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Review

The 'Jekyll and Hyde' of gluconeogenesis: early-life adversity, later life stress, and metabolic disturbances

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Abstract: The physiological response to a psychological stressor broadly impacts energy metabolism. Inversely, changes in energy availability affect the physiological response to the stressor in terms of hypothalamus, pituitary adrenal gland axis and sympathetic nervous system activation upon exposure to a stressor. Glucocorticoids, the endpoint of the HPA axis, are critical checkpoints in endocrine control of energy homeostasis. Glucocorticoid actions have been linked to many severe metabolic diseases including obesity, insulin resistance and type 2 diabetes. Glucocorticoids, through the glucocorticoid receptor, activate transcription of many genes associated with glucose and lipid regulatory pathways and thereby intricately control both physiological and pathophysiological systemic energy homeostasis. Here, we summarize the current knowledge of glucocorticoid functions in energy metabolism and systemic metabolic dysfunction, particularly focusing on glucose and lipid metabolism. There are many elements in the external environment that induce lifelong changes in the HPA axis stress response and glucocorticoid levels, the most prominent are early-life adversity, or exposure to traumatic stress. We hypothesise that when the HPA axis is so disturbed after early-life adversity, it will fundamentally alter hepatic gluconeogenesis, inducing hyperglycaemia, and hence crystalise the significant lifelong risk of developing either the metabolic syndrome, or type 2 diabetes. This gives a "Jekyll and Hyde" role to gluconeogenesis, providing the necessary energy in situations of acute stress, but driving towards pathophysiological consequences when the HPA axis has been altered.

Keywords: glucose; glycogen; gluconeogenesis; early life adversity; acute stress; chronic stress; psychosocial stress; hypothalamus-pituitary-adrenal axis; ageing; immuno-senescence; inflamm-ageing; Developmental origins of health and disease

1. Introduction

The psychophysiological stress reaction is the manner in which the body reacts to an external stressor that requires a fight or flight response disturbing physiological homeostasis. The stress reaction is primarily mediated by catecholamines and glucocorticoids. Initially, they maintain homeostasis and contribute to our overall survival. However, over the long-term, increased exposure to stress (allostatic load) has negative consequences. e.g. [1]. Activation of stress reaction mobilises stored energy, induces immune cell trafficking and biases the immune response as well as increasing heart rate and blood pressure, ensuring that oxygen and energy sources are available where needed.

Carbohydrate metabolism, in particular glucose homeostasis, is a key component of the metabolic reaction to an external stressor. It has become clear that stress hormones such as the glucocorticoids play an important role in maintaining glucose homeostasis. Glucose homeostasis is maintained by hepatocytes [2, 3] where glycogenesis (storage of glucose in glycogen chains), glycogenolysis (glucose release from glycogen), gluconeogenesis (de novo glucose production), and glycolysis (ATP release as glucose is converted

to pyruvate and ATP) are balanced to maintain plasma glucose levels with tightly controlled parameters.[4, 5]. Under normal physiological conditions insulin, the only known glucose-lowering hormone, is principally counterbalanced by glucagon to control glucose homeostasis [5]. Plasma insulin, glucagon and epinephrine levels are all intimately linked to blood glucose levels [6]. To maintain plasma glucose, insulin activates glucose consuming processes (glycolysis, glycogenesis) while glucagon and adrenaline increase glucose production (gluconeogenesis, glycogenolysis). During fasting, gluconeogenesis is triggered by glucagon via the cAMP/PKA/CREB/CRTC2 signaling pathway. This terminates at the peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1α), which in turn coactivates transcription factors, including hepatocyte nuclear factor 4 α (HNF4α), forkhead box O1 (FOXO1), and GC receptor (GR), to activate hepatic gluconeogenesis [7]. When blood glucose levels rise after a meal, the rise in insulin levels inhibits gluconeogenesis by down-regulating the transcriptional mechanisms (FOXO1, PGC1α, and CRTC2) [7] as well as by activating glucose uptake by peripheral tissues.

