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a complexity science approach

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How exposure to chronic stress contributes to the development of type 2 diabetes: A complexity science approach

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ABSTRACT

Chronic stress contributes to the onset of type 2 diabetes (T2D), yet the underlying etiological mechanisms are not fully understood. Responses to stress are influenced by earlier experiences, sex, emotions and cognition, and involve a complex network of neurotransmitters and hormones, that affect multiple biological systems. In addition, the systems activated by stress can be altered by behavioral, metabolic and environmental factors.

The impact of stress on metabolic health can thus be considered an emergent process, involving different types of interactions between multiple variables, that are driven by non-linear dynamics at different spatiotemporal scales.

To obtain a more comprehensive picture of the links between chronic stress and T2D, we followed a complexity science approach to build a causal loop diagram (CLD) connecting the various mediators and processes involved in stress responses relevant for T2D pathogenesis. This CLD could help develop novel computational models and formulate new hypotheses regarding disease etiology.

1. Introduction

The pathophysiology of type 2 Diabetes (T2D) is complex and its symptomatology involves dysregulation of multiple biological processes, such as metabolic, immune, cardiovascular and neuroendocrine systems (Galicia-Garcia et al., 2020; Schwartz et al., 2017). Because of its profound influence on all these biological systems, recent studies have increasingly recognized chronic (psychological) stress as a risk factor for T2D (Hackett and Steptoe, 2017). Chronic stress generally involves exposure to stress that persists for weeks to years, as e.g., occurs during unemployment or poor socioeconomic circumstances (Epel et al., 2018).

Indeed, not only have multiple longitudinal studies now shown that chronic stress increases the risk to develop T2D, the strength of reported associations for chronic stress was even comparable to those reported for more traditional health factors such as physical inactivity or adiposity (Akter et al., 2017; Hackett and Steptoe, 2017; Kelly and Ismail, 2015; Maddatu et al., 2017). Moreover, the observed associations were not fully explained by confounding behavioral risk factors, together strongly suggesting a direct involvement of biological stress responses in T2D pathogenesis (Steptoe et al., 2014).

The physiological stress response involves a rapid activation of the sympathetic nervous system (SNS), followed by a later and slower response of the hypothalamic–pituitary–adrenal (HPA) axis and results in a biphasic plasma hormonal response in (nor)adrenaline and glucocorticoids (GCs) (cortisol in humans, corticosterone in rodents) (Romero

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and Butler, 2007; Ulrich-Lai and Herman, 2009). Together, these hormones influence various aspects of neuronal, neuroendocrine, immune, cardiovascular and metabolic systems, all relevant to T2D, that act to establish homeostasis and thereby promote behavioral adaption to stress (De Kloet et al., 2005).

Repeated and continued activation of the SNS and HPA axis, however, as occurs during chronic stress, can ultimately lead to physiological disturbances that may result in a cumulative "wear and tear" and build up an "allostatic load" (Lucassen et al., 2014; McEwen, 2000). The concept of "allostatic load" has helped operationalize the concept of chronic stress into measurable physiological parameters that allow to identify relations between different types of stressors and stages of T2D development (Hackett and Steptoe, 2017). Chronic stress has notably been associated with inflammatory and/or cortisol-related dysregulations, two markers of allostatic load which predict an increased risk of T2D onset (Hackett et al., 2016; Hackett and Steptoe, 2017). However, understanding which specific pathophysiological mechanisms underlie these relationships has so far remained largely elusive. When expanding current perspectives on the links between chronic stress and T2D, and when trying to generate more mechanistic models, various limitations therefore need to be considered (Aschbacher et al., 2014; Epel et al., 2018; Johnson et al., 2017; Kagan, 2016).

First, the stress response includes a combination of cognitive, affective and (neuro-)biological responses. While these three dimensions are often considered separately, many interactions exist between them (Epel et al., 2018). For instance, uncontrollable stress and the psychological states induced by a threat, have been associated with distinct neuroendocrine and autonomic responses, that can in turn, impact health to a different extent (Dickerson and Kemeny, 2004; Epel et al., 2018). Also, specific stress paradigms that encompass uncontrollability have been associated with an increased risk for T2D. These are, for instance, exposure to stressful working conditions, an imbalance in effort and reward at work, traumatic events, low socio-economic-status (SES), or a higher incidence of racial/ethnic discriminations (Kelly and Ismail, 2015; Nordentoft et al., 2020; Whitaker et al., 2017). A more comprehensive integration of the possible links between cognitive, affective as well as biological aspects of the stress responses, and how they interact, might ultimately help to better understand the links between chronic stress and T2D.

Second, in addition to the activation of the SNS and HPA axis, several stress-related neurotransmitters and hormones act on multiple regions in the brain and in the periphery (Joëls and Baram, 2009; Stone et al., 2020). Their physiological actions often follow complex dynamics, e.g., due to the negative feedback they exert on their own release, and/or via modulating the release of other molecules, like glucose, insulin or cytokines, often in a non-linear or cyclic fashion (Dumbell et al., 2016; Koch et al., 2017; Oster, 2020). Depending on the timing, repetition, duration and frequency of a stressor, the physiological alterations induced can become persistent and also influence future stress responsivity, leading to complex feedback regulation and non-linear dynamics when considering larger temporal scales (Epel et al., 2018; Fitzsimons et al., 2016). For example, evidence suggests that the link between chronic stress and T2D is mediated by a dysregulation of the diurnal cortisol dynamics, rather than by alterations of cortisol levels per se (Adam et al., 2017; Hackett et al., 2016; Hackett and Steptoe, 2017). As such, alterations of the control on mediators involved in stress responses and affecting systems implicated in T2D pathogenesis might be an important phenomenon to consider in order to understand the contribution of chronic stress to T2D onset.

Third, various behavioral and physiological factors also influence HPA-axis physiology (Kudielka et al., 2009; Stenvers et al., 2019). The function of the HPA axis is influenced by patterns of sleep and/or light exposure such that disturbed patterns of sleep or light exposure during nighttime can disrupt the circadian control of the cortisol rhythm. This can in turn impair the regulation of both tissue insulin sensitivity and insulin secretion by pancreatic β-cells, which may further contribute to

insulin resistance (Stenvers et al., 2019) and T2D (Hackett et al., 2020; Vetter et al., 2018). Moreover, HPA axis activation can also result from, or be modified by, physical stressors, like infection or exposure to pollutants (Snow et al., 2018; Thomson, 2019; Ulrich-Lai and Herman, 2009). For instance, in both rodents and humans, acute exposure to ozone increased serum GCs and disrupted lipid metabolism, likely an activation of the HPA axis (Miller et al., 2016). Also, long-term exposure to ozone and air-pollution in general, have been associated with an increased T2D incidence (Li et al., 2021; Renzi et al., 2018). Such effects of chronic psychological and physical stress and related factors might further aggravate one another and increase T2D risk in a reinforcing, rather than additive manner (Kodavanti, 2016; Wright and Schreier, 2013; Zänkert et al., 2019).

So far, an integrative overview of all relevant, interacting factors in relation to the interaction between chronic stress and T2D is lacking (Hackett and Steptoe, 2017; Kelly and Ismail, 2015). If we are to better understand the link between chronic stress and T2D, a more complete picture of the diverse actions of the various mediators involved in the stress response and metabolic regulation, their interactions and nonlinear dynamics, is important to consider.

In this paper, we apply a complex systems approach to obtain an overview of the possible links between chronic stress and T2D. More specifically, based on evidence from both epidemiological and (pre) clinical studies, we built a causal loop diagram (CLD) that connects processes involved in the stress response to the pathophysiology of T2D at different spatiotemporal scales. A systems approach is a problem-solving paradigm that implies a holistic perspective, i.e., we consider the different components of an entire system and their interactions, rather than studying specific relations in isolation (Kenzie et al., 2018). The added value of a systems approach lies in the conversion of knowledge about psychological stress and T2D into an extensive conceptual model that can help explain how various relevant mechanisms and the structure of the system (e.g., feedback loops) relate to the behavior of the system (Aschbacher et al., 2014; Kenzie et al., 2018).

Considering the link between chronic stress and T2D from a complex system 'lens' enables us, for the first time, to connect contexts and concepts related to the large variety of human experiences, to the biological stress response and the dynamic interplay between these elements in relation to T2D etiology.

2. Methods

A CLD is a graphical model used to represent relationships between different variables (e.g., factors, processes, subsystem states, aggregate quantities) of a given system. In a CLD, variables and the relationships between them, are represented by nodes and directed edges, respectively, i.e., directed arrows that indicate an influence of the variable at the tail of the arrow (source variable), on the variable at the head of the arrow (target variable). The directed edges of a CLD are usually marked with a polarity indicating either a positive influence (an increase of the source variable induces an increase of the target variable), or a negative influence (an increase of the source variable induces a decrease of the target variable). By depicting how different elements influence other elements of the modelled system, CLDs provide a quasi-dynamic description of the possible outcomes of the evolution of a given variable on the system and therefore allow for a qualitative model of the progression from a given input to a given output.

CLDs reveal feedback loops that correspond to the influence of a variable's output on the same variable (e.g., variable A influences the evolution of variable B, which in turn influences the evolution of variable A). Reinforcing loops describe amplifying mechanisms and are characterized by an even number of negative influences. Balancing feedback loops describe mechanisms that oppose further change in a certain direction with an action in the opposite direction and are characterized by odd numbers of negative influences. When feedback loops are interconnected, each feedback loop's individual influence on the

whole system can progressively increase or decrease, for instance an amplifying feedback loop can become dominant over a balancing feedback loop and over time, thus drive an entire system towards imbalance.

Feedback loops are consequently an important part of CLDs and are critical for understanding the properties of a system and in describing the conditions under which homeostatic biological mechanisms are impaired and a biological system can change from a healthy into a pathophysiological state.

2.1. CLD development

The current CLD was built by a modelling team with expertise in public health, health inequalities, complexity science, (neuro)endocrinology, chronobiology, metabolism, obesity and T2D pathophysiology. The development of the CLD was based on a literature review translated into a conceptual model realized by NM. The CLD and its description were then presented to seven additional researchers with expertise in

(neuro)endocrinology, neurobiology, stress and plasticity of the brain, chronobiology, metabolism, gastroenterology, obesity and T2D pathophysiology. These domain experts were consulted through semi-structured interviews of 60–90 min conducted by NM and MN and/or written feedback. Their feedback was discussed in the modelling team and integrated in the paper by adapting and finalizing the CLD.

2.2. Literature review

Our literature review was organized following different steps that we identified from recommendations given by Miller et al. (2009) and we included clinical, laboratory and epidemiological studies and reviews.

Miller et al. (2009) recommended to use an "'approach that reverse engineers' adverse health outcomes into their specific biological determinants, and then identifies psychologically-modulated, neuroendocrine and immunological dynamics that modulate those pathological processes at the cellular and molecular levels".
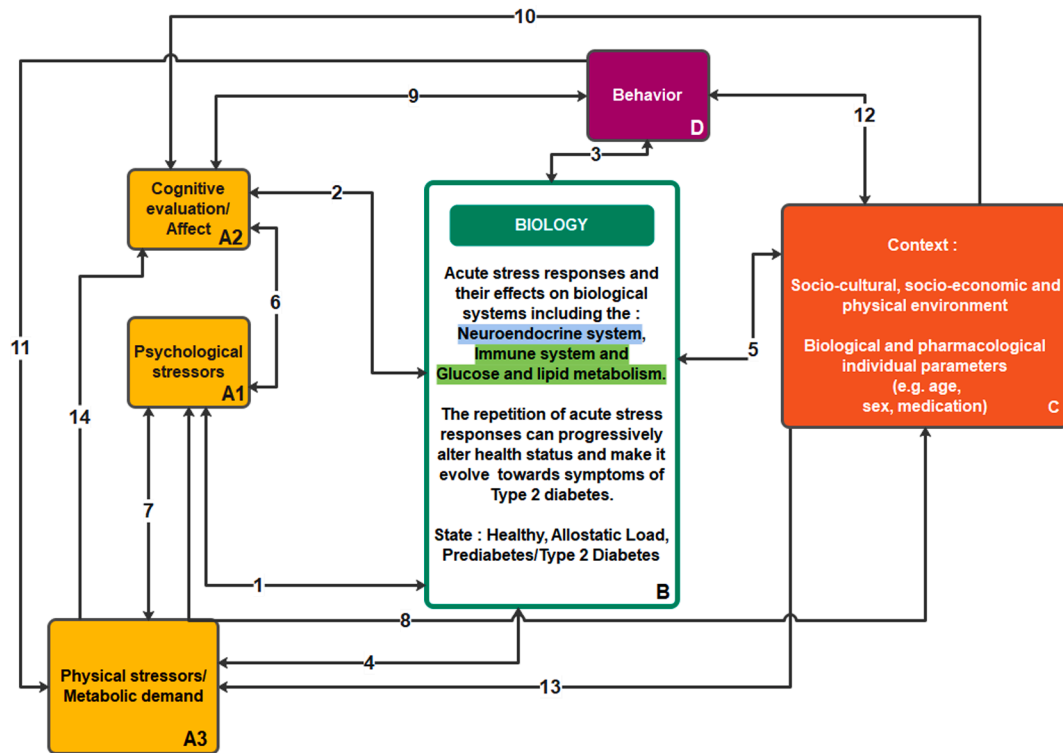
Fig. 1. Schematic representation of the possible relationships between different aspects of stress, context, behavior, physical environment and general health. **1:** A1 → B = Exposure to psychological stressors can result in biological stress responses. B → A1 = Biological processes can influence the exposure to stressors (e.g., pain can be perceived as a stressor) and their appraisal. **2:** B → A2 = Biological states can result in negative affect, for instance by making an individual more susceptible to anxiety. A2 → B = Cognitive and emotional aspects characterizing the perception of stressors can influence biological stress responses. **3:** B → D = Biological states can influence an individual's behavior, for instance their food intake. D → B = Behavioral-related aspects such as diet, physical activity and sleep can affect biological systems. **4:** B → A3 = Physical conditions, such as a leaky gut can for instance make an individual more prone to infection, which is a physical stressor. A3 → B = Physical stressors such as infections or exposure to pollutants, result in physiological stress responses. In addition, the metabolic demand generated by a stressor or the behavioral response to it, e.g., a physical and/or mental task, can influence the biological stress response and its impact on biological systems. **5:** B → C = Physical conditions (for instance fatigue, pain, digestive issues) can affect socioeconomic resources by impairing the ability to perform certain professional activities. C → B = Physical environmental elements such as exposure to pesticides, pollution or circadian dysregulation caused by shift-work can impact physical health. **6:** A1 → A2 = Psychological stressors can for instance be perceived as uncontrollable or threatening and thereby impact cognitive and emotional processes. A2 → A1 = Cognitive and emotional processes such as anticipation or rumination can constitute internal psychological stressors. **7:** Psychogenic stressors can be associated with physical stressors (A1 → A3) and vice-versa (A3 → A1). **8:** A1 → C = Exposure to psychological stressors can influence an individual's context: for instance, being discriminated can result in isolation, loneliness and/or becoming unemployed. C → A1 = The likelihood of being exposed to psychological stressors depends on an individual's context, for instance, low income and associated difficulties can constitute a psychological stressor. **9:** A2 → D = Cognitive and emotional aspects characterizing the perception of stressors might impact behavior. D → A2 = Behavior can impact the cognitive and emotional responses to stress. **10:** C → A2 = Cognitive and emotional aspects characterizing the perception of stressors can depend on an individual's context and will influence their subsequent stress responses. **11:** D → A3 = Certain behaviors such as excess alcohol consumption can modulate physical stressors. **12:** D → C = Behaviors can influence an individual's context, e.g., interpersonal relationships can influence the access to social support. C → D = An individual's context, for instance their cultural environment, can have an impact on an individual's behavior. **13:** C → A3 = The likelihood to be exposed to physical stressors depends on an individual's context such as their socioeconomic resources. **14:** A3 → A2 = Physical stressors can result in specific cognitive and emotional processes, e.g., fear.

