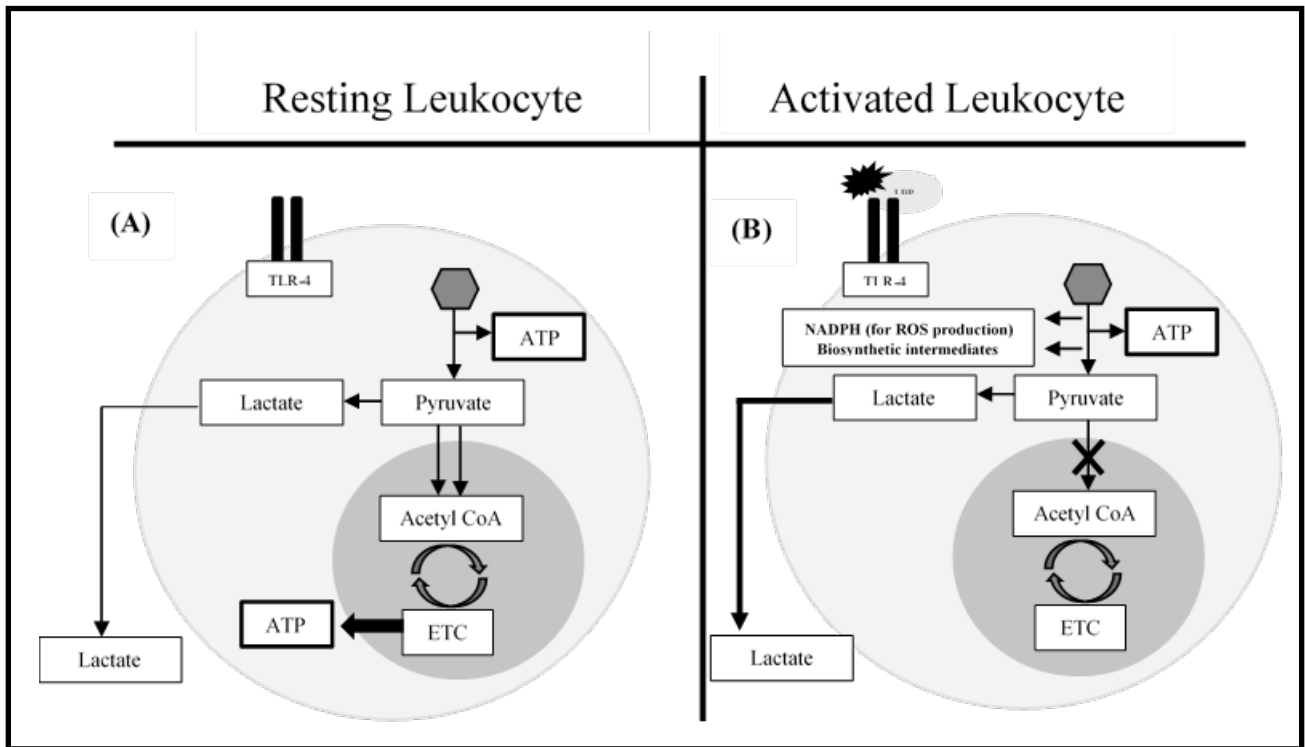**Figure 3.** Lipopolysaccharide (LPS) induced alterations in peripheral metabolism

Figure 4. Metabolic pathway of a resting (A) vs. activated (B) leukocyte.