The metabolic syndrome (MetS) is the umbrella term that includes impaired glucose metabolism, obesity and hypertension, all of which increases the risk of Type-2 diabetes (T2D) [8] Over the last decade, MetS has been linked to many chronic diseases by altered metabolic and pro-inflammatory pathways, and it has been demonstrated that it originates in early-life, with early-life socioeconomic position being the strongest lifelong driver of MetS [9]. There are two principal components of the early-life socioeconomic position that contribute to lifelong MetS and diabetic risk – early-life nutrition and early-life stress. Parental BMI, acting through a shared cultural environment and learned family eating patterns influences adiposity, BMI, and lipid profiles in their children [9, 10], passing through maternal education [11]. There is a strong epidemiological link between early-life stress or adversity and T2D [12, 13] as well as hypertension and dyslipidaemia [14] that was clear in meta-analyses over the last half-decade [15, 16]. It is probable that the risk of long-term metabolic disturbances passes through "programming" during sensitive developmental windows during early life. Such critical windows of developmental plasticity permit the body to adapt to the environment in which it is developing, and are thought to be mediated by epigenetic changes, potentially in systems such as the HPA axis that are sensitive to the external environment [17] .

Here we review how the early-life period programs the HPA axis, and how it interacts with metabolic pathways at baseline and under acute and chronic stress. We suggest that the link between exposure to chronic stress in early life and changes in the metabolic profile later in life with an the increased risk of metabolic syndrome and type 2 diabetes may occur either through changes in gluconeogenesis in the liver, or through the manner in which HPA axis glucocorticoids regulate gluconeogenesis. There are many "classic" results that have been generated over previous decades, however, only recently has detailed molecular evidence started to become available as to how glucocorticoids regulate gluconeogenesis [7], and to date, the role of glucocorticoids and gluconeogenesis in the development of MetS after exposure to ELA has been rather under-explored.

2. The physiological response to external psychosocial stressors

2.1 The ANS and the HPA axis stress response

Exposure to a stressor activates the paraventricular nucleus of the hypothalamus to secrete corticotropin-releasing hormone (CRH), which in turn activates two synergistic stress response systems, the rapidly responding autonomic nervous system (ANS) [18, 19] with an associated catecholamine release and the second, slower arm of the stress response is the hypothalamus— pituitary—adrenal (HPA) axis [20]. The catecholamines adrenaline and noradrenaline act rapidly and transiently upon stress exposure by increasing the heart rate and raising blood pressure. The sympathetic branch (SNS) of the ANS directly activates preganglionic neurons that project from CRH-containing neurons

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in the PVN, through noradrenergic centres in the locus coeruleus in the brainstem, then projecting directly through sympathetic preganglionic neurons in the adrenal medulla chromaffin cells from where catecholamines are secreted [21]. This is tempered, controlled, and negated by the parasympathetic branch (PNS) of the SNS, again projecting from the locus coeruleus returning the system to homeostasis. The locus coeruleus integrates signals and balances SNS and PNS activity through activation of the α1- and α2-adrenoceptors on the sympathetic and parasympathetic neurons respectively [22, 23]. Furthermore, SNS activation provides positive feedback, further increasing CRF secretion from the PVN [24]. The hippocampus, now thought to be a key element of the approach-avoidance system which involves weighing probabilistic profits and losses for an experience, thereby playing a prime role in anxiety generation. Hence, it is also part of the conscious stress response [25] and feeds direct inhibitory signals into the PVN, influencing basal GC levels, circadian GC rhythms, as well as inhibiting the HPA axis stress response [26, 27].

The end product of the HPA axis are the glucocorticoids (GC), cortisol in humans and corticosterone in rodents. GC are steroid hormones that act through their cognate receptor, the glucocorticoid receptor (GR), subsequently regulating e.g. inflammation, lymphocyte trafficking, metabolic, cardiovascular and behavioural processes amongst others [28]. Cortisol and corticosterone are regulated by a hormonal cascade. The cascade is initiated by the hypothalamic nuclei. Circadian messages from the suprachiasmatic nucleus (SCN) are integrated with physical, emotional and cognitive reactions in the PVN [29, 30]. Activated neurons in the PVN secrete CRH. The cascade is propagated *via* adreno-corticotropic hormone (ACTH) released from the anterior pituitary gland, which in turn stimulates the adrenal cortex to release glucocorticoids [31, 32]. Cortisol and corticosterone have ultradian and circadian rhythms which are chiefly regulated by the HPA axis (Figure 1). Circadian cortisol and corticosterone concentrations peaks around waking; cortisol peaks in the early morning hours while corticosterone levels peak mid-afternoon in nocturnal rodents. This circadian rhythm overlies an ultradian rhythm of the complete HPA axis signalling cascade. The frequency of secretory episodes is relatively stable at one every ~1 h while the amplitude of the secretory episode, and hence the mass secreted, provides variation in the measured concentrations [33-35] as shown in Figure 1. The corollary to the pulsatility model is that rapidly rising glucocorticoid levels in the secretory phase induce the necessary glucocorticoid receptor-mediated negative feedback that terminates the hormonal pulse, then, after a constant time interval (the inter-pulse interval) the SCN and the PVN trigger the subsequent pulse [36]. Thus, the HPA axis in conjunction with the ANS provides the molecular weapons needed to elicit a fight/flight reaction in response to stress.

