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Sepsis: a failing starvation response

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Abstract

Sepsis is involved in roughly 20% of annual global deaths. Despite decades of research, the current management of sepsis remains supportive rather than curative. Clinical trials in sepsis have mainly been focused on targeting the inflammatory pathway, however without success. Considering the recent data supporting metabolic dysregulation in sepsis lethality, targeting metabolic pathways might hold much promise for success at the bedside. Here, we suggest that sepsis yields a strong starvation response, including release of high-energy metabolites, such as lactate and free fatty acids. However, two major transcription factors, GR and PPARα, lose activity in hepatocytes thereby leading to accumulation and toxicity of these metabolites, and lack of transformation of these to useable molecules such as glucose and ketones. We review the literature and suggest mechanisms and potential therapeutic targets that might prevent or revert the fatal metabolic dysregulation in sepsis.

Keywords: sepsis, GR, PPARα, lactate, free fatty acids, ketone bodies

Sepsis

Sepsis is a syndrome that is associated with very high mortality: according to the latest global estimates of sepsis incidence and mortality, 49 million people are affected yearly, leading to 11 million casualties, which corresponds to 20% of all deaths worldwide [1]. The sepsis incidence is expected to increase further considering the aging of the world population, the increased use of invasive medical devices and bacterial multi-drug resistances. In 2017, the WHO has labelled sepsis as a global health priority and the most urgent unmet medical need of our times [2]. Despite most sepsis cases are of bacterial origin, the COVID-19 pandemic has increased sepsis awareness more than ever, since virus-borne sepsis is the main cause of death in COVID-19 patients [3]. Unfortunately, after decades of research, the pathogenesis of sepsis remains poorly understood and no successful therapeutic drug has emerged that has clear impact on the patient's outcome. To date, the management of sepsis is supportive rather than curative and essentially relies on antibiotic treatment, hemodynamic stabilization and support of organs at risk of failing [4]. It is clear that finding successful therapeutic targets for treating sepsis patients will have far-reaching impact. For that to happen, we first need to try to assemble the puzzle of sepsis carefully and completely.

In 2016, a new definition of sepsis (Sepsis-3) was introduced as "a life-threatening organ dysfunction caused by a dysregulated host response to infection" [5] which emphasizes the importance of a maladapted host response to infection, rather than the infection itself, causing disease progression. Classically, the pathophysiology of sepsis is considered as an initial hyperinflammatory phase that lasts for several days followed by a more protracted immunosuppressive phase [6]. However, numerous inflammation-blocking and immune-stimulating drugs have failed in clinical trials [7].

It is becoming increasingly clear that also a maladapted, or non-homeostatic, metabolic response contributes to the disease. The pathogenesis of sepsis involves tachycardia, fever, tachypnea, immune activation, coagulation, complement activation and acute phase response induction, all requiring supra-physiological energy supplies [4]. However, despite their increased energy needs, septic subjects are usually unwilling or unable to eat (i.e. **anorexia**, see Glossary), which leads to a negative energy balance [8–10]. Hence, sepsis progression appears to be associated with the induction of a **starvation** response (SR), and it needs to be examined whether the latter is cause of the former.

The starvation response (SR)

The physiological response of mammals to shortage in food is well-developed and conserved after millions of years of evolution on a planet showing seasons, ice-ages and periods of limited food accessibility. In response to food shortage, some species (e.g. arctic animals) reduce their energy consumption by reducing their metabolic needs, reducing their body temperature and entering into **hibernation** [11]. Other species (the house mouse *Mus musculus*, humans) can keep up their needs by addressing calorie reserves of different sorts, that have been built up in several organs. This is the highly conserved and strictly regulated SR, in which the liver, muscle and white adipose tissue play a central role [12] **(Figure 1)**. The SR is coordinated a.o. by several hormones (such as glucagon) and basically consists of two discrete parts. In the first part, peripheral tissues will consume reserves thereby generating ATP for own use as well as release high-energy metabolites, such as glucose and gluconeogenic amino acids upon resp. glycogenolysis and proteolysis in muscle, and fatty acids and glycerol upon lipolysis in white adipose tissue. In the second part of the SR, these metabolites are then transformed by the liver into molecules that can directly enter ATP-generating pathways in distant organs, such as heart and brain **(Box 1)**.

Sepsis and the SR

Several observations suggest that sepsis leads to the initiation of a typical SR. First, it is a well-known phenomenon that septic humans and animals do not eat or are unwilling to eat [8–10]. Second, in sepsis, the amount of cellular glycogen, white adipose tissue (WAT) as well as muscle mass are declining fast [8,13,14]. Third, several large proteomic and metabolic screens on plasma of sepsis patients identified glucose metabolism and fatty acid **beta-oxidation** pathways as being significantly different between sepsis survivors and non-survivors [15–17]. Indeed, the blood levels of high energy metabolites (**free fatty acids (FFA)**, glycerol, lactate and gluconeogenic amino acids) were found to be increased in a way which correlates directly with disease severity and lethality in both sepsis patients and animals [8,13,15,16]. In view of the increased requirements of energy in sepsis patients, and the reduced intake because patients 'are too sick to eat', the initiation of the first part of the SR could make sense. However, given the link between high energy metabolites and disease severity, we wonder whether the activation of the SR is of any benefit and successful in sepsis.

Is the SR sufficient and successful in sepsis?

Average human beings contain reserves to withstand a SR of up to 1-2 months, provided no excessive physical efforts are performed and water is consumed. In sepsis, however, the required amounts of energy increases drastically [18], and hence it seems conceivable that the SR in sepsis is insufficient to provide the required energy. If so, a persistent, inadequate SR in sepsis may prove to be contributing to lethality. Adding energy rich metabolites (e.g.

FFAs) to sepsis patients would be of interest, provided the second phase of the SR is functioning well. This is however not the case (see next chapter) and therefore, the addition of ketone bodies might prove to be the only possible energy rich supplement that might be of help in sepsis. Indeed, there is clear evidence, from animal sepsis models, that the success of the SR in sepsis is hampered because the key transcription factors (glucocorticoid receptor (GR) and peroxisome proliferator-activated receptor alpha (PPARα)) in the second phase of the SR appear to lose activity in hepatocytes [8,13]. The underlying mechanisms, as well as potential intervention strategies will be discussed in the next chapters.

Glucocorticoid resistance in sepsis leads to hypoglycemia and hyperlactatemia

The GR mediates the actions of glucocorticoids (GCs) in cells. GR belongs to the nuclear receptor superfamily of transcription factors and is a 97 kDa protein that is constitutively and ubiquitously expressed in most cells of the body. GR can regulate the expression of GC-responsive genes in a positive or negative manner. It is estimated that 1,000 to 2,000 genes are subject to GR mediated regulation, and some studies suggest that up to 20% of all genes are responsive to the GR [19,20]. GR can directly bind to DNA to modulate transcription, via GR-interacting transcriptional co-factors, mediator complex and RNA polymerase II, but it can also perform protein-protein interaction with other transcription factors (for example p65 member of NFkB) to modulate gene expression [19,20].

GR signaling is essential for surviving sepsis, because mice with cell- or tissue-specific deletion of the GR [21], or mutant $GR^{dim/dim}$ mice (which express a suboptimal functioning GR [22], have an increased risk of death following sepsis [23,24]. Similarly, pharmacological inhibition of GR with RU486, or surgical removal of adrenals, which disrupts endogenous corticosterone production, also sensitizes mice for sepsis [25–27]. Despite the indispensable role for GR in mediating protection during acute inflammation, defective GR signaling is observed in several organs of mice in sepsis models such as in tumor necrosis factor (TNF)-induced lethal shock [28,29] and **CLP**-induced polymicrobial sepsis [8]. Poor GR function has also been demonstrated in white blood cells of sepsis patients, and this defective GR activity might explain the limited benefits of GC therapy in sepsis patients [30,31]. In the CLP model, a genome-wide GC resistance is observed in the liver as assessed by transcriptome analysis upon administration of the GR ligand dexamethasone (DEX) during the course of sepsis, as compared to healthy animals treated with DEX [8]. This GR signaling defect is strongly associated with a reduced binding capacity of GR to DNA [8]. Besides its well-known anti-inflammatory effects, GR also controls critical metabolic functions such as **gluconeogenesis**. Mice with a hepatocyte-specific GR knockout have normal blood glucose levels under basal conditions but display hypoglycemia after food deprivation [32]. The septic body is depending on a SR to provide energy, however, as recently studied in detail in the CLP model, the GR response to ligands is already critically low less than 6 h after the onset of sepsis. In such condition, even though endogenous GCs are produced by the adrenals, the gluconeogenesis response cannot be activated successfully. The failure of GR to respond to GCs forms the basis of a poor gluconeogenesis and leads to hypoglycemia and, moreover, to the accumulation of gluconeogenic substrates, such as lactate and gluconeogenic amino acids [8,15,33].