Building on the work of these authors, our literature review was organized according to the following items:

1. identify "the most proximal biological pathways linked to clinical disease outcomes (i.e., *mechanism of pathogenesis*)" (Miller et al., 2009);
2. identify "psychologically modulated neuroendocrine dynamics" (Miller et al., 2009);
3. identify how these neuroendocrine dynamics modulate biological pathways leading to T2D.

2.3. Scope

Stress is a multidimensional construct which can be described through three different components: 1) stressors, i.e., stimuli that are hypothesized to induce distress or elicit a stress response in the body, 2) the processing of stressors which includes the subjective experience of stress and underlies interactions between cognitive evaluations and emotional/affective states, and 3) the biological stress responses, i.e. bodily or hormonal physiological responses in an individual who is exposed to a stressor (Kelly and Ismail, 2015; Ursin, 1991).

These different dimensions of stress interact, at various levels and spatiotemporal scales, via feedforward and feedback loops, ultimately aiming at restoring homeostasis. They do so through behavioral and physiological adaptations (de Kloet et al., 2019; Levine, 2005), and by interacting with an individual's context, behavior and physical environment (Epel et al., 2018). Fig. 1 maps the relations between these different aspects and defines the scope of the CLD built in the current paper.

Panel A1 (Fig. 1) corresponds to exposure to psychological stressors. Panel A2 (Fig. 1) corresponds to cognitive and emotional processing of stress (Epel et al., 2018). Panel A3 (Fig. 1) corresponds to physical stressors, which can also activate the HPA axis and SNS, and the metabolic demand, generated by a stressor or the behavioral response to it, that can influence the biological stress response and its impact on biological systems (Epel et al., 2018). Panel B corresponds to biological processes involved in acute and chronic stress in adulthood, their interplay and how their dynamics can evolve towards T2D onset. Panel B includes biological processes involved in acute stress responses and the effects of these processes on systems including the brain, systems related to glucose and lipid metabolism and the immune system. As stress responses are chronically occurring, these biological systems adapt and change and can, under certain conditions, progressively accumulate an allostatic load which may further develop into symptoms of prediabetes and T2D. Panel C (Fig. 1) corresponds to contextual factors like the socio-cultural environment and biological and pharmacological factors including age, sex or medication. These endogenous and exogenous factors can influence exposure to stressors, stress responses and the impact of chronic stress on biological systems. Panel D (Fig. 1) corresponds to behaviors.

Link 1 in Fig. 1 refers to the biological response induced by the appraisal of stressors in the direction A1 → B and to the influence of biological processes on exposure to stressors or their appraisal in the direction B → A1. Link 6 in Fig. 1 describes the influence of stressors' characteristics on cognitive and emotional processing in the direction A1 → A2 while it represents the influence on cognitive and emotional processing on the appraisal of stressors in the direction A2 → A1. Link 2 in Fig. 1 corresponds to the influence of cognitive and emotional processing on biological processes (A2 → B) and vice versa (B → A2). Link 9 corresponds to the influence of stress processing (cognitive and emotional) on behaviors in the direction A2 → D and inversely in the direction D → A2. Behaviors in panel D (Fig. 1) can include behaviors aimed at restoring homeostasis, addressing the source of stress and more generally health behaviors. Link 3 represents the influence of biological systems on behaviors in the direction B → D and inversely in direction D → B. The interactions between panels A2 and D also underlie coping

which Lazarus and Folkman defined as "constantly changing cognitive and behavioral efforts to manage specific external and internal demands that are appraised as taxing, or exceeding the resources of the person" (Lazarus and Folkman, 1984). Links 2 and 3 further underlie the role of coping in mediating the relationships between stress and health.

For panel A2 (Fig. 1), we integrated cognitive aspects in as much as they are related to the perception of stressors as being uncontrollable and threatening, and focused on their influence on central stress responses. We did not include emotional processes and psychological states associated with stress responses to the brain network regulating the activity of the HPA axis. This choice was made as the influence of emotion and cognition on neural patterns active during acute stress and further on the relationships between these patterns and HPA axis responses during acute stress is currently inconclusive (Epel et al., 2018).

Here, we did not include physical stressors or the influence of possible metabolic demands on stress and their links with T2D.

For panel B (Fig. 1), we included mechanisms related to the HPA axis and the SNS and the effects of GCs and catecholamines on glucose and lipid metabolism and immune regulation. These are not the only potential mediators linking chronic stress to T2D through non-behavioral pathways, but currently they are the most extensively studied, and disruptions in these systems have been associated with T2D risk (Epel et al., 2018; Hackett and Steptoe, 2017; Miller et al., 2009). In addition, GCs are among the most important 'master regulators' in the interaction between stress and TD2 development, both from a causal as well as a therapeutic perspective (Beaupere et al., 2021). Besides sex steroids, no signaling system exists with such a wide-ranging scope on multiple biological systems as GCs, and GCs are thus central when applying a complex systems perspective to the study of the relationships between stress and T2D. Regarding T2D etiology, we considered a global progression of the effects of chronic psychological stress, similar to the concept of allostatic load as proposed by McEwen, 1998. In this concept, a gradual alteration of the output of two main neural and neuroendocrine systems (i.e., the HPA-axis and SNS and their hormones cortisol, epinephrine and norepinephrine) is considered the primary mediator of the physiological disruptions induced by chronic psychological stress. These mediators are then thought to activate secondary effectors, including the immune, cardiovascular, glucose and lipid regulatory systems. Due to its gradual accumulation, T2D can then be considered a tertiary and final outcome (McEwen, 1998, 1993). Regarding the nonlinear interplay between acute and chronic stress, we focused more extensively on markers of HPA axis activity and the regulation and evolution of HPA axis activity in the context of chronic stress, the HPA axis reactivity appearing to be the most widely investigated aspect in relation to stress. In relation with behaviors, we included systems regulating food intake and circadian rhythms as they interact with the HPA axis and SNS and have been associated with T2D pathogenesis. We included temporal scales ranging from minutes/hours to months/years and spatial scales ranging from molecular to tissue scales. Finally, we detailed processes occurring in the periphery during acute stress and remained relatively generic regarding processes occurring in the central nervous system (CNS), since current evidence is not developed or consistent enough to infer possible mechanisms linking these aspects to HPA axis regulation and further on to T2D pathogenesis.

For panel C (Fig. 1), we included differences mainly related to sex/gender. Sex differences refer to biology-related differences caused by differences in e.g., sex chromosomes, sex-specific gene expression, sex hormones and their actions on biological processes, while gender differences emerge from sociocultural processes (Kautzky-Willer et al., 2016).

For panel D (Fig. 1), we focused on behaviors relevant to T2D and to HPA axis responsivity, including circadian and feeding-related behavior (Stenvers et al., 2019).

2.4. CLD format

The CLD (shown in Fig. 2) was rendered in Wondershare EdrawMax (version 10.5.4). In the current section we describe the graphical structure of the CLD.

2.4.1. Representation of the variables

Variables were represented using nodes of different colors in Fig. 2 (yellow, purple, orange, green, blue and pink), depending on the domains (as indicated in Fig. 1 and in section 2.3) of the variables the nodes referred to. The signification of each color is indicated in Table 1. Regarding blue and green nodes, which correspond to biological processes, different shades of blue and green indicate different spatial scales (a network scale which corresponds to processes occurring across multiple regions/organs, a cellular/tissue scale which corresponds to processes occurring in specific populations of cells and a molecular scale).

2.4.2. Structure of the CLD

The approximated progression towards T2D, across temporal scales was indicated on the top horizontal axis. Biological processes were further separated into central nervous system processes (upper part of the CLD) and peripheral ones (lower part of the CLD).

Furthermore, we grouped nodes into different clusters indicated by circular shapes of various colors, also indicated by letters (in Fig. 2). Cluster A in Fig. 2 groups variables that are related to the exposure to

psychological stressors (e.g., stressors characteristics and temporal related aspects, cognitive evaluation of stressors and affect). Clusters B1-B3 and clusters B4-B8 in Fig. 2 correspond to processes occurring, respectively, in the central nervous system and in the periphery. The description of each cluster is given in Table 1. Other characteristics such as sex/gender and age were grouped in cluster C and behavioral variables were grouped in cluster D.

2.4.3. Representation of the links between variables

Links were represented using arrows with 3 different types of lines: solid (black), dotted (red) and dashed (purple). Each represents a different type of influence of the source variable on the target variable: a positive or negative influence, or an influence that can be either positive or negative de depending on characteristics of the source variable or characteristics of the target variable, respectively (see Table 1). Two headed arrows were used to represent a higher difference between the temporal scales at which the source variable and target variable change as compared with simple headed arrows (e.g., minutes/months as compared to minutes/hours). All links in the CLD now have the same weight, but this representation does not reflect the actual importance of some source variables in terms of their proportional contribution to a given target variable. By default, the CLD is now depicted as a non-quantitative, graphical representation of the links between variables that are relevant in the relationships between stress and T2D. It was not possible at this stage, to attribute a relative, or quantitative weight to the
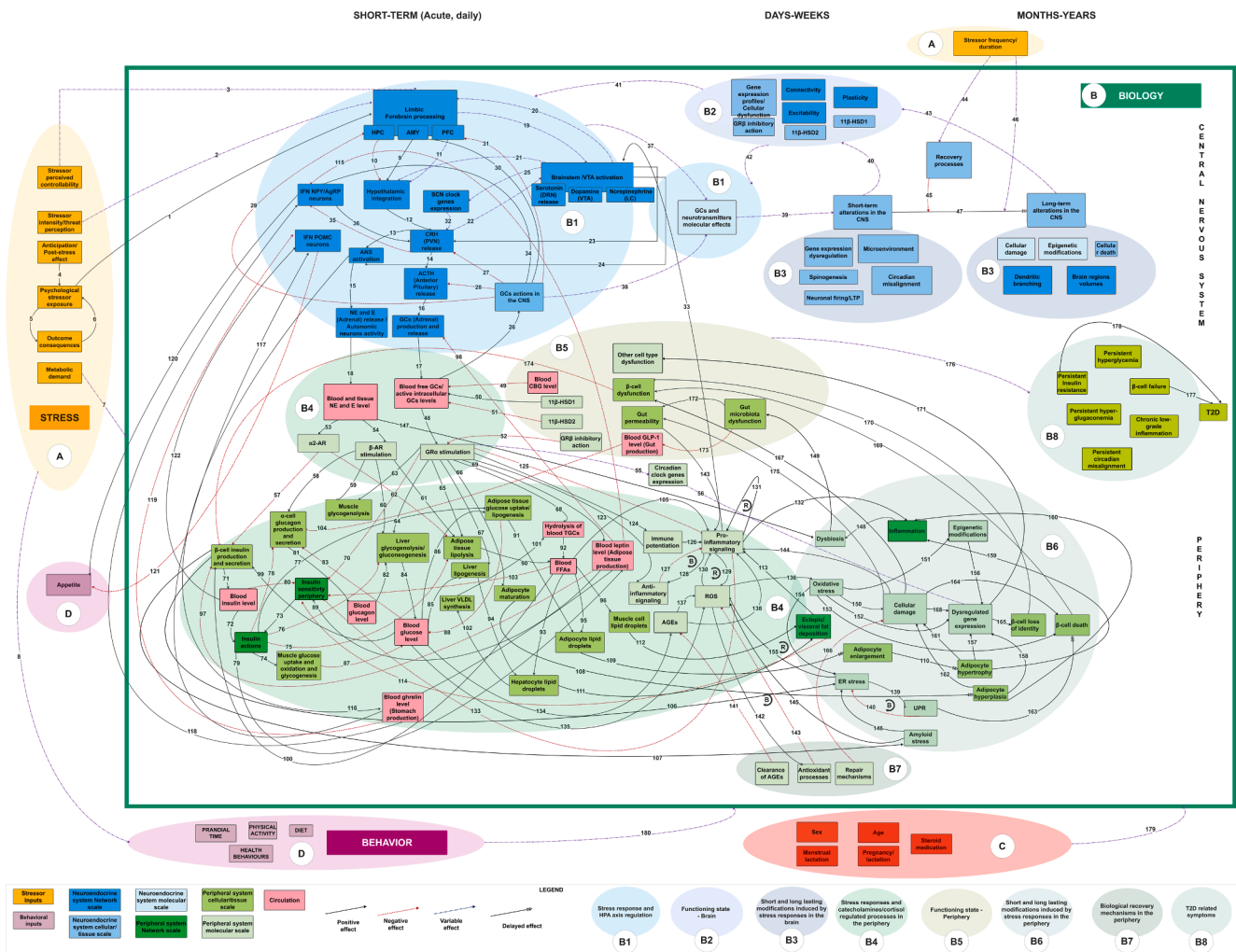

Fig. 2. Causal-loop diagram (CLD) connecting processes involved in the stress response to the pathophysiology of T2D at different spatiotemporal scales (the legend is described in section 2.4 and Table 1).

Table 1
Description of the different graphical items used in the CLD.