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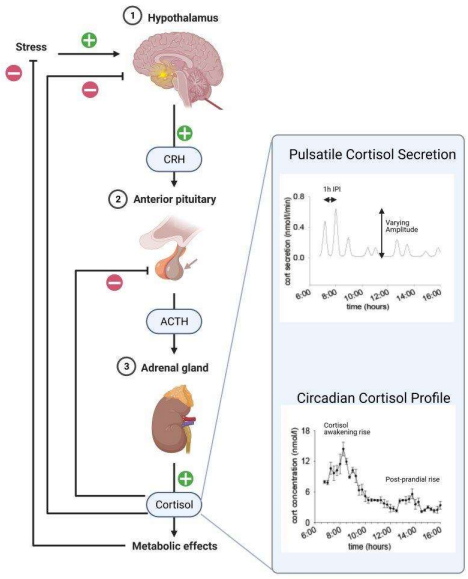

Figure 1: The Hypothalamus Pituitary Adrenal axis controls both ultradian and circadian cortisol rhythms to generate metabolic effects that help the body combat stress and re-establish homeostasis post stress. Pulsatile cortisol profiles adapted from [34]

2.2. *Metabolic adaption*

Metabolic adaptation during stress aims to preserve glucose as it is the primary energy source used in the brain, providing a short, transient, increase in blood glucose levels temporarily enhancing cognitive processes [37]. Hormones such as the glucocorticoid cortisol are reponsible for regulating glucose homeostasis under stress, promoting gluconeogenesis and concurrently reducing glucose uptake in white adipose tissue and skeletal muscle (reviewed in [37]) (Figure 2). Secondary active transport and facilitated diffusion are the two main ways in which glucose is trafficked within the body. Secondary active transport makes use of ATP to distribute glucose in the kidneys. Facilitated diffusion relies on special membrane proteins that allow the ferrying of glucose molecules against a concentration gradient, which may/may not be insulin driven.

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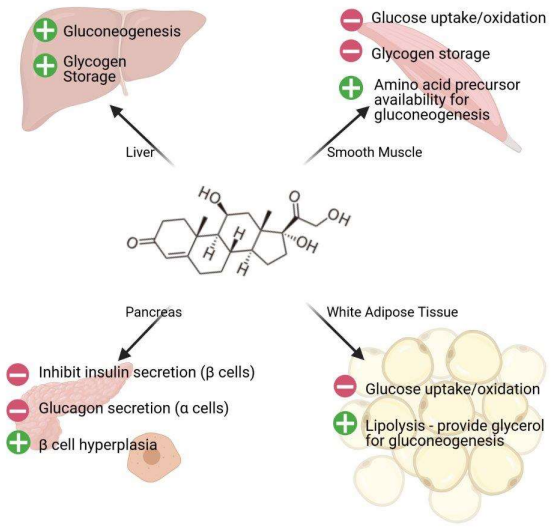

Figure 2: Cortisol triggers a cascade of events that affect glucose homeostasis. The liver, skeletal muscles, white adipose tissues and pancreas play a key role in ensuring continuous supply of useable energy for the fight/flight response.

GLUT receptors predominantly govern the uptake of glucose into the cells. There are 14 distinct glucose transporters, of which only GLUT 1-4 are particularly interesting [38]. GLUT 1, a key receptor in the brain and GLUT 3 have been reported to have high preference for glucose. GLUT 2 and GLUT 4 dictate the uptake of glucose in the pancreatic cells and muscles respectively [38, 39].