The role of lactate in sepsis

It is well known that lactate levels are high in septic blood and correlates well with disease severity in both humans and mice [34]. Although a normal SR does not cause accumulation of lactate, in sepsis lactate may increase because (1) it is produced in higher amounts and/or (2) it is cleared less during sepsis. The main mechanism to clear lactate is via hepatic gluconeogenesis (also called the **Cori cycle**) [35]. Based on our studies, we propose that, as a result of glucocorticoid resistance and concomitant gluconeogenesis failure, lactate cannot be cleared efficiently and further accumulates in the circulation during sepsis [8]. Both hypoglycemia and hyperlactatemia are key indicators of a poor prognosis in sepsis [36]. Further research is warranted to study whether reversal of glucocorticoid resistance in sepsis will reactivate gluconeogenesis and subsequently enhance lactate clearance, and whether this strategy is of benefit in sepsis, given the different biological activities of lactate, described in next point. To date, the mechanism underlying the reduced GR-DNA binding in CLP mice has not yet been uncovered. Oxidation of cysteines in the zinc fingers of GR [37], acetylation of lysine residues in the hinge region of the GR [38], or binding of non-coding RNAs to the DBD of the GR [39], are all possible causes. Alternatively, modifications at the level of the DNA (for example through DNA methylation or histone modifications) [40] can account for the reduced GR-DNA binding in sepsis. Whether other mechanisms such as reduced cofactor availability contribute to the GC resistance, as is observed in TNF model [28], remain to be studied. Understanding the mechanisms involved in GC resistance may open new opportunities to reverse its cause and preserve GR signaling in sepsis.

*Lactate as an **immune-metabolite***

Lactate is a validated marker of illness severity in sepsis patients [5]. The third international consensus definitions for sepsis and septic shock (Sepsis-3) has included hyperlactatemia within the clinical criteria for septic shock [5]. For years, lactate was considered as an inert by-product that accumulates at inflammatory sites. Elevated levels of circulating lactate were believed to be the result of inadequate oxygen delivery and impaired aerobic respiration in tissues [34]. However, it is becoming increasingly clear that other factors, such as activation of the stress response (and release of epinephrine), accelerated aerobic **glycolysis** flux, or reduced hepatic clearance as described above, also contribute to hyperlactatemia [34]. Lactate is now thought to play a causal role in sepsis as is illustrated below.

Intraperitoneal injection of lactate leading to peak blood lactate values of 20 mM, which is the value of lactate typically observed in the sickest mice after CLP surgery, are not causing detrimental effects in a normal, healthy mouse [8]. However, administration of this lactate dose to mice with a defect in their GR signaling pathway leads to acute lethality within 24 h. This lethality is caused by an uncontrolled production of vascular endothelial growth factor, resulting in vascular leakage, hypotension and organ damage [8]. Similarly, addition of lactate to CLP mice decreases their survival when compared to septic control mice [41]. As sepsis leads to both glucocorticoid resistance and hyperlactatemia, this combination can thus be the cause of lethal shock in sepsis as demonstrated in the CLP model. Liver biopsies harvested from human patients who had died of sepsis in the ICU show reduced expression of GR compared to the levels observed in elective surgery patients [24]. Whether these reduced hepatic GR levels in human sepsis patients also lead to a lack of GR responsiveness and concomitant decreased gluconeogenesis and increased lactate sensitivity in human sepsis patients, will need further investigation. Beyond unfettered VEGF production, lactate also causes vascular permeability by promoting macrophage high mobility group box-1 (HMGB1) **lactylation**, acetylation and exosomal release. These effects are mediated through the lactate receptor GPR81 (also known as hydroxy-carboxylic acid receptor 1 (HCAR1)), a Gi-protein coupled receptor) as treatment of lactate-treated macrophages or CLP mice with the GPR81 antagonist 3-hydroxybutyrate (3-OBA) reduces the release of exosomal HMGB1 [41]. Next to increasing vascular permeability, lactate has also been found to induce vascular relaxation in porcine coronary arteries [42]. Lactate-induced vascular relaxation is desirable in conditions of ischemia or exercise to increase blood flow. However, in septic condition, vasorelaxation poses risks for inducing vasodilatory shock [43].

From these studies, it follows that lactate has the potential to play a major detrimental role in sepsis, as endothelial permeability and vasodilation are thought to be key factors in the progression of sepsis [44]. Studies have shown that lactate, HMGB1 and VEGF are increased in human sepsis patients and correlate well with disease severity [45,46]. Further research is required to see whether inhibition of lactate signaling in human sepsis patients is able to reduce vascular permeability and shock, resulting in improved survival.

Besides the above-mentioned studies, many other studies have found a role for lactate in modulating the immune response. Recently, it has been shown that D-lactate derived from the gut microbiota promote Kupffer cell (KC) mediated pathogen clearance [47]. KCs are the major immune cell type in the liver and play a key role in sepsis [48]. Indeed, KCs act as an alarm system for the immune system and protect against pathogen dissemination during infection. Whether circulating host-derived L-lactate acts on KCs however remain to be studied. **Table 1** gives an overview of both the pro- and anti-inflammatory functions that L-lactate exerts in different cell types. The pro-inflammatory effects of lactate are in sharp contrast to its anti-inflammatory effects described in literature. Possible explanations for this discrepancy include the use of lactic acid versus sodium lactate, lactate dose and setup of the experiment (e.g. prophylactic administration of lactate to LPS-stimulated macrophages versus lactate alone to macrophages). Also, lactate may have opposing effects depending on the activation status of the cells or depending on the (patho)physiological conditions.

Not surprisingly, given the many effects that lactate exerts, interfering with lactate production and/or signaling can either sensitize or protect in sepsis. **Table 2** provides an overview of mechanisms used to interfere with lactate production or signaling and how this affects sepsis progression. **Figure 2** is an overview of drugs that interfere with lactate signaling. As interfering with lactate signaling targets sepsis progression at many different levels, this poses an interesting therapeutic opportunity for treating human sepsis patients.

Cardioprotective function of lactate

Besides the role of lactate as immune-metabolite and as mediator of vascular permeability, lactate also exerts cardioprotective functions. Indeed, lactate, and no longer FFAs, is used as a prime substrate for energy production preferentially utilized by the myocardium during shock [49]. In a healthy heart, the consumption of lactate is balanced by the concurrent production of lactate from glycolytic pyruvate. During heart failure, however, this balance is lost as glycolytic pyruvate is preferentially converted to lactate followed by excretion of lactate via its exporter MCT4/Slc16a3. This excretion limits lactate consumption by the heart and via this way mitochondrial pyruvate oxidation is prevented. Interestingly, pharmacological inhibition of MCT4 mitigates heart failure in mice by modulating the pyruvate-lactate axis [49]. In endotoxic shock, myocardial lactate deprivation with a selective β2-adrenergic blocker or enhancing lactate metabolism with dichloroacetate is associated with cardiovascular collapse and early death [50]. Infusion of low lactate doses during the first 18 h after CLP surgery protects septic mice against cardiac dysfunction, mesenteric microcirculation alteration, and capillary leakage and simultaneously reduces inflammation and increases ketone body levels [51]. Similarly, infusion of lactate increases cardiac performance in human patients with both cardiogenic and septic shock [36].

In conclusion, lactate possesses pleiotropic functions that can contribute to the sepsis pathobiology either in a positive or negative way. Further research is warranted to fully understand the implications of increased lactate levels in sepsis patients. Overall, it seems that low doses of lactate may have protective effects, for example by providing energy to the heart, whereas excessive lactate levels in plasma - as is observed in patients with septic shock - is causing lethality by inducing vascular dysfunction.