GRAPHICAL ITEM	SIGNIFICATION
Arrows	
Solid arrows (black)	Positive influence
Dotted arrows (red)	Negative influence
Dashed arrows (purple)	Influence that can be either positive or negative
Two headed arrows	Significant difference between the temporal scales at which the source variable and target variable change
Nodes	
Yellow nodes	Variables related to stress exposure
Purple nodes	Variables related to health behaviors
Orange nodes	Variables related to additional characteristics that may induce variability in described biological processes (e.g., sex/gender or age)
Blue nodes	Variables related to neuroendocrine biological systems and processes
Green nodes	Variables related to peripheral processes (e.g., glucose and lipid metabolism and inflammation).
Pink nodes	Concentrations of corresponding compounds in the circulation
Clusters of nodes	
A	Variables related to the exposure to psychological stressors (e.g., stressor characteristics and temporal related aspects, cognitive evaluation of stressors and affect)
B1	Biological processes occurring during acute stress responses in the CNS
B2	Biological variables regulating processes in B1
B3	Physiological alterations induced by stress responses in the CNS, at different temporal scales (ranging from days-weeks (short-term) to months/years (long-term))
B4	Biological processes occurring during acute stress responses in the periphery
B5	Biological variables regulating processes in B4
B6	Physiological alterations induced by stress responses in the periphery, at different temporal scales (ranging from days-weeks (short-term) to months/years (long-term))
B7	Recovery-related processes (e.g., biological processes aiming at restoring homeostasis) in the periphery
B8	Variables related to T2D pathophysiology
C	Other characteristics such as sex/gender and age
D	Behavioral variables
Feedback loops	
loop symbol "R"	Short reinforcing feedback loops
loop symbol "B"	Short balancing feedback loops

links and we consequently used a default weight for all the links. In terms of relative importance, master regulators like GCs, for example, deserve a stronger weight.

Links are listed in supplementary table S1 and referred to by their labelling numbers in the description of the CLD. When unspecified in the description of the CLD (section 3), described links refer to Fig. 2. Links 180–182 in Fig. 5 were not included in the CLD (Fig. 2) to facilitate the readability of the CLD. The links that we included in the CLD do not refer to deterministic processes but rather to a potential influence of the source variable on the target variable.

Links between variables corresponding to other characteristics such as sex/gender (in cluster C) or behavior (in cluster D) and biological processes (in clusters B) or stress exposure (in cluster A) were only partially represented in the CLD to facilitate the readability, and were more extensively described in the narrative of the CLD.

2.5. Feedback loops

We identified and described 3 types of feedback loops:

1. feedback loops related to mechanisms of T2D pathogenesis.
2. feedback loops related to how the stress response could influence stress regulating systems and thus subsequent stress responses.

3. feedback loops related to how alterations in the periphery, which can be due to past psychogenic stress responses, can activate the stress systems.

Feedback loops revealed by the CLD can be within specific biological scales, e.g., contain only processes at molecular scales, or across multiple scales, e.g., link processes at molecular scales to processes at tissue and network scales. They vary in complexity as they can involve multiple steps before a variable is fed back to its own derivative. We distinguished short-loops (e.g., containing two or less variables) by using the loop symbols "R" for reinforcing and "B" for balancing. These loops are within the same scale (molecular/intracellular). Most larger loops involve processes occurring at different spatial and/or temporal scales. Loops across different scales are composed of arrows going from left to right indicating an evolution towards more long-lasting processes, and of arrows going from right to left, linking long-term modifications and larger spatial scale variables to short-term processes and smaller spatial scales processes. Larger loops also link variables in distinct clusters (e.g., relations between acute stress responses, in clusters B1 and B4, and resulting modifications of stress-related systems that influence subsequent stress responses, in clusters B3 and B6).

3. CLD narrative

In line with the different steps followed during the reviewing process (section 2.2) and the different types of feedback loops that we identified (section 2.5), the descriptive narrative of the CLD in Fig. 2 was structured into four subsections. Section 3.1. focuses on T2D pathogenesis. Section 3.2. describes how alterations induced by the repetition of the stress response could influence T2D pathogenesis. Section 3.3 focuses on the regulation of stress responses, and more specifically HPA axis stress responses at different spatiotemporal scales. In section 3.4 we describe possible drivers modulating the regulation of HPA stress responses and their relations to T2D pathogenesis. Relevant feedback loops revealed by the CLD are described in the narrative.

3.1. Mechanisms underlying T2D pathogenesis

Most often, the pathogenesis of T2D is characterized by insulin resistance (link 178), which refers to reduced insulin effects on glucose uptake by insulin target tissues (adipose tissue, liver and skeletal muscle), which in turn leads to an increased metabolic demand on pancreatic β-cells and hyperinsulinemia. The over-activity of pancreatic β-cells and the consequences of reduced glucose uptake by insulin target tissues result in the progressive deterioration of β-cell function (link 177) and the establishment of sustained hyperglycemia (Galicia-Garcia et al., 2020; Schwartz et al., 2017).

One major risk for the occurrence of insulin resistance is (abdominal) obesity or excessive adiposity (Zheng et al., 2018) with more than 90 % of patients with T2D being obese or overweight (Bramante et al., 2017). Globally T2D is more prevalent in men than women and in Europe, men are also diagnosed at lower body mass index (BMI) and younger ages than women. However, obesity, which is the most important risk factor for T2D, is more prevalent in women with sex differences in obesity rates varying between countries (Kautzky-Willer et al., 2016) (link 179). Age is also an important risk factor for T2D onset (link 178), although, the prevalence of T2D in adolescents and young adults (below 40 years old) is increasing significantly (Kautzky-Willer et al., 2016; Lascar et al., 2018).

Chronic low-grade inflammation can result from excessive adiposity (especially from excess visceral adipose tissue (VAT), i.e., around the abdominal organs) and has been implicated in obesity-driven insulin resistance and T2D. Although the underlying mechanisms are not completely clear, adipose tissue expansion, characterized by adipocyte hyperplasia and/or hypertrophy (links 108–110) can result in multiple outcomes, e.g., hypoxia, mechanical stress, adipocyte death, that can

initiate an inflammatory response (links 157–162) (Longo et al., 2019; Zatterale et al., 2020).

Obesity and/or over-nutrition can also result in increased blood cholesterol and triglycerides (hyperlipidemia), transported by lipoproteins such as the very low-density lipoprotein (VLDL) produced by the liver (links 101, 102). Hydrolysis of triglycerides increases the concentrations of free fatty acids (FFAs) (link 92), which promote the expression of pro-inflammatory cytokines (link 105) (Hotamisligil, 2017; Tripathy et al., 2003). Excessive adiposity can also increase the amount of circulating FFAs via lipolysis (link 89).

Multiple studies have shown an altered expression of pro- or anti-inflammatory adipokines and cytokines, immune receptors and intracellular mediators of inflammation in obese humans and animal models of obesity. In particular, adipose tissue macrophages play an important role in obesity-driven inflammation. Increased infiltration of macrophages (which can constitute up to 40% of cells in the adipose tissue of obese subjects) and their shift towards "pro-inflammatory" phenotypes lead to the secretion of cytokines inducing insulin resistance in adipocytes (e.g., tumor necrosis factor-α (TNF-α) and interleukins (IL)-6 and −1β) (link 133) (Hotamisligil, 2017; Zatterale et al., 2020). Although a wide spectrum of different macrophage profiles has been observed in obese humans and animals, a binary model is often used, which distinguishes "pro-inflammatory" M1 macrophages from "anti-inflammatory" M2 macrophages, which are linked to tissue remodeling and the resolution of inflammation. Obesity-driven inflammation is therefore thought to result from an imbalance between M1 and M2 macrophages, induced by conditions arising from excess adipose tissue accumulation (Castoldi et al., 2016; Catrysse and van Loo, 2018; Hotamisligil, 2017).

Other immune cell types, including eosinophils and lymphoid cells are also hypothesized to regulate the differentiation of adipose tissue macrophages into an M1 or an M2 phenotype (Hotamisligil, 2017; Sun et al., 2012). Although the actions of several inflammatory mediators have been associated with insulin resistance, their influence on insulin sensitivity may depend on duration, dose of exposure and target sites. For instance, increased blood levels of IL-6 have been associated with

obesity and correlate with T2D risk. However, in-vivo animal studies have also shown that IL-6 acutely promotes insulin signaling in muscle. Duration of exposure and dose likely depend on complex interactions between different immune mediators and feedback mechanisms regulating their production rates (Hotamisligil, 2017).

Five possible feedback loops are included in the CLD and depicted in Fig. 3. The first feedback loop corresponds to the recruitment and differentiation of additional pro-inflammatory immune cells by pro-inflammatory signaling, resulting in an amplifying feedback loop (loop 131 in Fig. 3). In contrast in the second feedback loop, pro-inflammatory cytokines can later also promote the expression of anti-inflammatory cytokines, which will in turn inhibit the production of pro-inflammatory cytokines resulting in a balancing feedback loop (loop 127, 128 in Fig. 3). The third feedback loop corresponds to the induction of oxidative stress by pro-inflammatory processes via the production of reactive oxygen species by immune cells (Mittal et al., 2014). Uncontrolled levels of reactive oxygen species (ROS) (or oxidative stress which is defined as an imbalance between the production of ROS (link 136) and the capacity of the antioxidant system to detoxify them (link 143)) can result in the activation of pro-inflammatory processes which in turn can generate more ROS, constituting an amplifying feedback loop (loop 129, 130 in Fig. 3). ROS levels can be controlled by a fourth feedback loop: ROS activate antioxidant defenses which eliminate them, constituting again a balancing feedback loop (loop 142, 143 in Fig. 3).

Inflammatory mediators produced at the level of the adipose tissue can have systemic effects and induce insulin resistance in the liver and skeletal muscle. Moreover, accumulation of fat in ectopic tissues (e.g., the liver and skeletal muscle) and in VAT (links 111, 112) also leads to a local expression of pro-inflammatory cytokines and inflammation (link 113) which can affect hepatic and muscle insulin sensitivity (link 133) (Longo et al., 2019).

Men show a higher accumulation of VAT and liver fat compared to women of similar age and BMI. Women have more subcutaneous adipose tissue (SAT) which is more likely to accumulate in the gluteal-femoral region. In both sexes, central/abdominal (i.e., subcutaneous
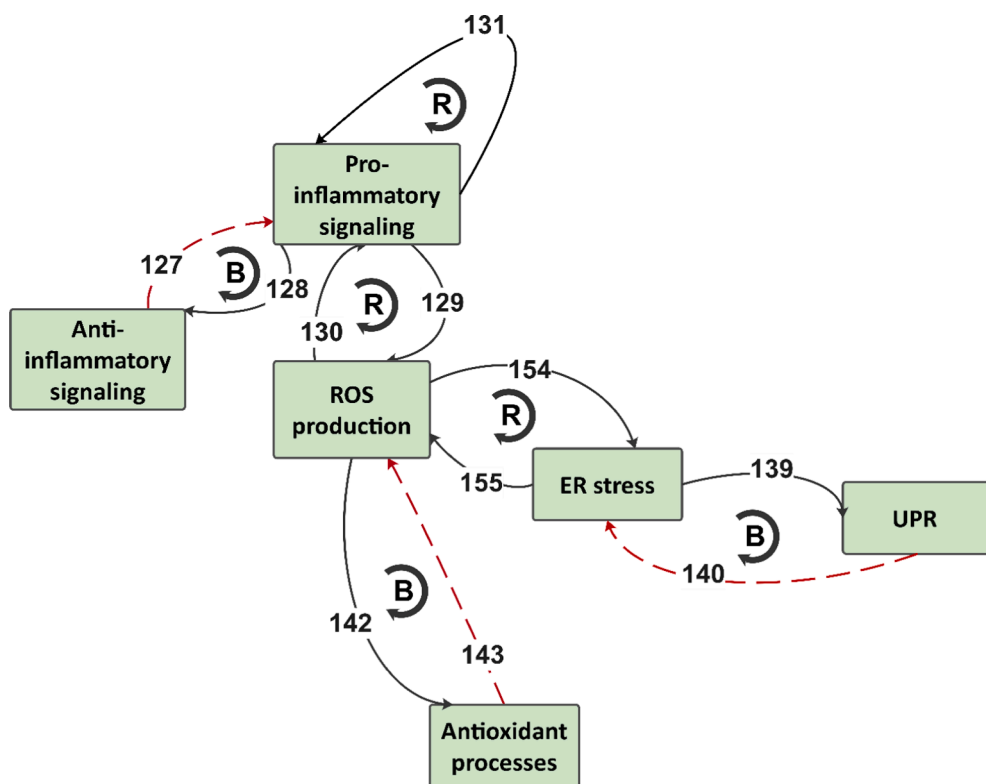
Fig. 3. Reinforcing and balancing short feedback loops. From left to right: pro-inflammatory cytokines can promote the expression of anti-inflammatory cytokines which will in turn inhibit the production of pro-inflammatory cytokines (balancing feedback loop 127, 128); production of reactive oxygen species (ROS) in the context of pro-inflammatory signaling promotes pro-inflammatory signaling (reinforcing feedback loop 129, 130); activation of antioxidant defenses by ROS which eliminate ROS (balancing feedback loop 142, 143) ; endoplasmic reticulum (ER) stress can lead to the production of ROS and ROS contribute to ER stress (reinforcing feedback loop 154, 155); ER stress activates the unfolding protein response (UPR) which restores the ER folding capacity (balancing feedback loop 139, 140).

upper body and visceral) adipose tissue is associated with an increased risk for T2D while lower body (gluteal-femoral) fat deposition is linked with decreased metabolic risk. In addition, VAT has greater rates of lipolysis and lipogenesis than SAT and the more pronounced VAT accumulation in men correlates with higher FFAs, and triglyceride (TG) levels. These differences could contribute to explaining the higher susceptibility for men to develop T2D at lower BMI and younger age, although with age and post-menopause, women are more likely to accumulate VAT (Kautzky-Willer et al., 2016; Tramunt et al., 2020). Another factor could be a higher sensitivity to insulin in women, as observed in a large cohort study in normoglycemic individuals that found higher insulin sensitivity in women than in men, even after controlling for age and BMI (Kautzky-Willer et al., 2012). Studies in rodents reported a protective effect of estrogens against diet-induced insulin resistance in the liver and skeletal muscle (Tramunt et al., 2020). In humans, this sex difference in insulin sensitivity disappears with the development of T2D (Tura et al., 2018).