Glucocorticoids are responsible for the inhibition of insulin mediated glucose uptake from the bloodstream [37]. The absorbed glucose is directed to enter the glycolytic cycle, the final product of which is pyruvate. The synthesised pyruvate is converted into either lactate or carbon dioxide and water depending on the absence or presence of oxygen respectively. Normal physiological conditions strike a balance between the lactate and pyruvate concentrations. Chronic stress increases the net lactate and pyruvate concentrations [40]. This happens so that the produced pyruvate can either enter the glycolytic cycle to produce glucose or be metabolised to generate high concentrations of lactate due to reduced action of pyruvate dehydrogenase (PDH), which normally functions under anaerobic conditions [41]. Chronic stress attenuates the activity of PDH owing to phosphorylation by increasing concentrations of PDH kinase [42]. Stress also causes lipolysis, which provides gluconeogenic substrates [43]. Allostatic adaptations during stress also result in increased activity of the citric acid cycle due to readily available acetyl coenzyme-A produced by the oxidation of fatty acids. This increased activity of the citric acid cycle also supplies substrates for gluconeogenesis such as oxaloacetate. Thus, these interconnected metabolic pathways adapt during stress to ensure that the body, in particular the brain, has useable glucose supply.

2.3 Metabolism and acute stress interactions

Acute laboratory stressors such as the trier social stress test (TSST) activate the HPA axis inducing cortisol secretion and then the negative feedback loop bringing cortisol levels back to baseline [44]. The increased cortisol levels, supporting the individuals' ability to cope with the stress paradigm, increase gluconeogenesis and consequently blood glucose levels [45, 46]. When the TSST was first developed, the role of energy availability was rapidly investigated. It was initially reported that an 8h fasting period prior to a Trier Social Stress test (TSST) significantly reduced HPA axis reactivity, while glucose

supplementation 1h before the paradigm significantly increased cortisol and HPA axis reactivity [47]. Furthermore, when this was extended to food components such as protein or fat, the fasting-induced blunting of the HPA axis response was not restored due to immediate unavailability of useable energy. Moreover, there was a strong link between the increase in cortisol levels during the stress paradigm, and the increase in blood glucose after administration of the glucose bolus [48]. When the mechanisms were further dissected in rats, hypothalamic nuclei such as the ventromedial and paraventricular nuclei (VMN, PVN respectively) stood out. It was proposed that the high insulin and glucose levels observed after glucose loading stimulated VMN, inputting into the PVN, subsequently activating the HPA axis. Importantly, this was pharmacologically validated by colchicine (VMN activity antagonist) disrupting the fasting-induced reduction in HPA axis responsiveness [6, 49] and moreover, low blood glucose levels significantly inhibit VMN and PVN activity consequently attenuating HPA axis activity and reactivity. The differential response to glucose, fat and protein loading prior to the TSST suggest that, similar to the rat, central mechanisms are also involved in the human situation rather than metabolic pathways such as the citric acid cycle [48].

At baseline, both hypo- and hyper-glycaemic states alter the HPA axis. In both the fasting and post-prandial state cortisol secretion was increased. Deconvoluting cortisol concentration to access the underlying HPA axis activity, hyper- and hypoglycaemic states had no effect on the number of secretory events, the inter-pulse interval, secretory burst length, or cortisol half-life, however, they modulated the mass secreted during each event [50, 51]. There is however, a gap in the literature on how a stressor such as the TSST activates gluconeogenesis.On the other hand, blood glucose levels are also dependent on catecholamine levels. Release of epinephrine induces a rapid rise in blood glucose levels through a combination of reduced glucose uptake in insulin-dependent tissues as well as a temporary increase in hepatic glucose production from both gluconeogenesis and glycogenolysis. Glycogenolysis wanes rapidly, while gluconeogenesis is mainly responsible for the resultant hyperglycaemia [52]. Therefore, it can be postulated that the status of the HPA axis may be extracted from blood glucose records, and vice versa, and that the nervous system plays a significant role in maintaining homeostasis/allostasis.

2.4 Metabolism and chronic stress

Chronic stress results in an allostatic state that complies with consistent hyperglycaemia. This in turn influences the glucose utilisation, trafficking, hepatic synthesis and insulin sensitivity. Normal (non-stressful) condition favours glycogen formation in the liver by glycogenesis. Stress however, inhibits glycogen synthesis by antagonising the enzyme glycogen synthase and instead encourages glycogenolysis, which normally occurs during starvation, to ensure useable energy to elicit a flight/fight response. This has been validated in a previous study, where Nirupama et. al showed declining levels of glycogen in the liver of stressed rats [41].