PPARα resistance leads to FFA accumulation and reduced ketogenesis

PPARα is a nuclear receptor, bound and activated by fatty acids and derivatives and has effects on both metabolism and inflammation. It is a 52 kDa protein highly expressed in metabolic tissues such as liver, kidney, heart, muscle and the vasculature, as well as in immune cells. Activated PPARα regulates the expression of many hundreds of genes and several of its transcriptional targets, such as *Cpt1*, *Cpt2* and *Slc25a20*, are responsible for fatty acid beta-oxidation, which occurs in peroxisomes and mitochondria, and leads to acetyl-coA [52]. This metabolite, under influence of PPARα-induced gene products is subject to **ketogenesis** [53] **(Figure 1)**. Ketogenesis ensures that not all energy which is contained in FFAs is entirely degraded to acetyl-CoA (and further to CO_2 and H_2O) in the liver TCA cycle, but that other organs, with much less FFA oxidation capacity can profit from the FFAs released after **lipolysis** [4].

PPARα is essential for survival in sepsis as PPARαKO mice display enhanced susceptibility in the LPS model [9] and in bacterial infection models [54,55], which is associated with increased heart injury and kidney failure [55,56]. Similarly, PPARα inhibitors sensitize in the mouse CLP model [13]. In the liver, PPARα expression is essential for ketone body production, as mice with hepatocyte-specific PPARα deficiency show lower ketone body production during infection and increased mortality similarly as observed in full KOs [9,54]. A clear association between ketone body levels (β-hydroxybutyrate) and survival is found in human sepsis patients. In one study, β-hydroxybutyrate levels in non-survivors were only 20.4 µM, whereas sepsis survivors had plasma levels of 54.9 µM [57]. It would be interesting to know whether the lower β-hydroxybutyrate levels in non-survivors could be linked to a PPARα defect in the livers of the patients when compared to sepsis survivors, and whether KB therapy has any survival benefit in such patients.

Despite the essential role of hepatic PPARα to survive sepsis, a genome-wide disturbance of PPARα function was observed in mouse septic liver, as assessed by transcriptome analysis upon administration of the PPARα ligand GW7647 [13]. This PPARα signaling defect could be attributed -at least in part- to reduced PPARα protein levels in sepsis hepatocytes, leading to reduced expression of several of its transcriptional targets responsible for FFA oxidation [13,58]. As sepsis leads to release of FFAs by lipolysis in WAT, the reduced activity of PPARα in sepsis is peculiar and counterintuitive. Since PPARα expression is dependent on GR [59], it is tempting to speculate that PPARα decline might be a consequence of GRs failure. As a consequence of failing PPARα signaling, FFAs are no longer oxidized, and instead, accumulate in liver and kidney where they cause **lipotoxicity** [13]. Increased levels of FFAs are sensed by KCs which react by producing TNF and IL-1β [60]. These cytokines in turn inhibit hepatic PPARα expression and via this way lipid metabolism in liver is further suppressed [61]. Preventing sepsis-induced PPARα downregulation with the PPARα agonist pemafibrate or with JNK inhibition leads to increased FFA oxidation, decreased lipotoxicity, reduced organ damage and ultimately improved survival [13,62]. A study using another PPARα agonist, CP868388, could however not find a significantly improved survival in an *E. coli* infection model [58]. Nonetheless, the use of tetracycline antibiotics could protect in this model - independently of pathogen load - through rescuing both FFA oxidation and GC signaling pathways [58]. It thus seems that rescuing both pathways simultaneously is necessary for successful protection in this infection model.

Ketone bodies in sepsis

In contrast to normal (lean) septic mice, which show reduced FFA metabolism and ketogenesis during sepsis (see above), obese septic mice display a unique metabolic profile, characterized by enhanced lipolysis and elevated hepatic FFA metabolism compared to lean septic mice. Through their elevated mobilization and oxidation of FFAs, obese mice are protected against sepsis-induced muscle wasting and weakness [14]. This might explain, to a certain extent, the better ICU survival of obese patients, or the so called 'obesity paradox' [63]. Preventing lipolysis in septic obese mice by knocking out adipose triglyceride lipase (ATGL) specific in the WAT profoundly aggravates muscle wasting and weakness. Conversely, supplementation of high lipid doses or ketone bodies to lean septic mice protects against sepsis-induced muscle weakness, however, in case of lipid supplementation, this strategy poses risks for side effects such as liver steatosis [14]. Furthermore, administration of ketone bodies reduces glycolysis and concomitant lactate production, whereas fat oxidation is enhanced as can be observed in muscle during exercise [64]. Whether supplementing ketone bodies will reduce lactate production and enhance fat oxidation in septic subjects requires further investigation. Moreover, ketone bodies protect in inflammatory disease models through inhibition of the NLRP3 inflammasome [65] and oxidative stress [9,66], and subcutaneous administration of ketone bodies protects against CLP-induced cognitive decline through limiting both neuroinflammation and peripheral inflammation [67]. Lastly, preventive administration of ketone bodies alters the gut microbiome resulting in decreased intestinal pro-inflammatory

Th17 cells [68] and via this way provide an extra potential mechanism to protect in sepsis. Taken together, administration of ketone bodies can play a protective role at multiple levels during sepsis (**Figure 3**). As PPARα is the major regulator of ketogenesis, and given the PPARα dysfunction observed upon CLP [13], one might wonder whether preventing PPARα dysfunction during sepsis might augment ketone body levels even further during sepsis and concomitantly enhance survival also via this way.

Also in human sepsis patients, reduced hepatic PPARα levels [54], increased plasma FFA and glycerol levels [13], and muscle wasting and weakness have been observed [63]. These metabolic perturbations are thus relevant to the clinic and understanding the mechanisms involved provides novel metabolic targets to treat septic patients, for example with the PPARα agonist pemafibrate or with ketone bodies.

Concluding remarks

Based on research of the last decade, a new picture of the lethal aspects of sepsis emerges. It is fair to conclude that sepsis causes a fast induction of an energy imbalance, based on increased needs and reduced food intake, leading to a SR to ensure the availability of calories from reserves. It strikes however as enigmatic, irrational and contradictory that sepsis requires a lot of energy, while at the same time is causing a refusal to eat. From a therapeutic point of view, the precise strategy of feeding sepsis individuals appears logical, but given the problems with GR and PPARα, the addition of KBs would appear as the most logical choice, as these do not need to be processed by GR or PPARα controlled pathways. Also, the potential blocking of specific SR signals to prevent accumulation of toxic metabolites, for example through inhibition of lipolysis in the WAT could be considered, provided the septic organism is supported by energy-rich molecules, such as KBs. Moreover, the short-term consequence of a failing SR in sepsis, is the accumulation of high energy molecules such as lactate and FFAs, and the reduced production of glucose and ketone bodies. The recent identification of novel mechanistic aspects of lactate biological functions have been reviewed here and hold promises for therapeutic intervention.

From an evolutionary perspective, mammals are well-adapted to food shortage (via hibernation and starvation), but it would also be logical that the potential of encountering a polymicrobial sepsis would have led to survival strategies. Why then sepsis causes the observed SR but also switches off GR and PPARα function, leading to a catabolic suicide, is not understood **(see Outstanding Questions)**. Potential clarifications to explain why septic subjects stop eating might be to prevent further gastrointestinal contamination with bugs or is simply a reflex to persistent stress. Another reflection could be that GR, which drives gluconeogenesis, should be switched off to allow hepatocytes to perform glycolysis and generate some ATP, while gluconeogenesis requires ATP/GTP. As GR has also strong anti-inflammatory effects, and as inflammation is required to coordinate anti-infectious immunity, switching off GR temporarily could also make sense. It is only by accumulating more data of pathways changed and involved in sepsis progression that the true reasons behind this failure of the SR in sepsis will be understood in a holistic picture.