In addition to stimulating glucose uptake, insulin has multiple other functions such as the regulation of gene expression and enzymatic activity and the modulation of appetite and energy homeostasis (Petersen and Shulman, 2018). Insulin actions are exerted on multiple target tissues and mediated by complex intracellular signaling cascades. In skeletal muscle insulin triggers the translocation of the glucose transporter GLUT4 to promote glucose uptake and stimulate glucose oxidation and glycogenesis (link 74) (Huang and Czech, 2007). Impairment of insulin signaling in skeletal muscle results in decreased glucose uptake. In the liver, insulin inhibits gluconeogenesis (link 76) (Fazakerley et al., 2019). As a result, when hepatic insulin resistance occurs, glucose production is not properly inhibited, resulting in increased blood glucose (link 84). In adipose tissue, insulin exerts anti-lipolytic effects (link 75) inhibiting the release of FFAs by adipocytes and stimulates the uptake of glucose via GLUT4 and lipogenesis (link 77) (Fazakerley et al., 2019). Therefore, insulin resistance in the adipose tissue can lead to increased circulating FFAs (link 90).

Glucose is the main trigger of insulin release by β-cells and also regulates transcription and translation processes involved in insulin synthesis (link 99) (Cerf, 2013). FFAs can also stimulate insulin secretion (link 100) (Cen et al., 2016; Nolan et al., 2006). Increased glycemia and circulating FFAs due to insulin resistance therefore increase the demand on β-cells. β-cells' mass and insulin production and secretion are consequently increased to compensate for insulin resistance leading to hyperinsulinemia (link 71 in Fig. 4). Hyperinsulinemia in turn can induce insulin resistance (link 80 in Fig. 4). The observation of fasting hyperinsulinemia in normoglycemic obese subjects has led to the hypothesis that hyperinsulinemia induced by FFAs could be an initial trigger leading to insulin resistance (Fryk et al., 2021). In both these hypotheses, insulin resistance and hyperinsulinemia influence one another due to amplifying feedback loops, for instance loop 71, 80, 73, 76, 84, 99, shown in Fig. 4, depicts how hepatic insulin resistance can result in higher glucose levels as a consequence of uninhibited hepatic glucose production (loop 71, 80, 73, 74, 87, 99 and loop 71, 80, 73, 77, 88, 99 in Fig. 4 describe the same phenomenon, respectively, in relation to glucose uptake by muscle and adipose tissue).

In the long-term, an increased demand on β-cells and the deleterious consequences of high glucose levels (glucotoxicity) and high levels of blood FFAs (lipotoxicity) can lead to β-cell dysfunction.

Insulin production by β-cells (link 71) involves the folding of the precursor proinsulin to insulin in the endoplasmic reticulum (ER). As the ER folding capacity is limited, a high physiological demand (e.g., hyperglycemia), or disturbances in protein folding, can lead to the accumulation of misfolded proteins in the ER, a process defined as "ER stress" (link 105). The unfolded protein response (UPR) is a cellular defense mechanism, which aims to restore ER folding capacity and protein homeostasis, constituting a balancing feedback loop (loop 139–140 in Fig. 3). However, upon persistent activation and chronic ER stress, the UPR signaling system can switch to induce (apoptotic) cell death (link 163) (Adams et al., 2019). Another result of the higher production of insulin by β-cells, could be amyloid stress (amylin is a peptide co-secreted with insulin (link 107) (Mather et al., 2002)), which would be induced by high levels of β-cell amylin, and has been proposed to also
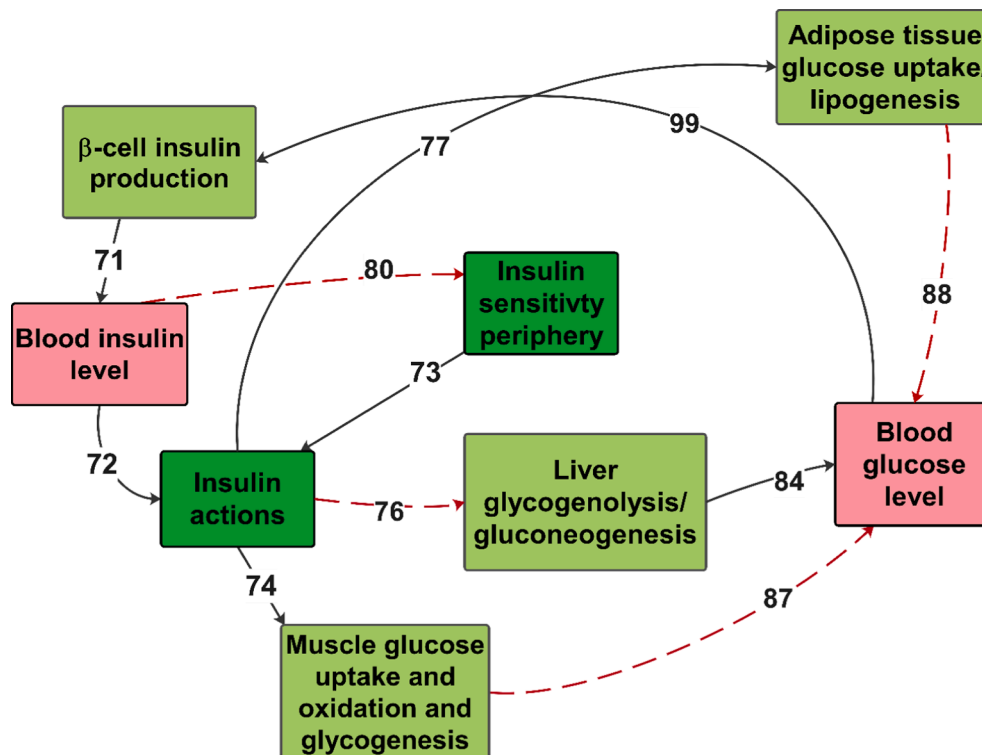

Fig. 4. Reinforcing feedback loops describing how insulin resistance in peripheral systems (corresponding to lowered insulin sensitivity) can induce hyperinsulinemia (elevated blood insulin levels) and how hyperinsulinemia can in turn induce insulin resistance.

contribute to ER stress (link 146) and ROS production (link 145) (Christensen and Gannon, 2019; Stumvoll et al., 2005; Swisa et al., 2017).

High glucose and FFAs concentrations in the circulation can further lead to oxidative stress due to an increased generation of ROS, for instance through increased oxidative metabolism (link 135) or due to the formation of advanced glycation products (AGEs) (links 134) (Bloemer et al., 2014). In addition to being part of amplifying feedback loops with inflammatory processes, ROS can cause oxidative damage to cell components and alter cellular functions (link 150). ROS also trigger signaling pathways by inducing transcription factor activation, gene transcription (link 152) and epigenetic modifications (link 151) (Schwartz et al., 2017). ROS induced gene transcription can ubiquitously promote cell proliferation, hypertrophy, loss of function and even apoptosis. These effects of ROS can be diminished by scavenging mechanisms (i.e. antioxidant systems) which eliminate ROS (link 143) or repair mechanisms (e.g., DNA repair processes) which counteract ROS-induced damage (link 166) (Chapple, 1997; Lee et al., 2004). β-cells, both of rodents and humans, have been reported to be highly vulnerable to ROS because of their low expression level of classical antioxidant enzymes (e.g., superoxide dismutases) in comparison to other cell types (Benáková et al., 2021; Swisa et al., 2017).

β-cell damage and dysfunction lead to an insufficient production of insulin to regulate blood glucose and lipid levels, resulting in multiple amplifying feedback loops which can progressively deteriorate pancreatic function. In the CLD (Fig. 2), these loops correspond to links going from cluster B4 (short-term processes) to cluster B6 (short and long-term modifications in the periphery) and subsequently from cluster B6 to cluster B5 (e.g., links 136, 152, 171), which corresponds to state variables regulating processes in cluster B4 (e.g., link 174).

β-cell failure has been traditionally associated with massive β-cell death (link 169) and decreases of more than 60% in β-cell mass have been reported to occur in T2D (Butler et al., 2003). More recent studies suggest that β-cells in T2D might in fact de-differentiate (link 165) and even gain characteristics of other pancreatic islet cell types, a process that might in principle be reversible, depending on the state of the β-cells (Swisa et al., 2017). In normoglycemic individuals, women show higher insulin secretion capacity than men. Specifically, endogenous estrogens stimulate the synthesis and secretion of insulin and preserve the function of the β-cells against metabolic or oxidative stress. However, similar impairments in β-cell function in T2D have been reported in both sexes (Tramunt et al., 2020).

Other pathways and feedback mechanisms contributing to T2D involve hypothalamic dysfunction, gastro-intestinal disturbances, defects in glucagon metabolism and circadian misalignment (Schwartz et al., 2017).

Hypothalamic dysfunction plays an important role in the development of T2D and obesity. Multiple studies have specifically investigated the hypothalamic infundibular nucleus (IFN), which is equivalent to the arcuate nucleus (ARC) in rodents. The IFN or ARC contain two neuronal populations involved in the regulation of energy homeostasis and food intake: anorectic pro-opiomelanocortin (POMC) expressing neurons, and orectic neuropeptide Y (NPY)/agouti-related protein–expressing (AgRP-expressing) neurons. These populations of neurons contain receptors that bind leptin or insulin. Diet-induced obesity and T2D have been associated with an imbalance between POMC and NPY/AgRP neurons (Alkemade et al., 2012; Kalsbeek et al., 2020). Animal studies have shown that inflammation in the hypothalamus plays an important role in the relationships between hypothalamic dysfunction and in the development of obesity and T2D, however the relevance of findings on hypothalamic inflammatory mechanisms in rodents remains so far unknown for humans (Kalsbeek et al., 2020).

Inflammation could impair the function of ARC neurons and might also induce insulin resistance. In rodents, insulin induces transcription of anorectic peptides in the ARC (e.g., α-melanocyte stimulating hormone (αMSH) produced by POMC neurons) (link 122) and promotes the synthesis of leptin by adipose tissue (link 79), which in turn can also increase transcription of anorectic peptides (link 117, 121) and inhibit transcription of NPY and AgRP (link 115, 120) (Diepenbroek et al., 2013). Leptin also inhibits the synthesis and secretion of insulin (link 97) while increasing insulin sensitivity (link 89) (Amitani et al., 2013). In the rodent brain, injection of NPY and AgRP lead to reduced insulin sensitivity (link 180 in Fig. 5) and increased glucose production, while injection of αMSH increases insulin action (link 181 in Fig. 5) (Diepenbroek et al., 2013).

Also, post-mortem studies in humans suggest that T2D is associated with changes that differently affect POMC and NPY neurons in the IFN. While NPY neurons seem unaffected in T2D, POMC neuron numbers appear lower and a higher vulnerability of POMC neurons, compared to NPY neurons, has been proposed (Kalsbeek et al., 2020). A lower activity of POMC neurons could allow the stimulatory regulation of food intake and insulin sensitivity by NPY neurons to become dominant over feedback loops involving POMC neurons. In particular if links 180 and 121 (Fig. 5) become less influential, then links 181 and 120 and associated feedback loops can have a stronger effect on the behavior of the system: for instance, loops 115, 182, 73, 79 and 120, 180, 99, 71, 80, 73, 79, 115 (Fig. 5) are amplifying and contribute to lowering insulin sensitivity, suppressing inhibition on NPY neurons and promote food intake. Rats subjected to a free-choice high-fat high-sugar (fcHFHS) diet can develop increased NPY sensitivity and leptin resistance in the ARC in association with persistent hyperphagia (van den Heuvel et al., 2014).

If POMC neurons become less active, these loops would in addition be less counterbalanced by amplifying loops 117, 182, 73, 79 and 117, 121, 180, 99, 71, 80, 73, 79 (Fig. 5), which could then contribute to an increased insulin sensitivity and an inhibition of food intake. This feedback loop has been described by Yi et al. (2017), who showed that the function of POMC neurons is impaired in diet-induced obese mice.

As compared with males, female mice are less susceptible to develop diet-induced hypothalamic inflammation. Furthermore, estrogen enhances leptin sensitivity in the central nervous system and amplifies the effect of leptin on food intake (Tramunt et al., 2020).

Concerning the link between gastro-intestinal disturbances and T2D, also an altered composition of gut microbiota has recently been implicated in the development of metabolic disorders (Berg et al., 2020). Different mechanisms have been proposed, including an increased harvesting of energy from diet, chronic low-grade endotoxemia, an altered regulation of adipose tissue metabolism (insulin sensitivity and energy expenditure) by the gut microbiota, low-grade inflammation and altered regulation of gut-derived peptide secretion (Musso et al., 2010; Sharma and Tripathi, 2019). Endotoxemia refers to the presence of endotoxins (i. e. lipopolysaccharides (LPS) from Gram-negative bacteria outer membrane) in the circulation (André et al., 2019) which can trigger inflammatory responses and worsen dysbiosis (e.g., feedback loop 132, 148, 151, 172, 144) (Musso et al., 2010; Scheithauer et al., 2020; Sharma and Tripathi, 2019).