Synthesis of glucose using “non-carbohydrate sources” occurs by gluconeogenesis, a central metabolic pathway that also operates during starvation. Stress regulated glucocorticoids transcriptionally trigger key players of the gluconeogenic pathway such as glucose-6-phosphatase (G6Pase), pyruvate carboxylase, pyruvate carboxy kinase (PEPCK) and fructose 1,6 bisphosphatase (FBPase). Interestingly, it has been shown that a doubling in PEPCK expression can lead to insulin resistance and a seven times increase can result in hyperglycaemia [53]. The GC-GR transcriptional dependence is clearly demonstrated in mice lacking hepatic GR that show an exaggerated hypoglycaemia after fasting as neither PEPCK, pyruvate carboxylase, nor G6Pase can be upregulated [54], although all three genes are involved in gluconeogenesis, G6Pase is however, also involved in hepatic glucose release from glycogenolysis [55]. This occurs through direct GR interactions with genomic glucocorticoids response elements (GREs). GR ligation and DNA binding provides a “transcriptional hub” where coactivators such as GR-associated PGC- 1α, FOXO1 and

HNF-4 interact to provide the full gluconeogenic response and expression of G6Pase and PEPCK (reviewed in [3]).

The concentration of other gluconeogenic substrates like oxaloacetate and pyruvate also increase during stress owing to increased activity of hormones such as glutamic oxaloacetatic transaminase (GOT) and glutamic pyruvic transminase (GPT). Thus, chronic stress increases glycogenolysis and gluconeogenesis, while it downweighs glycogenesis and insulin sensitivity, resulting in a diabetogenic physiological state, which can result in metabolic syndrome if left uncontrolled.

2.5 Glucocorticoids and diabetes

Type 2 diabetes is largely the result of uncontrolled hepatic gluconeogenesis [56], and glucocorticoids play a significant role in this dysregulation [3]. When the glucocorticoid actions are impaired by mutations in the GR, mice are protected from experimental models of hyperglycaemia, metabolic syndrome and have reduced gluconeogenic gene expression. The implication of glucocorticoids in T2D is well established, the underlying mechanisms are still not known, although there are data that suggest changes in expression of the GR itself [57], cofactors such as PGC-1 alpha [58], and inactivation of cortisol by 11-beta HSD, reducing GC signalling [59, 60]. GC effect are also seen in the pancreas.

During metabolic dysfunction, insulin secreting pancreatic beta cells can no longer compensate for hyperglycaemia, and long-term exposure to high levels of exogenous or endogenous GC during therapeutic administration of Cushing's syndrome respectively reduce insulin secretion and induce a diabetic-like phenotype [61]. Overexpression of the GR in pancreatic beta cells leads to reduced insulin secretion associated with an impaired glucose tolerance and eventually hyperglycaemia [62]. Moreover, GC signalling through the GR is a trigger of insulin resistance in muscles, supressing GLUT 4 translocation to the cell surface, as well as downregulating glycogen synthesis [63]. It would appear that the GR interacts directly with both the insulin and insulin-like growth factor 1 (IGF-1) pathways [64], although detailed mechanistic studies of GC effects in muscle carbohydrate metabolism are cruelly lacking [3].

The interaction between the HPA axis and T2D is bidirectional. There is a clear link between T2D, diabetic complications, and HPA axis hyperactivity [65]. Furthermore, hyperglycaemia from T2D can dysregulate the HPA axis, subsequently increasing the risk of major depression [66]. Mechanistically, this passes through altered secretion of ACTH from the pituitary gland, leading to altered GC levels [65, 66]. In a series of particularly well designed experiments, Mosili et al. demonstrated that as rats entered a prolonged pre-diabetic state baseline ACTH levels under non-stressful conditions dropped, but GC levels were significantly elevated [67]. The HPA axis negative feedback loop should, under normal conditions bring down GC levels when ACTH levels are low [68] suggesting that the negative feedback is somehow impaired [65]. Furthermore, when Mosili et al induced a chronic stress together with pre-diabetes, the rats were unable to mount a normal ACTH or GC response to subsequent acute stressor. further consolidating their observation of either impaired GC signalling or negative feedback [67]. Interestingly, diet would appear to affect the adrenal gland as increased GC secretion, adrenal cortical hyperplasia, and increased steroidogenesis have been reported in T2D- and obesity-inducing high fat diets [69]. Furthermore, certain sugars such as fructose can bind glucose transporter and can pass the blood-brain barrier and be absorbed in both the hippocampus and hypothalamus activating the HPA axis [70, 71]. Thus, poorly controlled T2D can result in an impaired HPA axis. This is in turn creates a vicious cycle, where excessive GCs antagonise glucose homeostasis and insulin sensitivity