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References

1 Rudd, K.E. *et al.* (2020) Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 395, 200–211

2 Reinhart, K. *et al.* (2017) Recognizing Sepsis as a Global Health Priority — A WHO Resolution. *N. Engl. J. Med.* 377, 414–417

3 Li, H. *et al.* SARS-CoV-2 and viral sepsis: observations and hypotheses. , *The Lancet*, 395. (2020)

4 Van Wyngene, L. *et al.* (2018) Reprogramming of basic metabolic pathways in microbial sepsis: therapeutic targets at last? *EMBO Mol. Med.* 10, e8712

5 Singer, M. *et al.* (2016) The Third International Consensus Definitions for Sepsis and Septic Shock {(Sepsis-3)}. 315, 801–810

6 Hotchkiss, R.S. *et al.* Sepsis and septic shock. , *Nature Reviews Disease Primers*. (2016)

7 van der Poll, T. *et al.* (2017) The immunopathology of sepsis and potential therapeutic targets. *Nat. Rev. Immunol.* 17, 407–420

8 Vandewalle, J. *et al.* (2021) Combined glucocorticoid resistance and hyperlactatemia contributes to lethal shock in sepsis. *Cell Metab.* 33, 1763-1776.e5

9 Wang, A. *et al.* (2016) Opposing Effects of Fasting Metabolism on Tissue Tolerance in Bacterial and Viral Inflammation. *Cell* 166, 1512-1525.e12

10 Peterson, S.J. *et al.* (2010) Adequacy of Oral Intake in Critically Ill Patients 1 Week after Extubation. *J. Am. Diet. Assoc.* 110,

11 Stanzani, G. *et al.* Do critical care patients hibernate? Theoretical support for less is more. , *Intensive Care Medicine*, 46. (2020)

12 Wang, T. *et al.* The comparative physiology of food deprivation: From feast to famine. , *Annual Review of Physiology*, 68. (2006)

13 Van Wyngene, L. *et al.* (2020) Hepatic PPARα function and lipid metabolic pathways are dysregulated in polymicrobial sepsis. *EMBO Mol. Med.* 12,

14 Goossens, C. *et al.* (2019) Adipose tissue protects against sepsis-induced muscle weakness in mice: From lipolysis to ketones. *Crit. Care* DOI: 10.1186/s13054-019-2506-6

15 Langley, R.J. *et al.* (2013) An integrated clinico-metabolomic model improves prediction of death in sepsis. *Sci Transl Med* 5, 195ra95

16 Wang, J. *et al.* (2020) Prediction of sepsis mortality using metabolite biomarkers in the blood: a meta-analysis of death-related pathways and prospective validation. *BMC Med.* 18,

17 Miao, H. *et al.* (2021) Evaluation of the Molecular Mechanisms of Sepsis Using Proteomics. *Front. Immunol.* 12,

18 Wischmeyer, P.E. Nutrition Therapy in Sepsis. , *Critical Care Clinics*, 34. (2018)

19 Vandewalle, J. *et al.* (2018) Therapeutic Mechanisms of Glucocorticoids. *Trends Endocrinol. Metab.* 29, 42–54

20 Timmermans, S. *et al.* A general introduction to glucocorticoid biology. , *Frontiers in Immunology*, 10. (2019)

21 Vandewalle, J. and Libert, C. (2020) Glucocorticoids in Sepsis: To Be or Not to Be. *Front. Immunol.* 11, 1318

22 Reichardt, H.M. *et al.* (1998) DNA binding of the glucocorticoid receptor is not essential for survival. *Cell* 93, 531-41 OD-1998/05/30

23 Kleiman, a. *et al.* (2012) Glucocorticoid receptor dimerization is required for survival in septic shock via suppression of interleukin-1 in macrophages. *FASEB J.* 26, 722–729

24 Jenniskens, M. *et al.* (2018) The hepatic glucocorticoid receptor is crucial for cortisol homeostasis and sepsis survival in humans and Male mice. *Endocrinology* 159, 2790–2802

25 Witek-Janusek, L. and Yelich, M.R. (1995) Role of the adrenal cortex and medulla in the young rats' glucoregulatory response to endotoxin. *Shock* 3, 434–439

26 Butler, L.D. *et al.* (1989) Neuroendocrine regulation of in vivo cytokine production and effects: I. In vivo regulatory networks involving the neuroendocrine system, interleukin-1 and tumor necrosis factor-α. *J. Neuroimmunol.* DOI: 10.1016/0165-5728(89)90108-2

27 Lazar, G. *et al.* (1992) Modification of septic shock in mice by the antiglucocorticoid RU 38486. *Circ. Shock* 36, 180–184

28 Dendoncker, K. *et al.* (2019) TNF-α inhibits glucocorticoid receptor-induced gene expression by reshaping the GR nuclear cofactor profile. *Proc. Natl. Acad. Sci. U. S. A.* 116, 12942–12951

29 Van Bogaert, T. *et al.* (2011) Tumor necrosis factor inhibits glucocorticoid receptor function in mice: a strong signal toward lethal shock. *J. Biol. Chem.* 286, 26555-67 OD-2011/06/08

30 Annane, D. *et al.* (2018) Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N. Engl. J. Med.* 378, 809–818

31 Venkatesh, B. *et al.* (2018) Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N. Engl. J. Med.* 378, 797–808

32 Opherk, C. *et al.* (2004) Inactivation of the glucocorticoid receptor in hepatocytes leads to fasting hypoglycemia and ameliorates hyperglycemia in streptozotocin-induced diabetes mellitus. *Mol. Endocrinol.* 18, 1346–53

33 Weis, S. *et al.* (2017) Metabolic Adaptation Establishes Disease Tolerance to Sepsis. *Cell* 169, 1263-1275.e14

34 Suetrong, B. and Walley, K.R. (2016) Lactic acidosis in sepsis: It's Not All anaerobic:

Implications for diagnosis and management. *Chest* 149, 252–261

35 Wang, Y. *et al.* (2020) Glycerol not lactate is the major net carbon source for gluconeogenesis in mice during both short and prolonged fasting. *Mol. Metab.* 31, 36–44

36 Revelly, J.P. *et al.* (2005) Lactate and glucose metabolism in severe sepsis and cardiogenic shock. *Crit. Care Med.* DOI: 10.1097/01.CCM.0000181525.99295.8F

37 Okamoto, K. *et al.* (1998) Restoration of the glucocorticoid receptor function by the phosphodiester compound of vitamins C and E, EPC-K1 L-ascorbic acid 2-[3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6- yl hydrogen phosphate] potassium salt), via a. *Biochem. Pharmacol.* 56, 79–86

38 Nader, N. *et al.* (2009) Circadian rhythm transcription factor CLOCK regulates the transcriptional activity of the glucocorticoid receptor by acetylating its hinge region lysine cluster: potential physiological implications. *FASEB J.* DOI: 10.1096/fj.08-117697

39 Kino, T. *et al.* (2010) Noncoding RNA Gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. *Sci. Signal.* DOI: 10.1126/scisignal.2000568

40 Binnie, A. *et al.* Epigenetics of Sepsis. , *Critical Care Medicine*. (2020)

41 Yang, K. *et al.* (2021) Lactate promotes macrophage HMGB1 lactylation, acetylation, and exosomal release in polymicrobial sepsis. *Cell Death Differ.* DOI: 10.1038/s41418-021-00841-9

42 Mori, K. *et al.* (1998) Lactate-induced vascular relaxation in porcine coronary arteries is mediated by Ca2+-activated K+ channels. *J. Mol. Cell. Cardiol.* 30,

43 Opal, S.M. and van der Poll, T. (2015) Endothelial barrier dysfunction in septic shock. *J. Intern. Med.* 277, 277–293

44 Lelubre, C. and Vincent, J.L. (2018) Mechanisms and treatment of organ failure in sepsis. *Nat. Rev. Nephrol.* 14, 417–427

45 Gibot, S. *et al.* (2007) High-mobility group box 1 protein plasma concentrations during septic shock. *Intensive Care Med.* 33,

46 Van Der Flier, M. *et al.* (2005) Plasma vascular endothelial growth factor in severe sepsis. *Shock* 23, 35–38

47 McDonald, B. *et al.* (2020) Programing of an Intravascular Immune Firewall by the Gut Microbiota Protects against Pathogen Dissemination during Infection. *Cell Host Microbe* 28,

48 Traeger, T. *et al.* (2010) Kupffer cell depletion reduces hepatic inflammation and apoptosis but decreases survival in abdominal sepsis. *Eur. J. Gastroenterol. Hepatol.* 22,

49 Cluntun, A.A. *et al.* (2020) The pyruvate-lactate axis modulates cardiac hypertrophy and heart failure. *Cell Metab.* DOI: 10.1016/j.cmet.2020.12.003

50 Levy, B. *et al.* (2007) Myocardial lactate deprivation is associated with decreased cardiovascular performance, decreased myocardial energetics, and early death in endotoxic shock. *Intensive Care Med.* 33, 495–502

51 Besnier, E. *et al.* (2020) Hypertonic sodium lactate improves microcirculation, cardiac function, and inflammation in a rat model of sepsis. *Crit. Care* 24,