Concerning gut-derived peptides, disturbances of gut microbiota could in turn be related to an impaired glucagon-like peptide 1 (GLP-1) secretion (Everard and Cani, 2014). GLP-1 normally downregulates the production of glucagon by pancreatic α-cells during prandial time (link 104) and increases insulin sensitivity (MacDonald et al., 2002). If GLP-1 secretion is decreased glucagon induced processes (liver glycogenolysis and gluconeogenesis (link 82) (Ramnanan et al., 2011)) might not be inhibited despite an increase of blood glucose following prandial time. Since insulin also inhibits glucagon production, insufficient insulin production when β-cells become dysfunctional might also explain the observation of hyperglucagonemia in T2D (Schwartz et al., 2017). In a clinical study, normoglycemic women exhibited a higher GLP-1 secretion capacity after an oral glucose test tolerance as compared with men, suggesting a sexual dimorphism in GLP-1 secretion capacity which would contribute to increase insulin secretory capacity in women. This sex difference disappeared in (pre-)diabetic individuals (Færch et al., 2015).
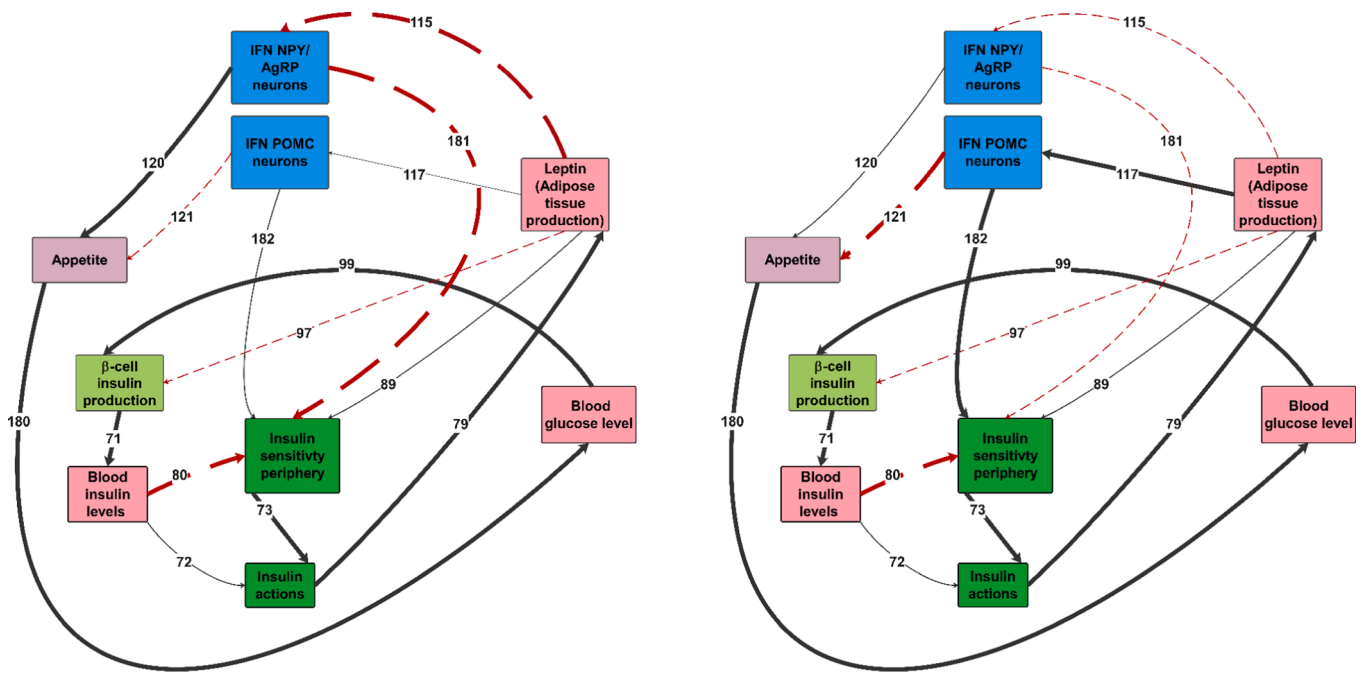
Fig. 5. Hypothetical feedback loops involved in the regulation of appetite and peripheral insulin sensitivity by the hypothalamic infundibular (arc) nucleus. On the left loops involving links 181 and 120 (loops 115, 182, 73, 79 and 120, 180, 99, 71, 80, 73, 79, 115) related to the influence of NPY/AgRP neurons activity and on the right loops involving links 182 and 121 (loops 117, 182, 73, 79 and 117, 121, 180, 99, 71, 80, 73, 79) related to the influence of POMC neurons activity are shown.

Finally, insulin resistance or insufficient insulin production in response to circulating glucose levels, has been proposed to result from an impaired circadian coordination between tissues involved in glucose metabolism (Stenvers et al., 2019). Indeed, in humans, significant correlations between circadian disruption, as e.g., induced by shiftwork, and an increased risk for T2D have been reported in several epidemiological studies (Knutsson and Kempe, 2014; Mason et al., 2020).

In mammals, the circadian timing system consists of a central clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, and of multiple peripheral clocks in other brain regions, as well as in peripheral organs, notably including the pancreas, muscle, adipose tissue, liver and immune cells. The molecular mechanisms of the SCN and the peripheral clocks is based on an internal transcriptional-translational feedback loops, found in almost every human cell. The molecular clock of the SCN produces an oscillatory signal with a period of about 24 h, that is reset everyday by timed and predictable exposure to environmental light. The entrained signal from the SCN is then transmitted to other clocks, through neural and hormonal signals (including GCs) and body temperature (Carroll et al., 2019; Stenvers et al., 2019).

The central clock regulates food intake, energy expenditure and insulin sensitivity throughout the whole body and peripheral clocks to further fine-tune these functions. Specifically, the pancreatic clock regulates insulin secretion, clocks in adipose tissue, muscle and liver regulate local insulin sensitivity and gut clocks regulate glucose absorption. Misalignment between the different components of these circadian systems has been proposed to contribute to the development of insulin resistance and obesity (Stenvers et al., 2019). Circadian clocks also regulate the expression of cytokines, receptors on immune cells and expression of other immune mediators (Carroll et al., 2019; Stenvers et al., 2019). A desynchronization between the regulatory processes that control immune responses could also favor a state of persistent inflammation (Carter et al., 2016; Castanon-Cervantes et al., 2010).

3.2. Possible effects of the repetition of stress responses in the periphery in relation to T2D pathogenesis

Most bodily responses to an acute stressor subside in minutes to

hours after stressor onset. These responses are thought to promote behavioral adaption and re-establish homeostasis via several well-coordinated endocrine responses (Chrousos, 2009). However, when repeated over time, they could alter homeostasis by disrupting elements of glucose and lipid metabolism, immune and appetite regulation, and circadian alignment.

The HPA axis and the ANS are two prominent mediators of the stress response that integrate signaling from higher brain structures and mediate peripheral GCs and catecholamines levels (links 12–18) (see supplementary Text Box 1). Increased GCs and catecholamines levels influence the function of the brain, glucose and lipid metabolism, immune processes, appetite and the circadian entrainment of peripheral clocks. GCs also promote coping and behavioral adaptation to stress (de Kloet et al., 2019). The numerous actions of GCs are mediated in a complementary fashion by nuclear, membrane-bound and mitochondrial glucocorticoid receptors (GRs) (link 48) as well as mineralocorticoid receptors (MRs) (Kadmiel and Cidlowski, 2013; Koning et al., 2019; Yang and Young, 2009). Only free GCs can bind to GRs and MRs (Gulfo et al., 2019). By binding to GRs and MRs receptors, GCs orchestrate the transactivation or the repression of genomic transcription and induce fast non-genomic effects as well. GR is expressed in almost all human organs and tissues while MR is expressed in the kidney, adrenal (Pascual-Le Tallec and Lombès, 2005), heart, adipose tissue (Lee and Fried, 2014), liver, colon, salivary glands (Chapman et al., 2013) and in specific immune cells (Bene et al., 2014; Hawkins et al., 2012) and brain regions. Within the brain, MRs and GRs have their respective anatomical distributions in among others, the hippocampus, basal ganglia, lateral septum and medial amygdala of rodents and human (de Kloet et al., 2018; Joëls et al., 2012; McEwen, 2007; Qi et al., 2013; ter Heegde et al., 2015; Wang et al., 2013, 2014; McEwen, 2000).

For the human GR, at least 2 different receptor isoforms exist: a hormone-binding α-isoform (GRα) and a non-hormone-binding isoform (GRβ). GRα mediates most identified GR-mediated GCs actions, while the GRβ isoform has been reported to inhibit GRα-induced transcriptional activity by exerting a dominant-negative effect (link 52) (He et al., 2016; Oakley and Cidlowski, 2013). This function of GRβ suggests that high levels of GRβ, as found in specific cell-types such as epithelial cells

or neutrophils, could induce glucocorticoid resistance in these cells. However, an endogenous physiological role for GRβ, e.g., in the brain, remains subject to debate (DeRijk et al., 2003; Oakley and Cidlowski, 2013).

The free portion of plasma GCs represents about 5% of the total pool of GCs while the remaining pool binds to the high affinity corticosteroid-binding globulin (CBG) (link 49) and to a lesser extent to albumin (Gulfo et al., 2019). MR binds GCs with a 5 to 10-fold higher affinity than GR does. The high affinity of nuclear MRs for GCs makes these receptors unoccupied only at very low levels of GCs (during the rest phase, generally night in humans) and remain occupied during the day. In contrast GR becomes activated mainly during stress and at the peak of GCs circadian and ultradian variation, when levels of GCs reach a critical threshold.

While GR is only occupied at high GC concentrations and then orchestrates the termination of the stress response, MR exerts a tonic inhibitory influence on HPA axis activity, which regulates the threshold of corticosterone reactivity during stress (de Kloet et al., 2018). Furthermore, pharmacological and genetic studies in humans and behavioral experiments in rodents have led to the hypothesis that MR specifically regulates processes important for attention, coping, learning and memory retrieval, while GR is important for contextual memory, recovery, decision-making and memory storage of the stressful experience (de Kloet et al., 2018; Vogel et al., 2016).

The action of GC on target tissues is modulated by the enzyme 11β-hydroxysteroid dehydrogenases (11β-HSDs) 1 and 2, which together, determine the actual GC effect on cellular activation and gene expression. 11β-HSD type 1 (11β-HSD1) is widely expressed in multiple brain regions, the pancreatic islets, the liver, muscle, adipose tissue, inflammatory cells and gonads, and catalyzes the conversion of inert cortisone and 11-dehydrocorticosterone into active cortisol and corticosterone that activates GRs (link 50). In contrast, 11β-HSD2 inactivates bioactive cortisol and corticosterone into the inert and inactive metabolite cortisone and 11-dehydrocorticosterone (link 51) (Chapman et al., 2013; Walker and Stewart, 2003). 11β-HSD2 is mostly expressed in the endothelial cells regulating the electrolyte balance in the kidney, colon, salivary glands, where co-localized MR becomes aldosterone-specific (Chapman et al., 2013; de Kloet et al., 2019; Walker and Stewart, 2003). MR has the same affinity for aldosterone, cortisol and corticosterone and in cells in which MR co-localizes 11β-HSD1, MR will then preferentially bind cortisol/corticosterone, since levels of free GCs normally exceeds those of aldosterone by about 100-fold (de Kloet et al., 2019; Gomez-Sanchez and Gomez-Sanchez, 2014; Koning et al., 2019; Meijer and de Kloet, 2017). In relation with T2D pathogenesis, MR mediates the action of aldosterone in adipose tissue. The renin-angiotensin-aldosterone system has been involved in adipose tissue dysfunction and in the development of insulin resistance (Jing et al., 2013).

The penetration and effects of GCs into specific tissues and their actions on specific cell types, further depend on the presence of, for example, specific multidrug resistance genes (Karssen et al., 2001; Meijer et al., 1998; Tissing et al., 2003), genetic and epigenetic variations (de Kloet et al., 2018; Motavalli et al., 2021), and the presence and actions of chaperone proteins (Binder, 2009; de Kloet et al., 2018; Kaziales et al., 2020) and co-activators/co-repressors (Meijer et al., 2006; van der Laan et al., 2008).

The actions of catecholamines are mediated through their interactions with adrenergic receptors. Different subtypes of adrenergic receptors (ARs) have been identified: α1, α2, β1, β2 and β3 receptors. Norepinephrine stimulates α1, α2 and β1 receptors while epinephrine activates all subtypes of adrenergic receptors (Motiejunaite et al., 2021). Here we mainly focused on the effects of catecholamines that are mediated by adrenergic receptors found in cell types related to the regulation of glucose and lipid metabolism and to the immune system. These include α2-ARs which are found in pancreatic β-cells, β2-ARs which are present in the liver and in skeletal muscle and β3-ARs which are abundantly expressed in adipose tissue (Motiejunaite et al., 2021).

3.2.1. Effects on glucose and lipid metabolism

Elevations of GCs and catecholamines in the circulation, due to acute stress responses, may temporarily result in "diabetogenic effects". GCs and catecholamines stimulate glycogenolysis, gluconeogenesis and liver glucose secretion (Andrews and Walker, 1999; Parker, 2003; Romero and Butler, 2007; Sapolsky et al., 2000). The role of GCs and catecholamines elevations in lipid metabolism is more complex. "Diabetogenic effects" include an increase of FFAs in the circulation, by GCs-stimulated hydrolysis of circulating TGCs (link 68) (Peckett et al., 2011), which are then available for further distribution over ectopic fat pads (links 92, 93, 95, 111, 112).

GCs also increase de novo lipid production in hepatocytes through increased expression of fatty acid synthase (link 67) and play a role in adipogenesis by promoting pre-adipocytes conversion to mature adipocytes (link 66) (Campbell et al., 2011; Lee et al., 2014; Macfarlane et al., 2008; Peckett et al., 2011). In adipose tissue, catecholamines stimulate lipolysis through binding to β-adrenergic receptors (link 61) (Parker, 2003; Stich et al., 2003). They can also have anti-lipolytic actions, in particular in adipocytes through other adrenergic receptors (α2-AR) (link 62) (Stich et al., 2003). GCs anti-lipolytic action is less clear and could be specific to SAT (Peckett et al., 2011). The overall consequences of repeated elevations of GCs could promote the development of abdominal obesity and ectopic fat deposition, as observed in Cushing's syndrome (Lee et al., 2014), which are in turn important risk factors for the onset of T2D. In addition, GCs directly decrease insulin sensitivity (link 70) and also catecholamines induce insulin suppression (link 57) and glucagon production (link 58) (Parker, 2003). Therefore, repeated, acute stress responses could induce repeated exposure to transient hyperglycemia and hyperlipidemia, and insulin resistance, which could evolve towards T2D onset in the long-term if positive feedback loops described in section 3.2.1, e.g., feedback loops contributing to the progression of insulin resistance and β-cell dysfunction, become dominant over balancing loops.

3.2.2. Effects on immune and inflammatory processes

GCs have pleiotropic effects on various immune processes that have traditionally been attributed to GR-mediated alterations in gene expression. The actions of GCs on inflammation are known to favor anti-inflammatory (link 123), and inhibit pro-inflammatory processes (link 125) (Cain and Cidlowski, 2017)). For instance, GCs inhibit the pro-inflammatory cytokines IL-1β and TNF-α (increased levels of these cytokines have been associated with increased T2D risk) (link 54) and promote the differentiation of macrophages into, anti-inflammatory, M2 phenotypes (which are assumed to be downregulated in obesity) (Cain and Cidlowski, 2017).

Although GCs actions on immunity are mostly described in terms of suppressing adaptive immunity and promoting innate immunity, GCs can also enhance certain adaptive immunity processes (e.g., favoring the differentiation of Th cells into a Th2 phenotype, which also promotes the differentiation of macrophages into an M2 phenotype) and enhance the reactivity of innate immunity to danger signals, exerting a permissive effect on inflammatory processes (link 124). Specifically, GCs promote the expression of toll-like receptors (TLRs) 2 and 4 (Busillo and Cidlowski, 2013; Chinenov and Rogatsky, 2007; Newton et al., 2017), which have also been characterized as receptors for FFAs and are involved in obesity-driven inflammation (Hotamisligil, 2017).