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3. Early life Adversity

3.1 Early-life Adversity and changes in the HPA axis

Early-life adversity (ELA) is a broad term that covers all negative experiences affecting an infant's security or safety. It ranges from growing up in a dysfunctional household, abuse or maltreatment to low socioeconomic status, victimisation, bullying or exposure to crime [72, 73]. In all societies studied so far, ELA is prevalent, with, for example 59% of the US population reporting at least one adverse event in the BRFSS (Behavioural Risk Factor Surveillance System) study [74]. ELA has broad long-term consequences on the neuroendocrine, immune and metabolic systems (reviewed in [73]) as well as on neuroplasticity and neuronal morphology altering the overall cerebral maturation trajectory (reviewed in [75]). Although the literature is somewhat unclear, "mild" stress in the neo- and pre-natal period appears to induce HPA-axis hyperactivity such as increase the cortisol responses to a standardized stressor in pre-adolescent children [76, 77]. Slightly higher "moderate" levels linked to more clear forms of early life adversity (e.g., frequent emotional maternal withdrawal, corporal punishment, or interparental aggression) increases both the baseline cortisol level [78], and the HPA axis response to stress [79]. Severe early life stress or adversity e.g., institutionalization, neglect, abuse, or deprivation lowered basal cortisol levels [80, 81] and blunted HPA axis reactivity [82, 83]. Hypocortisolism and reduced HPA axis responsivity was initially proposed to be either due to a reduced pituitary response to hypothalamic CRF [84] or by the hypersensitivity of the final glucocorticoid target tissues and the HPA axis tissues in the negative feedback loop [85]. The latter would appear to be excluded since in our EpiPath institutionalization/adoption "severe" early life stress cohort, peripheral glucocorticoid receptor signaling and functionality was essentially preserved and indistinguishable from non-exposed controls [86].

The situation may be somewhat more complicated and dependent on the timing of the adversity. Adversity in early childhood, was associated with a decreased hippocampal volume, whilst prefrontal cortex volume was reduced if exposed during adolescence [87, 88]. Psychopathologically, exposure to adversity or trauma before age 12 increased the lifelong risk of developing major depressive disorder, but when occurring between age 12 to 18 the risk of PTSD was increased [89]. It has been suggested that since the human hippocampus is not fully developed before age 2, the frontal cortex primarily matures between age 8 -14 and the amygdala continues developing until early adulthood [90], that the hippocampus is most probably the brain area most affected by early life stress [75]. The sensitivity of the hippocampus to ELA is particularly important, as, outlined above, it plays a key inhibitory role in PVN activation of the HPA axis. Hence, ELA renders the HPA axis impaired, which in turn causes insidious changes to the stress response mechanism along with glucose metabolism, eventually contributing to MetS (Figure 3).

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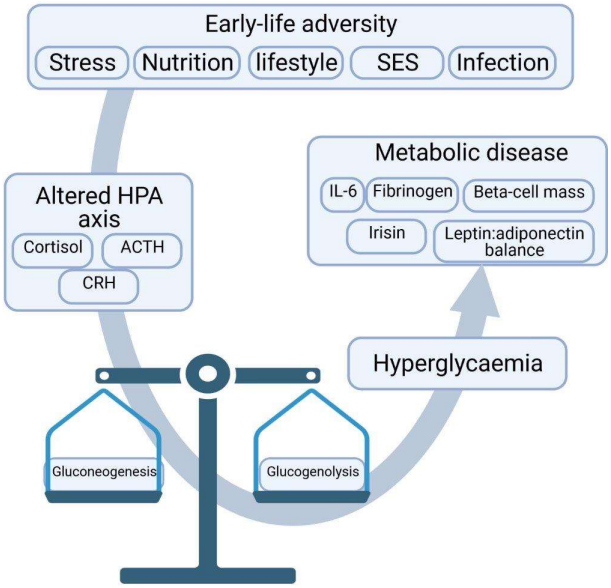

Figure 3: Early life adversity dysregulates the HPA axis and its key effector molecules, which in turn disrupts glucose homeostatic balance leading to hyperglycaemia and metabolic syndrome if left unchecked.