52 Montaigne, D. *et al.* PPAR control of metabolism and cardiovascular functions. , *Nature Reviews Cardiology*. (2021)

53 Pawlak, M. *et al.* (2015) Molecular mechanism of PPAR a action and its impact on lipid metabolism , inflammation and fibrosis in non-alcoholic fatty liver disease. *J. Hepatol.* 62, 720–733

54 Paumelle, R. *et al.* (2019) Hepatic PPARα is critical in the metabolic adaptation to sepsis. *J. Hepatol.* DOI: 10.1016/j.jhep.2018.12.037

55 Standage, S.W. *et al.* (2017) PPARα augments heart function and cardiac fatty acid oxidation

in early experimental polymicrobial sepsis. *Am. J. Physiol. - Hear. Circ. Physiol.* DOI: 10.1152/ajpheart.00457.2016

56 Iwaki, T. *et al.* (2019) PPARα contributes to protection against metabolic and inflammatory derangements associated with acute kidney injury in experimental sepsis. *Physiol. Rep.* DOI: 10.14814/phy2.14078

57 Acar, R. (2021) Association between Beta-Hydroxybutyrate Levels and Survival in Sepsis Patients. *Eurasian J. Med. Investig.* DOI: 10.14744/ejmi.2021.15575

58 Colaço, H. *et al.* (2020) Host-dependent induction of disease tolerance to infection by tetracycline antibiotics. *Immunity* DOI: 10.1101/833269

59 Rando, G. *et al.* (2016) Glucocorticoid receptor-PPARα axis in fetal mouse liver prepares neonates for milk lipid catabolism. *Elife* 5,

60 Diehl, K.L. *et al.* (2020) Kupffer Cells Sense Free Fatty Acids and Regulate Hepatic Lipid Metabolism in High-Fat Diet and Inflammation. *Cells* 9,

61 Stienstra, R. *et al.* (2010) Kupffer cells promote hepatic steatosis via interleukin-1β-dependent suppression of peroxisome proliferator-activated receptor α activity. *Hepatology* 51,

62 Drosatos, K. *et al.* (2011) Inhibition of c-Jun-N-terminal kinase increases cardiac peroxisome proliferator-activated receptor α expression and fatty acid oxidation and prevents lipopolysaccharide-induced heart dysfunction. *J. Biol. Chem.* DOI: 10.1074/jbc.M111.272146

63 Goossens, C. *et al.* (2017) Premorbid obesity, but not nutrition, prevents critical illness-induced muscle wasting and weakness. *J. Cachexia. Sarcopenia Muscle* DOI: 10.1002/jcsm.12131

64 Cox, P.J. *et al.* (2016) Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes. *Cell Metab.* 24,

65 Youm, Y.H. *et al.* (2015) The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat. Med.* DOI: 10.1038/nm.3804

66 Shimazu, T. *et al.* (2013) Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science (80-.).* DOI: 10.1126/science.1227166

67 Wang, X. *et al.* (2020) Subcutaneous administration of β-hydroxybutyrate improves learning and memory of sepsis surviving mice. *Neurotherapeutics* DOI: 10.1007/s13311-019-00806-4

68 Ang, Q.Y. *et al.* (2020) Ketogenic Diets Alter the Gut Microbiome Resulting in Decreased Intestinal Th17 Cells. *Cell* 181, 1263-1275.e16

69 Hashimoto, T. *et al.* (2000) Defect in peroxisome proliferator-activated receptor α-inducible fatty acid oxidation determines the severity of hepatic steatosis in response to fasting. *J. Biol. Chem.* 275,

70 Zhang, W. *et al.* (2019) Lactate Is a Natural Suppressor of RLR Signaling by Targeting MAVS. *Cell* DOI: 10.1016/j.cell.2019.05.003

71 Zhang, D. *et al.* (2019) Metabolic regulation of gene expression by histone lactylation. *Nature* DOI: 10.1038/s41586-019-1678-1

72 Colegio, O.R. *et al.* (2014) Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. *Nature* 513, 559–563

73 Vadevoo, S.M.P. *et al.* (2021) The macrophage odorant receptor Olfr78 mediates the lactate-induced M2 phenotype of tumor-associated macrophages. *Proc. Natl. Acad. Sci.* 118,

74 Hoque, R. *et al.* (2014) Lactate reduces liver and pancreatic injury in toll-like receptor- and inflammasome-mediated inflammation via gpr81-mediated suppression of innate immunity. *Gastroenterology* DOI: 10.1053/j.gastro.2014.03.014

75 Yang, K. *et al.* (2020) Lactate Suppresses Macrophage Pro-Inflammatory Response to LPS

Stimulation by Inhibition of YAP and NF-κB Activation via GPR81-Mediated Signaling. *Front. Immunol.* DOI: 10.3389/fimmu.2020.587913

76 Fischer, K. *et al.* (2007) Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood* DOI: 10.1182/blood-2006-07-035972

77 Gottfried, E. *et al.* (2006) Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. *Blood* DOI: 10.1182/blood-2005-05-1795

78 Brand, A. *et al.* (2016) LDHA-Associated Lactic Acid Production Blunts Tumor Immunosurveillance by T and NK Cells. *Cell Metab.* DOI: 10.1016/j.cmet.2016.08.011

79 Morioka, S. *et al.* (2018) Efferocytosis induces a novel SLC program to promote glucose uptake and lactate release. *Nature* DOI: 10.1038/s41586-018-0735-5

80 Xie, M. *et al.* (2016) PKM2-Dependent glycolysis promotes NLRP3 and AIM2 inflammasome activation. *Nat. Commun.* 7,

81 Yang, L. *et al.* (2014) PKM2 regulates the Warburg effect and promotes HMGB1 release in sepsis. *Nat. Commun.* 5, 1–9

82 Kaushik, D.K. *et al.* (2019) Enhanced glycolytic metabolism supports transmigration of brain-infiltrating macrophages in multiple sclerosis. *J. Clin. Invest.* 129, 3277–3292

83 Pucino, V. *et al.* (2019) Lactate Buildup at the Site of Chronic Inflammation Promotes Disease by Inducing CD4+ T Cell Metabolic Rewiring. *Cell Metab.* DOI: 10.1016/j.cmet.2019.10.004

84 Khatib-Massalha, E. *et al.* (2020) Lactate released by inflammatory bone marrow neutrophils induces their mobilization via endothelial GPR81 signaling. *Nat. Commun.* 11,

85 Awasthi, D. *et al.* (2019) Glycolysis dependent lactate formation in neutrophils: A metabolic link between NOX-dependent and independent NETosis. *Biochim. Biophys. Acta - Mol. Basis Dis.* DOI: 10.1016/j.bbadis.2019.165542

86 Shen, Z. *et al.* (2015) Inhibition of G Protein-Coupled Receptor 81 (GPR81) Protects Against Ischemic Brain Injury. *CNS Neurosci. Ther.* DOI: 10.1111/cns.12362

87 Wang, X. *et al.* (2021) Aerobic exercise improves LPS - induced sepsis via regulating the Warburg effect in mice. *Sci. Rep.* DOI: 10.1038/s41598-021-97101-0

88 Suhara, T. *et al.* (2015) Inhibition of the oxygen sensor PHD2 in the liver improves survival in lactic acidosis by activating the Cori cycle. *Proc. Natl. Acad. Sci.* 112, 11642–11647

89 Mainali, R. *et al.* (2021) Dichloroacetate reverses sepsis-induced hepatic metabolic dysfunction. *Elife* 10,

90 McCall, C.E. *et al.* (2018) Pyruvate dehydrogenase complex stimulation promotes immunometabolic homeostasis and sepsis survival. *JCI insight* DOI: 10.1172/jci.insight.99292

91 Zheng, Z. *et al.* (2017) Enhanced glycolytic metabolism contributes to cardiac dysfunction in polymicrobial sepsis. *J. Infect. Dis.* 215, 1396–1406

92 TAN, C. *et al.* (2021) Inhibition of aerobic glycolysis alleviates sepsis-induced acute kidney injury by promoting lactate/Sirtuin 3/AMPK-regulated autophagy. *Int. J. Mol. Med.* 47,

Glossary

- **Anorexia**: Reduced food intake.
- **Beta-oxidation:** Metabolic pathway in which fatty acids are metabolized to generate energy.
- **Cecal ligation and puncture (CLP)**: Gold standard to introduce peritonitis in animal models. It involves a combination of three insults: tissue trauma due to laparotomy, necrosis caused by ligation of the cecum, and infection due to the leakage of peritoneal microbial flora into the peritoneum.
- **Cori cycle**: metabolic pathway in which lactate produced by anaerobic glycolysis in the muscles moves to the liver and is converted to glucose, which in turn is metabolized back to lactate in the muscles.
- **Free fatty acid (FFA)**: A non-esterified fatty acid, released by the hydrolysis of triglycerides within adipose tissue. Free fatty acids can be used as an immediate source of energy by many organs and can be converted by the liver into ketone bodies.
- **Gluconeogenesis**: Metabolic process in which glucose is formed from smaller precursors, such as amino acids and glycerol
- **Glycolysis**: Generation of ATP through degradation of glucose, usually associated with anaerobic conditions.
- **Hibernation**: A way of animals to conserve energy (by reducing activity and/or metabolism) to survive adverse weather conditions or lack of food.
- **Immune-metabolite**: Metabolite that serves as signal transducer to regulate immune cell function and disease outcome.