GCs upregulate the expression of another receptor involved in the recognition of danger signals, the inflammasome (Busillo and Cidlowski, 2013) which has been shown to play an important role in the development of diet-induced insulin resistance and pancreatic β-cell deterioration in mouse models and in human diabetes (Hotamisligil, 2017). This potentiation of the immune system can again indirectly enhance pro-inflammatory processes. In addition, GCs can inhibit many wound-healing processes (Cain and Cidlowski, 2017) which could delay the

resolution of certain inflammatory responses.

GCs could also exert pro-inflammatory effects through the presence of MRs in specific immune cell types. Indeed, MR promotes the activation of macrophages to a pro-inflammatory M1 phenotype and regulates the differentiation of Th cells into a Th1 and Th17 phenotypes, which are also pro-inflammatory. MR also downregulates anti-inflammatory T regulatory lymphocytes. As macrophages do not express 11β-HSD2, the pro-inflammatory influence of MR on macrophages is likely to be induced by GCs rather than via aldosterone, whereas the possibility that T lymphocytes express 11β-HSD2 remains an open question (Bene et al., 2014).

Catecholamines are also involved in the regulation of multiple immune-related processes including immune cell activation, proliferation and apoptosis. Notably, effects of catecholamines on immune and inflammatory processes are bidirectional: while β-adrenergic receptor signaling has been mostly associated with anti-inflammatory effects, α-adrenergic receptor stimulation has been linked to pro-inflammatory effects (Barnes et al., 2015; Elenkov, 2007).

Acute stress, through the release of norepinephrine, can also transiently increase IL-6 levels and other inflammatory mediators in the circulation (Barnes et al., 2015; Elenkov, 2007).

Depending on the dose, duration and the general context (e.g., state of metabolic and immune systems) under which GCs and catecholamines are elevated, acute stress responses could favor a suppression or enhancement of inflammatory processes. The permissive actions of GCs on immunity (link 124 in Fig. 6) could lead to a condition of chronic inflammation, provided sufficient triggers enable its initiation, and provided the inhibitory actions of pro-resolving factors are insufficient. For example, amplifying feedback loops 143, 129, 135, 149, 175 in Fig. 6 favor pro-inflammatory processes because of endotoxemia (see section 3.2.1), or because of a chronic triggering of pro-inflammatory

processes to which GCs elevations can also contribute (links 124, 126 in Fig. 6). Repeated elevations of plasma GCs could e.g., enhance (links 66–68 in Fig. 6) excess visceral fat depots (links 161, 162 in Fig. 6) or hyperlipidemia-induced inflammation (link 105 in Fig. 6).

3.2.3. Effects on gut microbiota

Stress and the activity of the HPA axis impact the composition of the gut microbiome. Studies on mice show alterations of the gut microbiota composition due to exposure to chronic stress. More specifically, these alterations have been, among others, associated with increased levels of circulating "pro-inflammatory" cytokines, like IL-6 (Cryan and Dinan, 2012). Chronic stress has also been associated with a disruption of the intestinal barrier which makes individuals more vulnerable to inflammation. Stress-related disorders such as depression are associated with disruptions in the composition of their gut microbiome and an increased leakiness of the gut (Cryan and Dinan, 2012). Different aspects of the stress response could thus affect the gut microbiota. In particular, in-vitro studies have found that catecholamines stimulate the proliferation of various enteric pathogens (link 147) (Mayer et al., 2015). In addition, the effect of the stress response on the enteric nervous system can influence substrate availability for the microbiome and changes in blood pressure during the stress response affect its oxygenation, which can, for example, result in oxidative stress and inflammation (Karl et al., 2018). Repeated stress responses could therefore induce dysbiosis and gut leakiness and in this manner possibly increase the risk to develop T2D.

3.2.4. Effects on appetite

Stress can affect food intake in a bidirectional manner, resulting in both increases and decreases in feeding behavior in humans and animals. In humans, divergence between these two different outcomes on
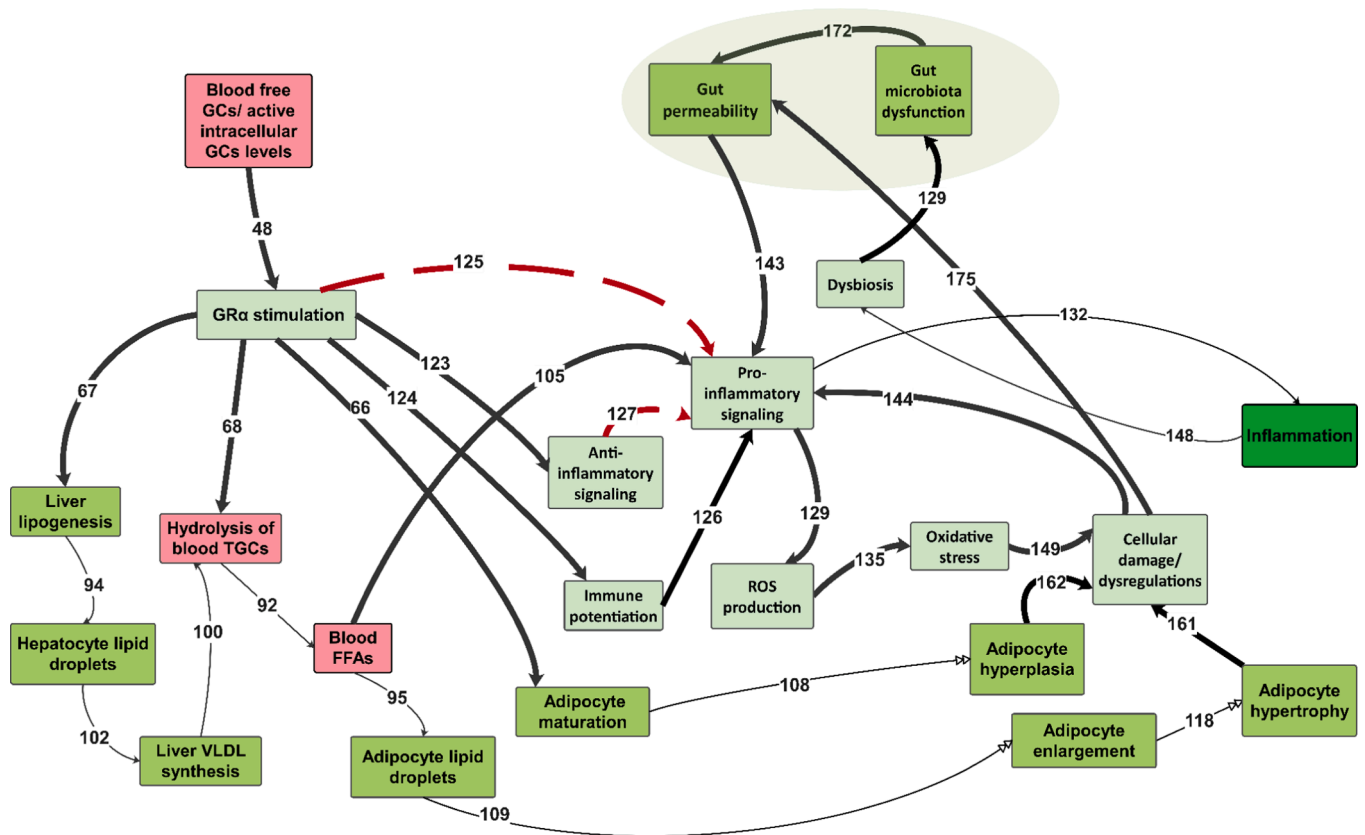
Fig. 6. Examples of feedback loops involving GCs regulation of inflammatory processes. Amplifying feedback loop 143, 129, 135, 149, 175 favors pro-inflammatory processes because of endotoxemia, or because of a chronic triggering of pro-inflammatory processes to which GCs elevations can also contribute (links 124, 126). Repeated elevations of plasma GCs could e.g., enhance (links 66–68) excess visceral fat depots (links 161,162) or hyperlipidemia-induced inflammation (link 105).

appetite might be explained by complex interactions between different physiological and psychological mechanisms. Psychological factors such as stressor perceptions or emotions have been shown to be important moderators of how stress exposure affects feeding. On the other hand, stress responses correspond to a changed expression of appetite-regulating hormones and neuropeptides, which may also affect eating behavior (Begg and Woods, 2013; Maniam and Morris, 2012; Sominsky and Spencer, 2014).

The decrease in food intake observed in animals exposed to acute stress has been, among others, attributed to the anorectic effects of CRH, which is thought to downregulate the expression and release of NPY in the ARC (link 35) (Sominsky and Spencer, 2014). Chronic stress, on the other hand, has been associated with a decreased food intake and weight loss but also with an increased food intake, especially of palatable food. Most often, in animal models, chronic exposure to severe stress induced anorectic effects, whereas chronic exposure to mild stress increased food intake (Begg and Woods, 2013). Altogether, the interactions between the HPA axis responses to stress (e.g., increased GCs levels), the nature and frequency of stressors and the history of earlier exposure to chronic stress may all play an important role in determining how chronic stress affects feeding behavior.

GCs upregulate the expression of NPY and AgRP in the ARC (link 34) and inhibit the expression of CRH in the PVN (link 27). These actions correspond to an orectic effect. Even though GCs stimulate the secretion of leptin by the adipose tissue (link 69), elevated concentrations of GCs have further been associated with a decrease in leptin sensitivity in the brain. This results in increases in food intake (Sominsky and Spencer, 2014). Chronic exposure to GCs has also been linked to a lowered insulin sensitivity in the hypothalamus resulting in a reduced potency of insulin to inhibit NPY/ AgRP neurons in the ARC and their orectic actions. The tendency to take in more palatable food when exposed to chronic stress, could also be mediated by GCs' effects on insulin brain sensitivity; insulin acts on the ventral tegmental area (VTA) and contributes to the reduction of the dopamine-mediated rewarding effect of food (Sominsky and Spencer, 2014). It has thus been proposed that by inducing insulin resistance in the brain, the chronic exposure to increased GCs levels could lead to an increased need for "reward" to be obtained from the food ingested (Sominsky and Spencer, 2014). This can at least partly explain why chronically stressed animals favor calorically-dense foods (Begg and Woods, 2013; Maniam and Morris, 2012; Sominsky and Spencer, 2014). In addition, ghrelin, which increases appetite, is upregulated under acute and chronic stress, although the underlying mechanisms remain unclear (Maniam and Morris, 2012; Sominsky and Spencer, 2014).

Studies on the correlation between cortisol reactivity and food intake diverge. Several studies have shown that higher cortisol reactivity to stress or CRH administration, was associated with an increased food intake in healthy weight-individuals (Epel et al., 2001; George et al., 2010; Newman et al., 2007). A recent study showed no difference in food intake, however, between healthy-weight individuals with a low cortisol reactivity and those with a high cortisol reactivity to an acute stressor (Herhaus et al., 2020). Moreover, obese individuals with a higher cortisol response to stress demonstrated a significantly higher food intake in comparison to obese individuals with a low stress reactivity (Herhaus et al., 2020). Individuals with higher cortisol stress reactivity and obese individuals may have a higher vulnerability to develop stress-induced dysregulated eating patterns. Exposure to stressors might lead to an increased intake of palatable food which, as a result, could make orectic amplifying feedback loops dominant, as described in section 3.1 (e.g., loops 115, 182, 73, 79 and 120, 180, 99, 71, 80, 73, 79, 115 in Figure 5) which further stimulates the intake of more palatable foods.

3.2.5. Effects on circadian alignment
The SCN regulates circadian rhythms of adrenal activity via projections to the PVN of the HPA axis (link 32) (Dai et al., 1998) and

sympathetic innervation to the adrenal. Specifically, GCs follow marked circadian rhythms that are entrained by SCN signaling. The cortisol circadian rhythm reaches a peak before the onset of the active period, which in humans is in the morning about 30–45 min after awakening, and subsequently declines throughout the day (Hackett and Steptoe, 2017; Spencer and Deak, 2017).

GCs are one of the main hormonal signals mediating the entrainment of peripheral circadian clocks by the SCN, by regulating the expression of specific circadian clock genes (link 55) (Stenvers et al., 2019). Therefore, repeated elevations of GCs and epinephrine during acute stress responses possibly disrupt diurnal rhythms in the periphery and, more specifically, repeated elevations of GCs could disturb the entrainment of peripheral clocks (link 56). Such a disturbance of peripheral clock rhythms could induce a desynchronization between the insulin-regulating clock in the pancreas and clocks regulating glucose uptake and lipid metabolism (e.g., in the liver, muscle or adipose tissue) or between clocks regulating immune processes. Due to circadian misalignment, repeated stress responses could contribute to the development of T2D by inducing insulin resistance or inflammation (see section 3.2.1). In line with this hypothesis, a study in mice has shown that acute stress transiently but significantly altered expression of peripheral clock genes, notably in the liver, the adrenals and the pituitary (Ota et al., 2020; Tahara et al., 2015). Reported stress effects on peripheral clock genes expression differed in the different tissues and was dependent on the time of exposure to stressors.

Plasma GCs levels also follow a marked ultradian rhythm with an approximate frequency of 60–90 min that is superimposed on the circadian GC rhythm (Fitzsimons et al., 2016; Russell and Lightman, 2019). In rodents, blocking the activity of the SCN removes circadian rhythms of corticosterone but does not affect the ultradian rhythmicity (Waite et al., 2012). In contrast, GC ultradian rhythmicity depends on the ultradian rhythmicity of ACTH (Kalafatakis et al., 2019). GC ultradian rhythms have been shown to play an important role for metabolic function in rodent models (Kalafatakis et al., 2019; Oster et al., 2017) and also for regulating GC mediated-genomic actions (Russell and Lightman, 2019). Repetition of increased levels of GCs during exposure to stress could also interfere with GC ultradian rhythm-mediated regulation of, e.g., metabolism, and through this pathway might increase the risk for T2D.

3.3. Regulation of the HPA axis activity at different spatiotemporal scales

HPA axis responses to acute psychosocial stress show large intra- and inter-individual variability. A meta-analysis of 208 laboratory stress studies showed that in humans, motivated performance tasks reliably induced HPA axis responses (ACTH and cortisol) if they were perceived as uncontrollable or characterized by a social-evaluative threat. Tasks having both components were associated with the largest increase in hormone levels and the highest recovery times (Dickerson and Kemeny, 2004; Kudielka et al., 2009). The acute reactivity approach assumes that affective experiences modulate acute responses to stress. When such affective experiences occur repeatedly, they are thought to increase the intensity or duration of the stress response. As such, they contribute to biological changes that accumulate over time and result in an 'allostatic load' on several biological systems. In particular, anticipatory reactions can lead to a heightened response before exposure to a stressor, whereas rumination would lead to a delayed recovery following stress (Epel et al., 2018; McEwen, 1998). It has also been proposed that women show a greater cortisol response to interpersonal stressor whereas men would be more sensitive to achievement stressors, although this finding remains inconsistent (Zänkert et al., 2019).