3.2 Early-life adversity, diabetes and the metabolic syndrome

A cluster of metabolic abnormalities including hyperinsulinemia and insulin resistance are often found in association with impaired glucose tolerance, obesity, dyslipidemia, and hypertension, forming what is now known as the Metabolic Syndrome (MetS) [28, 91]. MetS predicts not only cardiovascular mortality, but also the progression to full type 2 diabetes (T2D) [92]. There is growing evidence that early-life nutritional and psychosocial stress or disadvantage determine the trajectory and transition into metabolic dysfunction, MetS, and T2D later in life [9]. There are now many reports from ourselves and others of early-life adversity affecting either the metabolic profile, obesity, or type 2 diabetes [93-95]. Socioeconomic status in early life has a similar effect [13], and is associated with T2D 50 years later [96].. ELA also predisposes individuals towards a chronic inflammatory phenotype [95, 97-99]. Furthermore, cardiometabolic disease markers such as fibrinogen, C-reactive protein, and interleukin-6 were elevated [15, 100], as were endothelial dysfunction markers such as ICAM-1, E-selectin [101], as well as clinical measures such as arterial stiffness [102] or poor blood pressure trajectories with age [103]. Recently, this was replicated by Chandan et al (2020) confirming the role of ELA in determining "a significant proportion of the cardiometabolic and diabetic disease burden may be attributable to maltreatment" [104, 105].

Although there are few mechanistic data available, these metabolic abnormalities may be due to changes in circulating adipokine levels. ELA has been directly associated with an increased leptin:adiponectin ratio [106]. Leptin, secreted by adipocytes, regulates energy balance through decreasing appetite and is associated with the metabolic syndrome [107, 108], whilst adiponectin, has insulin-sensitizing effects. Low adiponectin levels are associated with type 2 diabetes and insulin resistance [108, 109]. Furthermore, Irisin levels were increased by ELA [106]. Irisin, mediates glucose metabolism as well as exercise-related energy expenditure and is a peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α)-dependent myokine [106, 110]. Glucocorticoids may also play a role, as, in utero exposure to maternal under nutritional affects beta-cell number and function lifelong in a manner dependent upon GR and GC since deletion of the GR in foetal pancreatic cell abrogated this effect [3]. These changes may, in part be due to

the effects of ELA on the methylation of genes involved in obesity and metabolic pathways [111, 112]. Furthermore, adverse early life conditions induce lifelong changes in gene transcription [113]. Low SES, for example, has been associated with inflammatory and diabetic genes such as TLR3 [114], NLRP12 [115], F8[116], KLRG1 [117], CD1D [118], as well as the stress-associated genes OXTR [119], FKBP5 [120], and AVP [121], Suggesting, as we have previously proposed, that a negative early life environment acts through inflammatory pathways that are also associated with T2D, targeting pathophysiological factors such as stress and inflammation, participating in the aetiopathology of T2D [105]. Thus, it appears logical to conclude that ELA can effectively alter glucose homeostasis and that the aetiology of MetS and eventual T2D may have strong roots in ELA. Moreover, ELA would appear to be associated with more advanced or complicated diabetic-pathologies requiring more aggressive management [122].

3.3 Glucose metabolism, allostasis and allostatic load

Ever since Hans Selye described the "general adaptation syndrome" as our response to external stressors [123], there has been a paradox. The ANS and HPA axis protect in the short-term, but over the long-term they may accelerate disease as well as causing lasting damage. When physiological parameters deviate from homeostatic thresholds and set-points we enter a state of allostasis, preparing to react to the stressors. The related allostatic load (AL) then refers to the "wear and tear" that regulatory systems undergo during long periods of allostasis and chronic stress exposure. (10,11), AL is fundamentally a chain of causal events from the primary stress response of SNS and HPA axis activation with epinephrine and cortisol secretion, inflammation [124], leading to secondary markers of stress exposure including hyperglycaemia, hypertension, hyperlipidaemia, and central adiposity. The AL cascade, the overall sequence of responses, as well as their contribution to disease development are not fully understood, and somewhat under-investigated although markers of AL are associated with increased glycaemic measures in women [125]. Similarly, rat chronic stress models, a proxy for AL, consistently report high blood glucose levels up 6 months later [41] In allostasis these rats also had dysregulated glucose metabolism pathways, in particular increased gluconeogenesis [41]. Furthermore, this stress induced hyperglycaemic state resulted in impaired glucose tolerance and reduced insulin sensitivity [41]. This may be due to metabolic memory, which causes the body to recall the influence of metabolic regulators for a much longer duration. This, in conjunction with persistent stress can lead to maladapted allostasis and eventually allostatic load. Prolonged allostatic load can give rise to metabolic syndrome. There is also recent evidence that diet may act as a stressor. Increased glycaemic load (i.e. dietary sugar intake) is associated with increased markers of AL, particularly in women, suggesting that dietary carbohydrate intake may contribute towards dysregulation of the AL response [125]. It is well established that carbohydrate intake can stimulate the ANS [126], and hypothesised to cascade down increasing AL markers and blood glucose levels [125]. Thus, chronic stress/allostatic load can adversely affect glucose metabolism and mount a faulty bodily adaptation that ultimately leads to MetS.