- **Ketogenesis**: Production of ketone bodies by breaking down fatty acids and ketogenic amino acids. This process supplies the needed energy of certain organs, especially the brain.
- **Lactylation**: Addition of a lactyl group to a residue.
- **Lipolysis**: The process of breaking down of lipids into fatty acids and glycerol.
- **Lipotoxicity**: Refers to the accumulation of lipid intermediates in tissues other than adipose tissue and causes cell damage in these tissues
- **Starvation**: Malnutrition following, for example, anorexia, gastrointestinal disease, cancer, and coma. The metabolic response to starvation is to provide energy via catabolism of body tissues (muscle, adipose tissue, liver).

Box1: Starvation Response: Release and transformation of high-energy metabolites

Part 1 of the starvation response (SR) basically consists of (i) glycogenolysis, releasing glucose monomers from the polymer glycogen, (ii) proteolysis (mainly in muscle) yielding gluconeogenic amino acids, and (iii) lipolysis in white adipose tissues (WAT) leading to free fatty acids (FFAs) and glycerol. Part 2 of the SR deals with the metabolic transformation of the catabolic metabolites generated in part 1 (about 90% in hepatocytes and 10% in kidney epithelium).

The released glycerol and gluconeogenic amino acids form glucose via a process termed **gluconeogenesis**. This metabolic process (1) requires ATP and NAD^+, (2) is under control of the essential transcription factor called glucocorticoid receptor (GR), because GR is essential for the transcriptional induction of genes, encoding enzymes involved in the process, such as *Pck1*, encoding Phosphoenolpyruvate carboxykinase (PEPCK) and *G6p*, encoding Glucose 6 phosphatase. Gluconeogenesis also (3) needs functional mitochondria to be successful (because one particular step, the transformation of pyruvate to oxaloacetate by pyruvate carboxylase, can only occur there). Finally, (4) it is also essential to realize that gluconeogenesis largely overlaps with glycolysis, in terms of essential enzymes and metabolites, but moves in opposite direction, and hence that cells engaged in a glycolysis flux can impossibly perform gluconeogenesis (**Figure 2**).

The **FFAs** released by WAT via lipolysis, are taken up by hepatocytes to form acetyl-CoA in a process termed **FFA beta-oxidation**, whereby acetyl-CoA can enter the TCA cycle, but can also lead to **ketogenesis**. Both processes (beta-oxidation and ketogenesis) are under control of the transcription factor called peroxisome proliferator-activated receptor alpha (PPARα). The ketone bodies (beta-hydroxy butyrate, acetoacetate and acetate) add up to the glucose produced and provide brain and other organs with a minimal amount of calories, sufficient to survive food shortage (**Figure 1**).

Increased blood levels of FFAs as well as gluconeogenic substrates are not harmless and thus this second part of starvation is essential. For example, FFAs, when left unmetabolized, can cause lipotoxicity, associated with coma and death, as is shown in PPARα-deficient mice [69]. It is interesting that the second part of the SR is mainly depending on ligand-activated transcription factors (GR and PPARα), and thus novel gene expression, and that these transcription factors perform complex crosstalk by protein-protein interaction in the nucleus between GR, PPARα and many other partners.

Cell type	Effect of lactate	Ref
	Anti-inflammatory effects	
Macrophages	inhibits type I IFN production through directly binding mitochondrial antiviral-signaling protein thereby limiting retinoic-acid-inducible gene I-like receptor signaling	[70]
	modulates nuclear histones through addition of lactyl groups to lysine residues of histones (known as lactylation) and via this way activates M2-like gene expression in an epigenetic way	[71]
	induces differentiation into an M2-like phenotype via the lactate receptors Gpr132 and Olfr78	[70,72,73]
	reduces TLR4-mediated induction (via LPS) of gene expression of the genes *Il1β*, *Nlrp3*, and *Casp1*, activation of NF-κB, release of IL1β and cleavage of caspase1. These effects are exerted through GPR81 as signaling through GPR81 down-regulates the NLRP3 inflammasome via β-Arrestin-2	[74]
	suppresses pro-Inflammatory response to LPS Stimulation by inhibition of YAP and NF-κB activation via GPR81	[75]
T-cells	suppresses proliferation and cytokine production, resulting in a significant decrease in cytotoxic activity	[76]
Dendritic cells	inhibits dendritic cell differentiation and activation, resulting in impaired antigen presentation	[77]
NK cells	diminishes IFN-γ production	[78]
Phagocytes	contributes to actin polymerization and to the continued uptake of corpses by the phagocytes and modulates the expression of anti-inflammatory genes in neighboring cells	[79]
	Pro-inflammatory effects	
Macrophages	promotes HMGB1 lactylation, acetylation and exosomal release	[41]
	induces IL1β and HMGB1 release by promoting the activation of NLRP3 and AIM2 inflammasomes	[80,81]
	promotes VEGF transcription	[8]
	increases macrophage transmigration	[82]
T-cells	promotes CD4+T cells to produce IL17 via PKM2/STAT3 signaling and fatty acid synthesis	[83]
Neutrophils	promotes neutrophil mobilization by reducing endothelial VE-cadherin expression and increasing bone marrow vascular permeability via endothelial GPR81 signaling. Moreover, lactate administration induces the release of neutrophil chemokines, such as G-CSF, CXCL1 and CXCL2	[84]
	stimulates neutrophil function by inducing the formation of neutrophil extracellular traps	[85]

Table 1: Effect of lactate in different cell types

***IFN**: interferon, **TLR4**: toll like receptor 4, **LPS**: lipopolysaccharide, **GPR132**: G-protein coupled receptor 132, **Olfr78**: Olfactory receptor 78, **GPR81**: G-protein coupled receptor 81, **NLRP3**: NLR family pyrin domain containing 3, **AIM2**: absent in melanoma 2, **HMGB1**: high mobility group box 1, **VEGF**: vascular endothelial growth factor, **IL**: interleukin*

Mode of lactate inhibition	Effect on sepsis progression	Ref
Sensitizing		
siRNA for GPR81	worsens liver and pancreas injury in respectively the LPS/GalN and LPS/Caerulein mouse models, by increasing inflammation	[74]
Inhibition glycolysis (with dichloroacetate)	decreases cardiovascular performance and myocardial energetics leading to early death in endotoxic shock	[50]
Protective		
PKM2 inhibition (with shikonin)	improves survival from LPS and CLP-induced sepsis	[81]
GPR81 inhibition (with 3-OBA)	protects against ischemic brain injury and limits neuroinflammation and peripheral inflammation in septic mice	[67,86]
	reduces HMGB1 release in CLP mice	[41]
LDH inhibition (with oxamate)	improves survival in CLP-induced sepsis	[41]
Regulate Warburg effect through aerobic exercise	improves survival from LPS through preventing hyperlactatemia, hypoglycemia, MODS, and aortic injury	[87]
Inactivation of PHD2 (with GSK360A)	improves survival from LPS and protects against lactic acidosis by activating gluconeogenesis from lactate	[88]
Inhibition glycolysis (with dichloroacetate)	improves survival in CLP model by restoring levels of key redox metabolites and ameliorating sepsis-induced steatosis	[89,90]
2-DG	reduces inflammation and organ damage in LPS and CLP-induced sepsis resulting in improved survival	[9,91]
	alleviates kidney injury in CLP model by attenuating the inhibitory effect of lactate on autophagy	[92]