Higher elevations of GCs levels and a delayed return to baseline enhances the area under the curve of total GC exposure, and could negatively impact peripheral systems e.g., immunity and glucose and lipid metabolism-related systems.

In humans, chronic stress has been associated with both lower and

higher basal levels of cortisol. Also, the cortisol responses have been reported to be either prolonged or blunted (Epel et al., 2018; Hackett and Steptoe, 2017; Miller et al., 2007). While chronic stress can sensitize the responses to new stressors, several (pre-)clinical studies show a decline of the HPA response to a psychological stressor with repeated exposure to a homotypic stressor. This decline has been defined as "habituation", which refers to a form of non-associative learning (Grissom and Bhatnagar, 2009). However, habituation of the HPA axis probably only partially explains this decline.

The observed decline of HPA responses could depend on the perceived stressor controllability (e.g., if the perceived control over a stressor increases, current stress responses (during exposure) or subsequent stress responses to the same or similar stressor might be attenuated), and could also depend on other aspects of cognitive and emotional processing of the stressor (e.g., changes in vigilance, or fear of being evaluated or rejected). In the acute reactivity approach, a lack of habituation results in more intense and longer stress responses, which, when repeated, tend to increase the allostatic load (Epel et al., 2018; McEwen, 1998). Also, the timing of stress exposure and the negative feedback inhibition could determine response magnitude (Grissom and Bhatnagar, 2009). A study in rodents, e.g., shows that re-exposure to a stressor before GCs return to baseline, decreases the magnitude of the subsequent HPA response to a stressor (de Souza and van Loon, 1982). In addition, this phenomenon might be regulated by alterations of stress-related neuronal circuits (Grissom and Bhatnagar, 2009).

In relation to stress, many MRI studies in humans have focused on the consequences of post-traumatic stress disorder (PTSD) and depression on the brain, and less so on those of chronic stress per se (Chattarji

et al., 2015; Czéh and Lucassen, 2007; Lucassen et al., 2014). Studies focusing more specifically on chronic stress exposure alone, suggested similar outcomes to those associated with PTSD. For instance, chronic occupational stress has been associated with decreases in the volume of hippocampal and mPFC regions, alterations of functional connectivity between the AG and PFC regions and an increase in the volume of AG regions. Alterations of the PFC and HPC volumes seem to be reversible after a recovery period, while alterations of amygdala volume may persist longer (links 39, 47) (Blix et al., 2013; Golkar et al., 2014; Savic, 2015; Savic et al., 2018).

Similar alterations have been reported in older adults after exposure to chronic stress and in adults who have been exposed to stress in early life (Ansell et al., 2012; Gianaros et al., 2007; Hanson et al., 2012). Alterations of volumes could be preceded by detectable, yet still reversible alterations in function: alterations in mPFC function were e. g., associated with impaired attentional control in healthy adults exposed to one month of psychosocial stress. Both the functional and behavioral changes were reversible after another month (Liston et al., 2009).

These alterations in volume and function of limbic structure regulating the HPA axis response to stress might impact HPA axis responses and be associated with the higher, lower or more blunted cortisol responses to stress after exposure to chronic stress (links 40, 41, 42, 43). In humans, the roles of the different limbic structures in the initiation and termination of the HPA axis response to stress (links 9–11 in Fig. 7) are not fully understood and likely depend on the characteristics of stressors and multiple other factors, such as psychological aspects or chronic stress history.
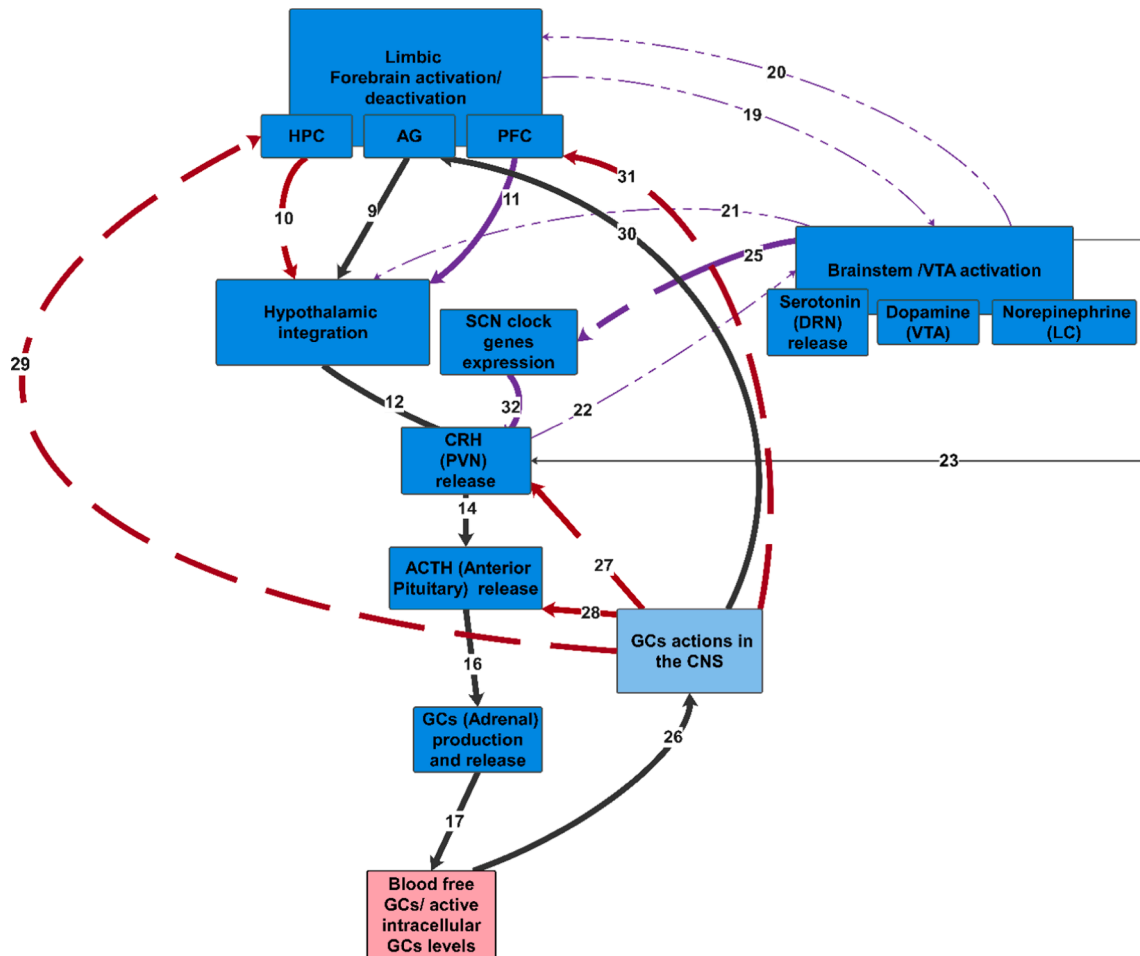
Fig. 7. Feedback loops regulating plasma levels of GCs: inhibition of the stress response via feedback in the HPA axis and in the limbic system and regulation of GCs circadian rhythm.

Higher levels of cortisol during psychological stress exposure have been associated with a decreased activity in the ventromedial prefrontal cortex (vmPFC) and perigenual anterior cingulate cortex (Harrewijn et al., 2020), while increased activity in the orbitofrontal mPFC (part of the vmPFC) has been associated with higher cortisol levels during psychological stress exposure (Dedovic et al., 2009). Different and bidirectional roles of the different subareas of the vmPFC on HPA axis responses have been proposed in both humans and rodents (Dedovic et al., 2009).

Altered activities in the HPC, amygdala and inferior frontal gyrus, found in relation to higher levels of cortisol during psychological stress, are inconsistent across studies (increased or decreased activity) (Dedovic et al., 2009; Harrewijn et al., 2020). Increased cortisol responses have been linked to increased amygdala activity in studies using fear-evoking images, and decreased amygdala activity occurs after stress

that combined an arithmetic task and social evaluation. The amygdala might be specifically involved in fear reaction and not necessarily in responses to psychosocial stress (Dedovic et al., 2009; Muscatell and Eisenberger, 2012). Both positive and negative correlations have been reported between HPC activation and the magnitude of the cortisol response (Dedovic et al., 2009; Harrewijn et al., 2020; Kern et al., 2008); higher levels were associated with a decreased activity of the HPC during tasks combining cognitive and social evaluation, and with an increased HPC activity after fear evoking paradigms (Harrewijn et al., 2020). Stressor controllability has been further shown to modulate fear extinction in humans (Hartley et al., 2014). Studies more specifically investigating the impact of controllability have used physical mild electric stressors and stressor control decreased responses in brain regions related to the processing of threatening signals (Limbachia et al., 2021).
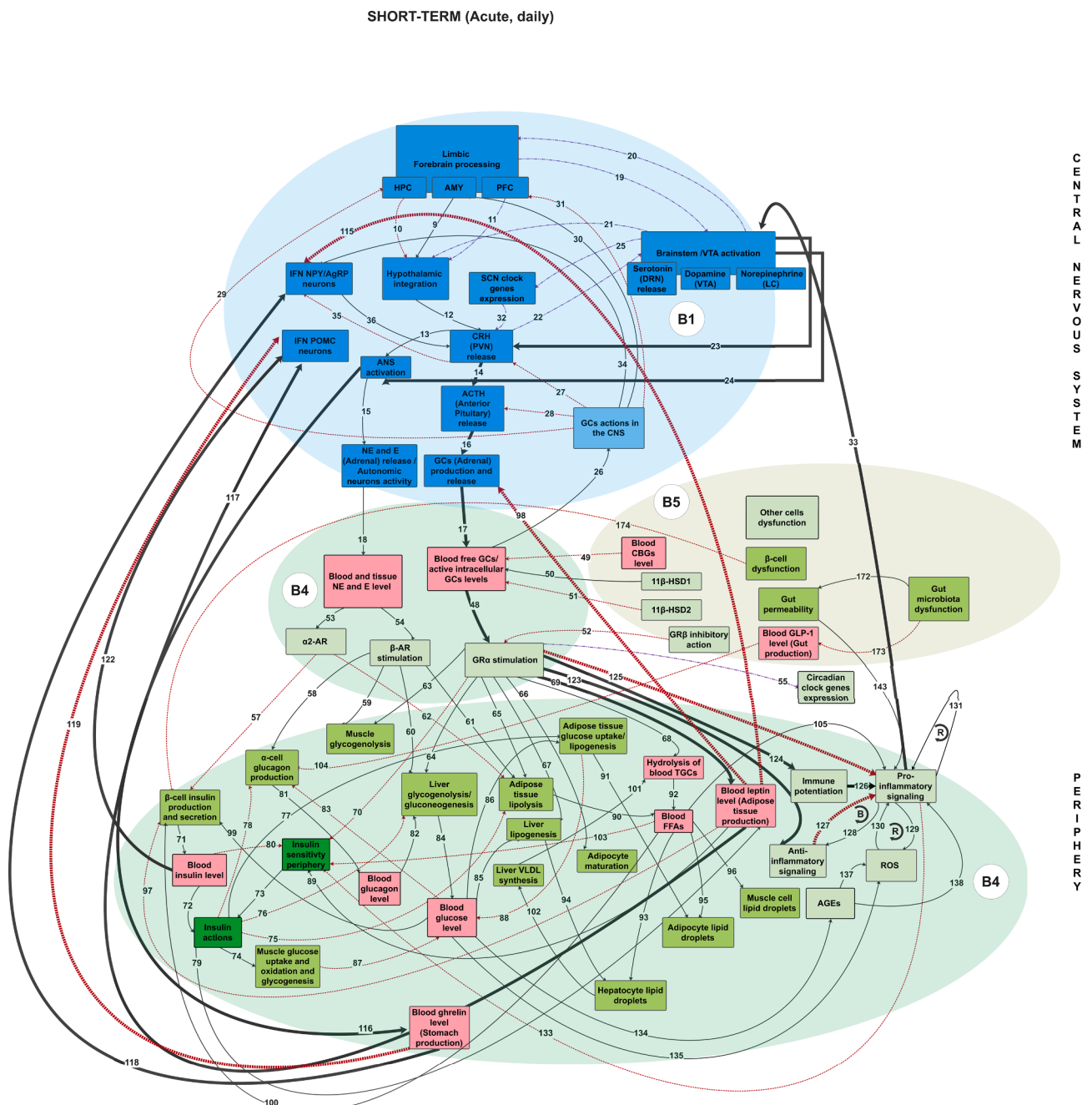
Fig. 8. Feedback loops involving interactions between neuroendocrine and peripheral processes involved in stress responses.

Uncontrollable stress might therefore result in higher and longer HPA axis responses to acute stress and if repeated, amplify the responsivity of the HPA axis to subsequent stress exposure. However, physiological processes and gain-of-control over a stressor might also lead to a lower responsivity of the HPA axis when re-exposed to a homotypic stressor.

Biology-related changes in HPA axis reactivity and stress response recovery may be due to the specific impact GCs and neurotransmitters (link 39), released during exposure to uncontrollable stress, could have on the CNS including the HPA axis.

Feedback loops corresponding to these mechanisms are represented in a generic manner in the CLD. For instance, loops 37/38, 39, 40, 41/42 in Fig. 9 describe how repeated exposure to high cortisol and other stress mediators, as occurs during chronic stress, may alter the physiology of the brain. GR occupancy can further repress certain target genes and contribute to GR downregulation. This could modify subsequent stress responses if those occur before the restoration of GRs density. Because the termination of the stress response is an important consequence of GR occupancy in the PVN and pituitary, such a local downregulation could lead to a longer GCs stress response and subsequently also alter peripheral GC actions. The extent, nature and persistence of these modifications likely depend on the frequency of exposure to psychological stressors, in addition to the intensity of the induced responses (links 44–47).