4. Gluconeogenesis at the crossroads between adversity and metabolism

It is well established that energy metabolism and psychosocial stress are intimately intertwined. It would also appear that psychosocial adversity in early life sets the individual on a negative trajectory towards either MetS or T2D. The available literature suggests that ELA can effectively alter glucose homeostasis and participate in the aetiology of MetS and eventual T2D. It is possible that MetS and T2D may have very strong roots in the early life environment, with ELA a strong driver of the eventual diabetic phenotype. This suggests that gluconeogenesis, originally named because of the intimate link between corticoid levels and glucose levels, may be at the heart of the mechanism. We suggest that this

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may be a double-edged sword. Gluconeogenesis is an integral part of energy homeostasis in response to an external stressor. However, it may show its true "Jekyll and Hyde" nature when the HPA axis is perturbed. Furthermore, the interaction between the HPA axis, glucocorticoids and mechanisms of glucose homeostasis such as gluconeogenesis or insulin resistance may be the link between ELA and lifelong metabolic disturbances.

Energy homeostasis during psychosocial stress is somewhat underexplored, however, a number of recent studies have started to investigate the full nature of the bi-directional regulation in more detail. There are many avenues that remain to be explored. There is a wealth of data on how glucose availability modulates the corticosteroid response to psychological and psychosocial stressors, however, the data is sparse or inexistent in the reverse direction. Glucose or levels of gluconeogenesis need to be determined after stress. Furthermore, they need to be recognised as genuine measures e.g. the Trier Social Stress test, providing insight into how the stress axes interact with energy homeostasis. Elucidating these GC-glucose interactions during laboratory stressors is now essential. We need to initially understand the normal blood glucose response to an external stressor. This will subsequently permit investigation of glucose-cortisol coupling in situations such as exposure to ELA where the HPA axis has been significantly programmed, with lifelong changes in reactivity, setpoint, and secreted hormone levels. Recent work on the direct transcriptional control of gluconeogenesis [7], together with recent interest in stress-energy balance [127] open the field for more detailed investigation of the bi-directional regulation of these two essential physiological systems. Thus, it is extremely important to identify if the "Jekyll" or the "Hyde" of gluconeogenesis, and how it balances energy homeostasis under stress, while avoiding gluconeogenesis driven T2D.

5. Conclusions

In light of the presented narrative, it is clear that there is a direct link between ELA, the HPA axis, glucose metabolism, MetS, and potentially T2D. It is now essential to understand how early life programming of the HPA axis, with lifelong changes in glucocorticoid secretory profiles, influences energy metabolism and processes such as hepatic gluconeogenesis. To do this, and to provide the missing piece of the puzzle we need to consider glucose and energy homeostasis as genuine output measures in standardised laboratory psychological stress tests such as the TSST or the socially evaluated cold pressor test. We need to initially investigate the normal physiological interaction between the HPA axis (or the complete stress system), and energy homeostasis. We hypothesise that lifelong programming of the HPA axis after ELA will fundamentally alter hepatic gluconeogenesis, inducing hyperglycaemia, and the significant lifelong risk or MetS or T2D. This gives a "Jekyll and Hyde" role to gluconeogenesis, providing the necessary energy in situations of acute stress, but driving towards pathophysiological consequences when the HPA axis has been altered. Furthermore, if our hypothesised link is correct, does this output have the predictive power to identify individuals at a higher risk of developing MetS at a later stage in life, identifying people at risk of developing T2D or MetS before symptom onset?

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