Table 2: Effect of lactate inhibition on sepsis progression

GPR81*: G-protein coupled receptor 81,* ***GalN****: D-galactosamine,* ***LPS****: lipopolysaccharide,* ***SLC****: solute carrier family,* ***CLP****: cecal ligation and puncture,* ***3-OBA****: 3-hydroxy-butyrate,* ***LDH****: lactate dehydrogenase,* ***MODS****: multiple organ dysfunction syndrome,* ***PHD2****:* prolyl *hydroxylase domain-containing protein 2, MCT4: monocarboxylate transporter 4,* ***CNS****: central nervous system,* ***EAE****: experimental autoimmune encephalomyelitis,* ***CHCA****: α-Cyano-4-hydroxycinnamic acid ,* ***2-DG****: 2-deoxy-D-glucose*

Figure Legends

Figure 1: A failing starvation response (SR) in sepsis

During a SR initiated by an absence of food, the body is able to provide high energy molecules based on its reserves. Glycogenolysis (i.) produces glucose; muscle breakdown (ii.) produces gluconeogenic amino acids; lipolysis in WAT (iii.) produces gluconeogenic glycerol and free fatty acids (FFAs). Apart from glucose, all other molecules have to be transformed by hepatocytes (and to a lesser extent kidney epithelium) to lead to glucose and Acetyl-CoA (AcCoA), the latter of which can lead to ketone bodies. These transformations are mainly controlled by GR and PPARα. Sepsis also leads to a SR, but it is unclear how exactly it is initiated. Based on the fast consumption of WAT and muscle mass, the SR and sepsis are leading to weight loss. Due to failure of the two key metabolic transcription factors GR and PPARα, the SR in sepsis is however dysfunctional. On the one hand, a failing SR leads to reduced production of glucose, Acetyl-CoA and ketone bodies (KBs). On the other hand, toxic metabolites such as FFAs and lactate accumulate, thereby contributing to disease progression in sepsis (see arrows in red boxes).

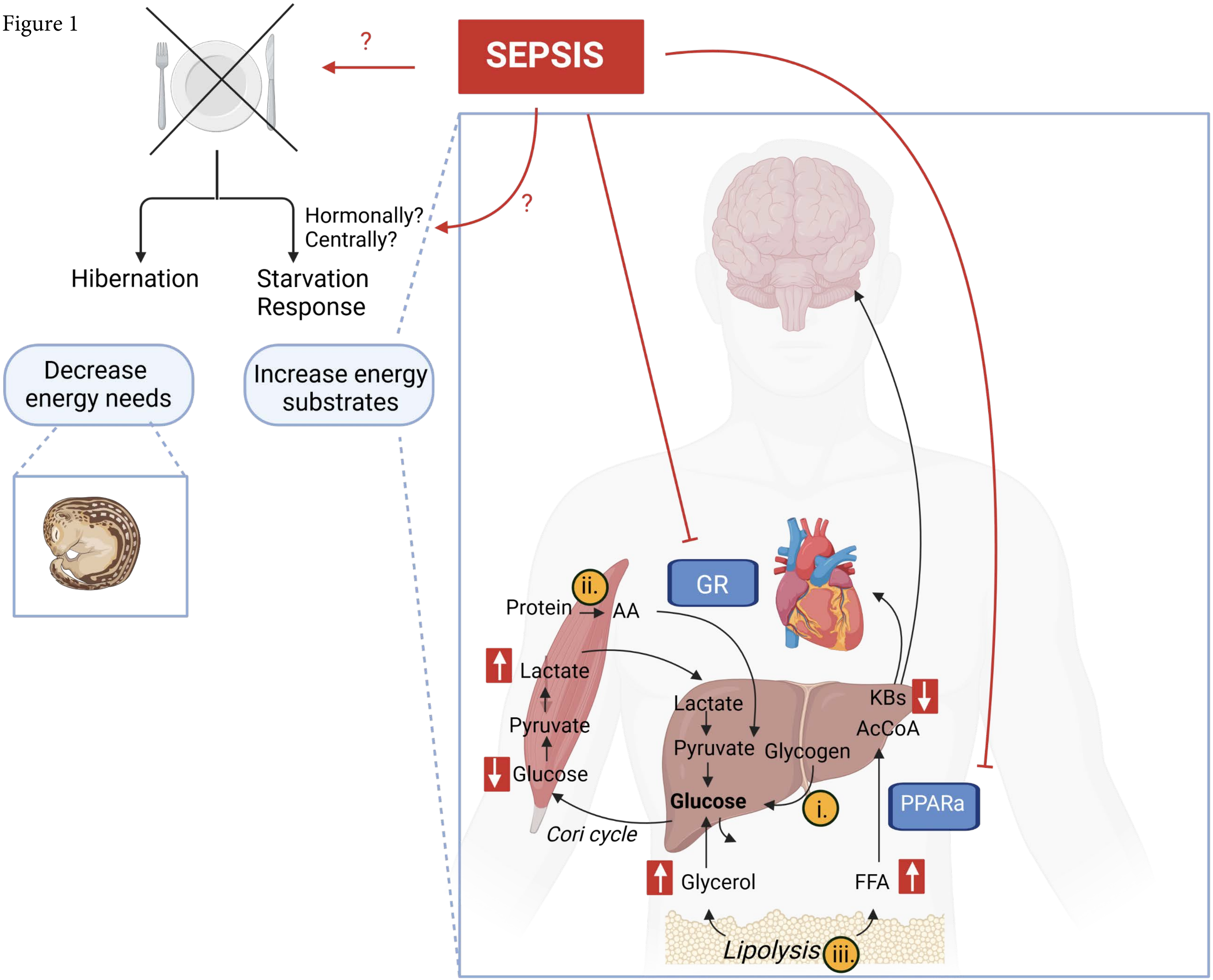
Figure 2: Therapeutic targets to prevent lactate-induced toxicity

Lactate is produced in large amounts during sepsis and correlates positively with disease severity. Inadequate oxygen delivery, increased glycolysis, impaired aerobic respiration (all three organized by hypoxia-inducible factors, HIFs), and/or reduced clearance, contribute to the high lactate levels in septic subjects. The produced lactate exerts pleiotropic biological functions by interacting with potential lactate receptors, such as Olfr78, Gpr81, Gpr132 or after transport across plasma membranes via monocarboxylate transporters (MCTs). Several MCTs have been suggested as lactate transporters (slc5a12, slc16a1, slc16a3, slc16a7, slc16a8, slc21a1). Inside target cells, lactate can be converted to glucose via the gluconeogenesis pathway (red arrows), or to pyruvate followed by the TCA cycle. Interfering with lactate production and/or lactate signaling affects disease progression in many different inflammatory disease models (see **Table 2**). The green boxes indicate drugs that can be applied to target enzymes or receptors involved in lactate signaling.

Figure 3: Therapeutic targets to prevent downstream effects of PPARα dysfunction in sepsis

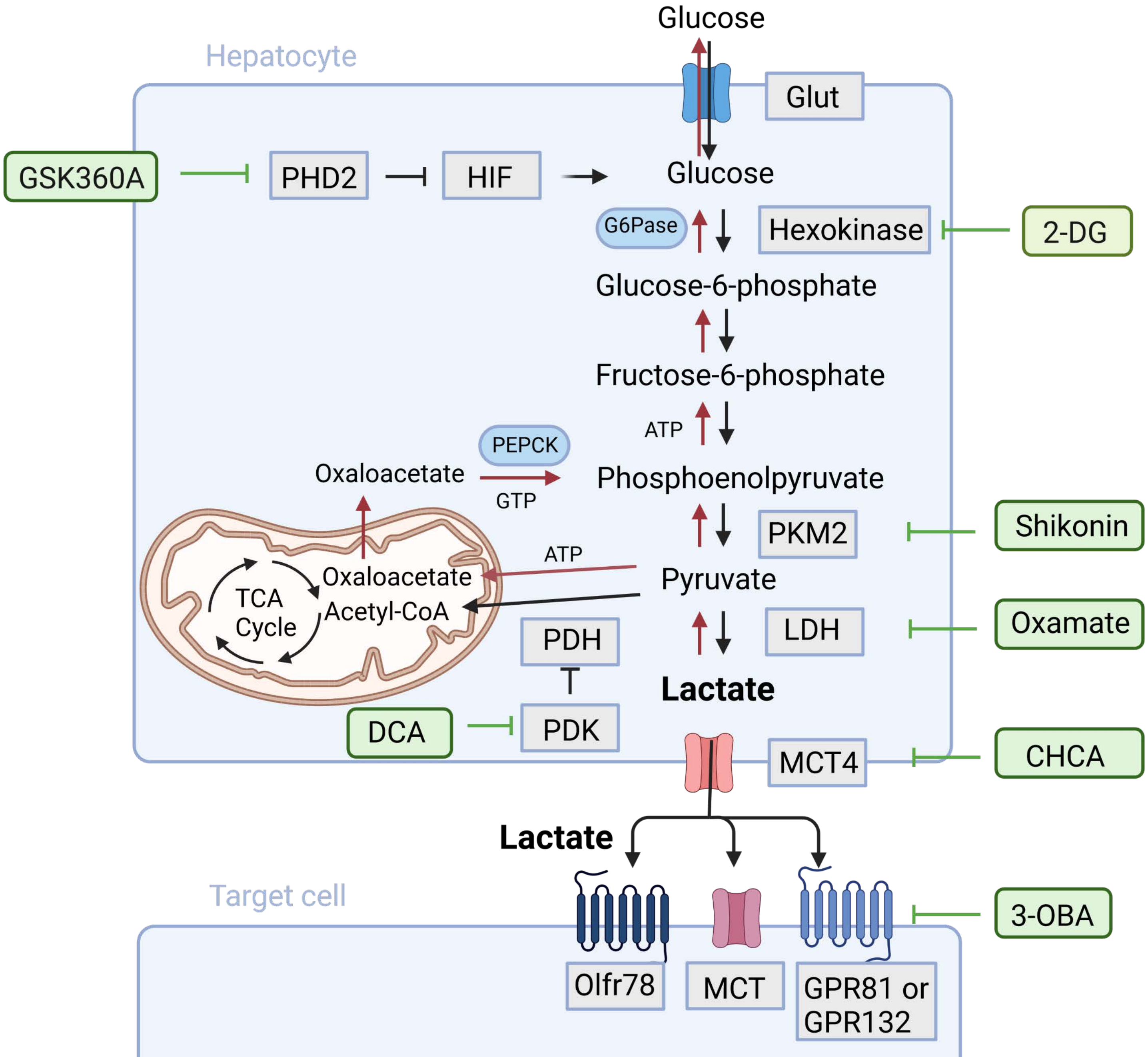
Lipolysis following starvation releases free fatty acids (FFAs) into the bloodstream that are taken up by peripheral organs, such as liver and kidney. Under physiological starvation conditions, FFAs are transformed to acetyl-Coa (AcCoA) by fatty acid beta oxidation (FABO) and further to ketone bodies by ketogenesis. Ketone bodies can play a protective role at multiple levels. The rapid decrease of PPARα function in sepsis however leads to reduced FABO and the accumulation of lipids leading to lipotoxicity. Moreover, not enough ketone bodies can be produced, which negatively influences disease progression. The green boxes indicate which drugs can be applied to prevent downstream effects of PPARα dysfunction in sepsis. Pemafibrate protects during sepsis by preventing PPARα downregulation and increasing ketone body production. Doxycycline enhances FABO through perturbing the electron transport chain. Alternatively, direct supplementation of ketone bodies has beneficial effects at the level of inflammation and reduced muscle degradation.

Figure 1



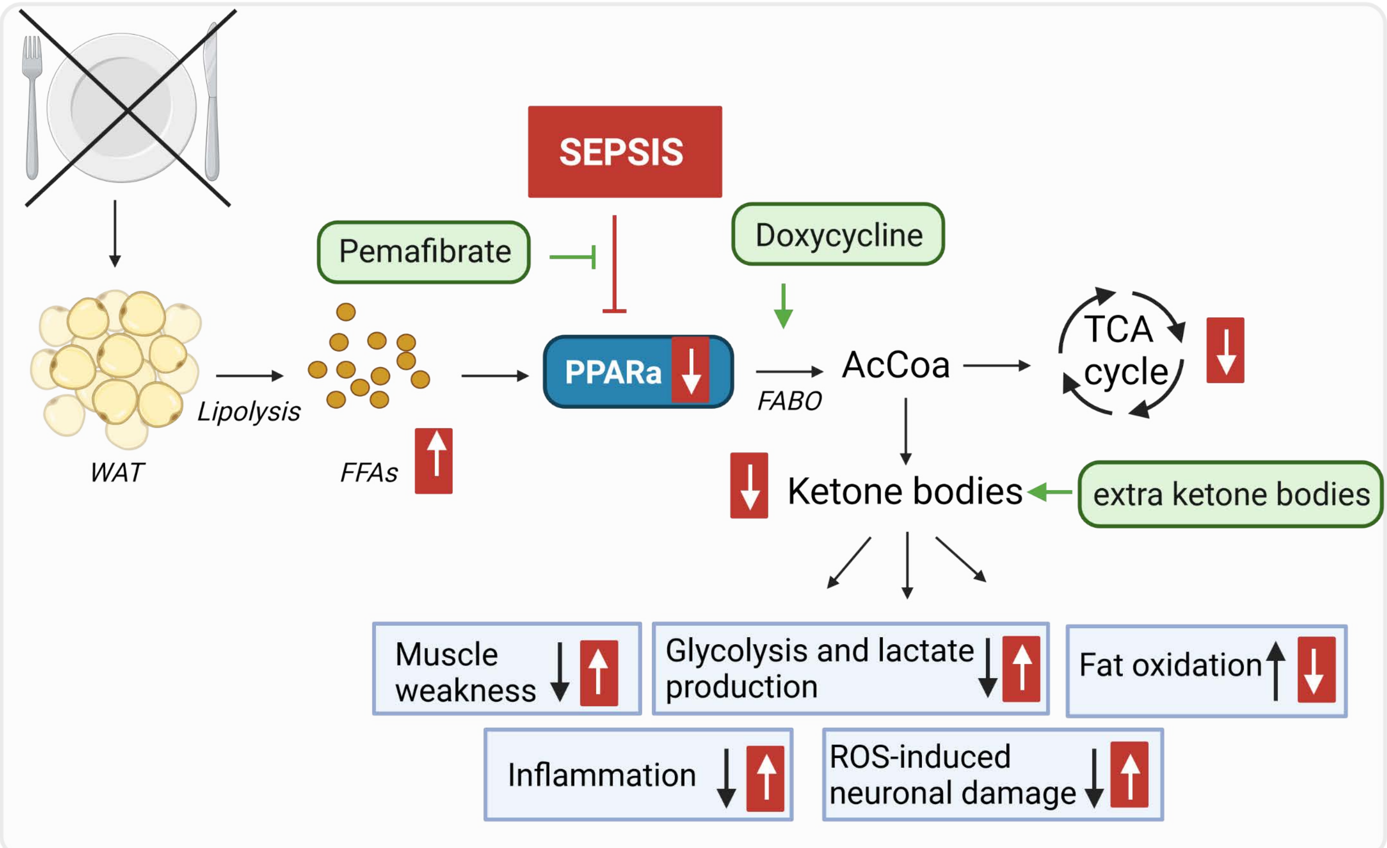
?
SEPSIS
?
Hormonally?
Centrally?
Hibernation
Starvation
Response
Decrease
energy needs
Increase energy
substrates
GR
ii.
Protein
AA
Lactate
Pyruvate
Glucose
Lactate
Pyruvate
Glycogen
Glucose
i.
KBs
AcCoA
PPARa
Cori cycle
Glycerol
FFA
Lipolysis
iii.

Figure 2



Glucose
Hepatocyte
Glut
GSK360A
PHD2
HIF
Glucose
G6Pase
Hexokinase
2-DG
Glucose-6-phosphate
Fructose-6-phosphate
ATP
PEPCK
Oxaloacetate
GTP
Phosphoenolpyruvate
PKM2
Shikonin
ATP
Oxaloacetate
TCA
Cycle
Acetyl-CoA
Pyruvate
LDH
Oxamate
PDH
Lactate
DCA
PDK
MCT4
CHCA
Lactate
Target cell
3-OBA
Olfr78
MCT
GPR81 or
GPR132

Figure 3


SEPSIS
Pemafibrate
Doxycycline
PPARa
Lipolysis
WAT
FFAs
FABO
AcCoa
TCA cycle
Ketone bodies
extra ketone bodies
Muscle weakness
Glycolysis and lactate production
Fat oxidation
Inflammation
ROS-induced neuronal damage