Signaling from the periphery, e.g., via immune responses, via the microbiome, or via metabolic signals, can also activate the HPA axis or modulate its activity. In particular, cytokines, such as IL-1β, IL-6, and TNF-α, were shown to increase the release of CRH in the PVN in rodents, indicative of an activation of the HPA axis (Dunn, 2000; Fan et al., 2021). The subsequent release of GCs can in turn influence immune and inflammatory processes generating feedback loops, that can be balancing or unbalancing (see section 3.2.1). For instance, loops 33, 23, 14, 16, 17, 48, 125 and 33, 23, 14, 16, 17, 48, 124, 127 in Fig. 8 are balancing. Another loop including cortisol plasma levels and pro-inflammatory signaling, in contrast, can be reinforcing: GCs may also exert a permissive effect on the expression of pro-inflammatory cytokines via immune potentiation (loop 33, 23, 14, 16, 17, 48, 125, 126 in Fig. 8).

Additional feedback loops involved in the regulation of plasma levels of GCs involve peripheral and neuroendocrine processes. For instance, GCs stimulate the production of leptin by adipocytes which downregulates GCs production via an inhibition of adrenal activity and inhibition of NPY and AgRP release in the ARC nucleus (loops 48, 69, 98, 17 and 48, 69, 115, 36, 14, 16, 17, respectively in Fig. 8), resulting in two balancing feedback loops. In contrast, secretion of ghrelin stimulates the activity of ARC NPY and AgRP neurons and consequently of PVN CRH neurons (loop 13, 116, 118, 36 in Fig. 8).

The overall impact of immune processes and other systemic signals on the HPA axis might be also determined by previous exposure to psychological stress and other causes. For instance, obesity, infection, diets high in inflammatory fatty acids, or oxidative stress might also activate inflammatory processes and stimulate the HPA axis.

Chronic stress exposure also modifies basal cortisol levels. In humans, a dysregulation of the cortisol circadian rhythm, and more particularly, a flatter slope in the decline of cortisol, appears associated with chronic stress exposure and a predictor of physical and mental health disorders. This has led to the concept of a flattened cortisol rhythm as a mediator between chronic stress and, in time, negative health outcomes (Adam et al., 2017; Hackett and Steptoe, 2017). One longitudinal study, on the Whitehall cohort, examined the link between circadian cortisol patterns and T2D in an initially healthy population. They found that elevated evening cortisol levels and a flat slope predicted the onset of T2D at later follow up (Hackett et al., 2016). This association was controlled for a wide range of covariates including age, sex, BMI, smoking status, occupation grade and a measure of social position as well as factors likely to influence cortisol diurnal pattern like waking up time (Hackett et al., 2016).

Certain chronic stressors, such as repeated restraint stress or chronic unpredictable stress, further affect the amplitude of the rhythm of PER and vasopressin, of which the latter is involved in the entrainment of the HPA axis by the SCN. The functional consequences of these alterations are however poorly understood (Ota et al., 2021). GCs can have direct effects on CRH and vasopressin in the hypothalamus and on SCN activity (Erkut et al., 1998; Liu et al., 2006) but GCs and stress have also been proposed to target GRs in the hippocampus and hence, via modulating negative feedback via this brain region, also indirectly influence the regulation of basal GCs (Buchanan et al., 2004; Jacobson and Sapolsky, 1991).

Importantly, the measured dysregulation of cortisol circadian rhythms might also be due to other factors than brain and neuroendocrine variables. These could include GCs catabolism in the periphery, or when measuring salivary cortisol, CBG levels and the control of free
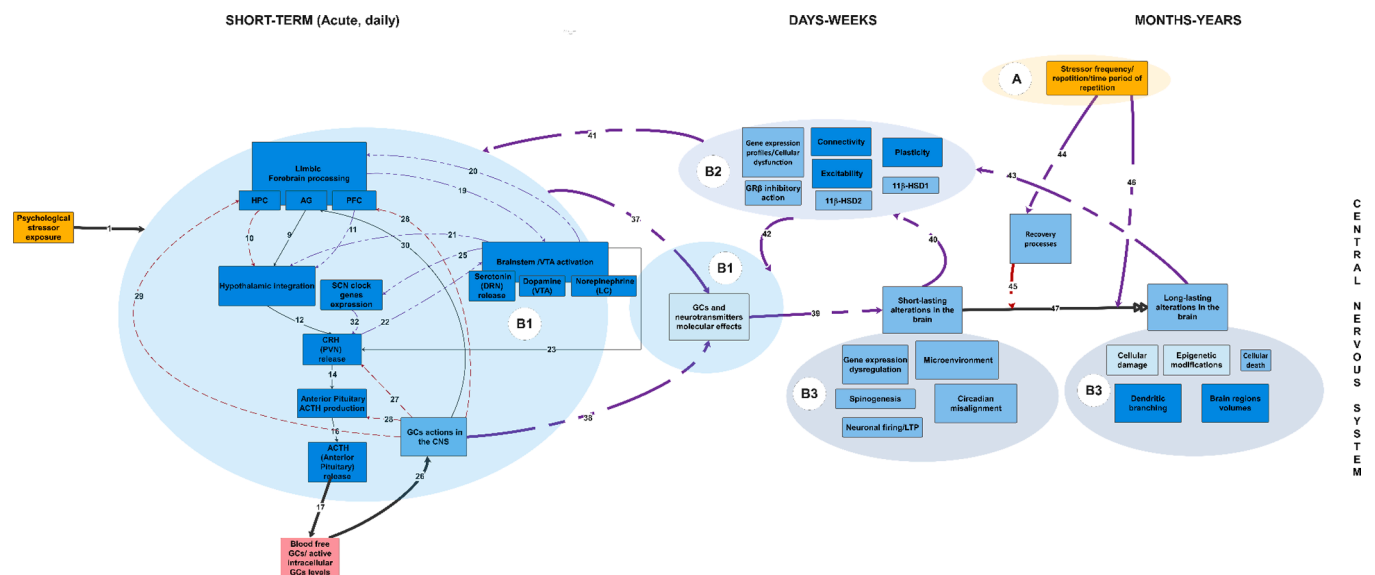
Fig. 9. Feedback loops describing modifications of central nervous and neuroendocrine systems by acute stress responses and the impact of these modifications on subsequent stress responses.

cortisol levels.

Multiple studies have also examined the possible links between HPA axis reactivity and basal activity and, among others pregnancy related factors, pre-natal/post-natal/early life conditions (stress/adversity), genetic and epigenetic effects, lifestyle and behavioral variables and psychological aspects/factors (Zänkert et al., 2019).

3.4. Possible drivers modulating the role of HPA stress responses in T2D pathogenesis

Some of the described feedback mechanisms can either amplify towards a metabolic imbalance, and in the long-term progressively evolve towards T2D, or function as countervailing mechanisms that can balance deleterious processes, preventing or slowing the development of T2D in the long term when exposed to chronic stress.

Different internal and external factors can make specific loops dominant in the system by modulating HPA axis activity and the effects of biological stress responses on e.g., glucose and lipid metabolism or the immune system. Such internal factors include sex, age and genetic and epigenetic effects.

Sex hormones, for instance, interact with GR expression and GR action directly and indirectly by acting on chaperone and co-chaperone complexes (Bourke et al., 2012). Sex hormones may also modulate GC intra-tissue availability. In animals, estrogens decrease while androgens increase the expression and activity of 11β-HSD1 in white adipose tissue (Kaikaew et al., 2021). In relation to this mechanism, postmenopausal women show a greater activity of 11β-HSD1 in their adipose tissue (Kaikaew et al., 2021). Systems including the HPA axis, metabolism and the immune system (Bourke et al., 2012) in men and women, might thus be differently affected by GCs elevations during acute stress or by dysregulations of GCs levels induced by chronic stress, possibly contributing to sex-specific associations between chronic stress and T2D.

Epigenetic changes might be due to effects of earlier HPA activation during critical developmental periods (Li et al., 2020; Szyf, 2021), or in relation to psychological stressors, or to environmental stressors (e.g., pollution or smoking) and have been involved in the non-linear interplay between acute and chronic stress and their impact on T2D risk (Matosin et al., 2017; Xiao et al., 2020).

External factors like specific health behaviors, exposure to physical stress and medication (links 158, 190) might also modulate HPA activity or the effects of GCs in the periphery. For instance, certain oral contraceptives can alter the concentrations of CBG and therefore the plasma levels of free GCs (Zänkert et al., 2019).

Behavior might also dysregulate physiological mechanisms, e.g., the effect of increased GCs levels during the stress response could affect individuals with different chronotypes, differently (Kautzky-Willer et al., 2016).

Thus, epigenetic and genetic effects, external factors and behaviors can render biological systems more or less prone to biological dysregulation resulting from stress exposure and its implication in T2D etiology.

4. Discussion

In this paper, we built a conceptual model to provide an overview of the possible interactions and feedback loops between different elements involved in chronic stress and T2D. The model was built using a complexity science approach and it maps relationships between many of the different aspects related to stress and T2D pathogenesis. We focused on biological processes involved in acute and chronic stress and their relationships, and more specifically on the interactions of HPA axis activity and its involvement in pathways leading to T2D onset.

Epel et al. (2018) published the first conceptual model describing how exposure to psychological stress across a life time, in interaction with an individual context and specific behaviors, could affect health, providing an important element for the development of the CLD.

Building on the work of these authors, the current CLD focuses on the possible role of stress in T2D etiology. The current and more detailed conceptual model constitutes to our knowledge the first example of a complexity-based description of to describe T2D and how it relates to stress. Its development allowed us to connect evidence from multiple research domains that are usually considered separately, into a joint and comprehensive framework, providing a more overall perspective on the role of stress in relation to T2D onset.

Even though our focus was on the role of chronic stress in the development of T2D pathogenesis, the CLD may be comprehensive and general enough to also be of use to research investigating the role of chronic stress in individuals already affected by T2D, particularly in relation to the worsening of the condition due to psychological stress. Notably, the inclusion of the influence of current state system variables (e.g., clusters of nodes B2 and B5) can support this extension of application.

The current CLD reveals multiple reinforcing biological feedback loops and balancing feedback loops. We analyzed how exposure to chronic stress and external factors could push the interactions between reinforcing and balancing biological feedback mechanisms towards a dominance of deleterious unbalancing mechanisms that can progressively result in T2D onset. For instance, physiological stress responses resulting in elevated plasma concentrations of GCs can lead to increased glycemia promoting oxidative stress and inflammation which can result in a further activation of the HPA axis, constituting a reinforcing feedback loop. On the other hand, GCs exert anti-inflammatory effects which contribute to lower the activation of the HPA axis by inflammatory cytokines like IL-1β, IL-6 or TNF-α, constituting a reinforcing feedback loop with an opposite effect. Depending on the current state of the system, the increase in circulating GCs and external factors (e.g., shift-work might disrupt circadian rhythms which can impact GCs levels and the function of the immune system (Stenvers et al., 2019)), these two reinforcing feedback loops might be in equilibrium or one might exert a stronger influence on the whole organism. This may or may not result in an amplification or a continuation of inflammation as a result of exposure to stress.

In addition, the current CLD displays feedback loops across different temporal scales highlighting the need to understand the relationships between the acute and chronic dimensions of stressor exposure in a non-linear manner from a life course perspective. While acute stress is often considered as "positive" and enabling "adaption", chronic stress is considered as harmful with potentially deleterious consequences for health. The CLD describes how exposure to stress and resulting acute stress responses modulate the HPA axis responses through their influence on brain and peripheral systems and display the possible evolution of the biological systems under repeated stress responses across temporal scales, ranging from minutes/hours to months/years.

The development of the CLD led us to identify current literature gaps that potentially hinder a better understanding of the role of chronic stress in T2D development. These literature gaps, however, are often characterized by elements that, at the present, are difficult to investigate. For instance, a precise understanding of brain molecular mechanisms occurring during stress responses and their impact on HPA axis activity during stress, shortly after stress and after chronic repetition of stress remains unfeasible in humans and represents a considerable challenge even for experimental non-human animal research. However, a conceptual model such as the current CLD, in relation with clinical and epidemiological studies, integrating a wide range of confounding factors might help to gain a deeper understanding of the role of chronic stress in T2D pathogenesis in humans. Such confounding factors may have previously been associated with T2D onset such as adiposity or shiftwork or may modulate measurements of biomarkers associated with chronic stress and T2D pathogenesis, such as waking time when measuring cortisol diurnal rhythm.

In clinical research, the CLD can serve to connect different elements associated with chronic stress (e.g., stress exposure, related perceptions

and behaviors and individual biological factors) in relation to dysregulations of glucose and lipid metabolism, inflammation, and pathways connecting CNS processes to peripheral processes, which play an important role in T2D pathogenesis at various spatiotemporal scales. The CLD for instance links the regulation of glucose and lipid metabolism by GCs to behaviors influencing these systems such as circadian behaviors and diet, and stressor characteristics including uncontrollability and threat perception.

The CLD further aims to explain heterogeneity between individuals because of variations in exposure to stressors and individual conditions such as their age or factors influencing health behaviors and - rather than listing potential risk factors - aims to connect these different factors dynamically. In doing so, the CLD can help refine current correlations established in the literature for T2D risk factors. The feedback loops revealed by the CLD show the importance of considering stressor characteristics and feedback dynamics, and elements such as behaviors and physical environments, in addition to non-modifiable factors (e.g., sex, age) to better understand the conditions under which the system can be driven towards a diseased state. As such, the CLD can help to better understand the role of chronic stress in the etiology of health disparities. For instance, the relationship between low socioeconomic status and an increased risk for T2D onset (Agardh et al., 2004; Zheng et al., 2018) might be explained by multiple factors including increased exposure to chronic stress, increased exposure to environmental stressors or lower access to a healthy diet, where these different factors likely interact in a non-linear manner with underlying biological mechanisms.

Therefore with this CLD, we propose a model that can help in considering multiple aspects related to chronic stress and T2D pathogenesis simultaneously, when studying the development of T2D in a specific individual (e.g., enabling a more holistic and personalized care in clinical practice) or a specific population (e.g., for studying the aggravation by chronic stress of obesity-driven insulin resistance), or when investigating the relationships between inequalities in chronic stress and inequalities in T2D onset.

We further would like to acknowledge various limitations of our CLD for its potential applications. First, the model is not exhaustive and may miss additionally relevant processes in terms of links between chronic stress and T2D onset. Processes like inflammation and the impact of elevated or lowered levels of GCs on the immune system were, for instance, not represented in details in the CLD. Reasons for this are that on the one hand, the effects of GCs on different components of the immune system have been described in an extensive manner in existing reviews (Cain and Cidlowski, 2017), and on the other hand, exhaustively detailing the impact of variations in GCs levels, due to acute and chronic stress, on the immune system, would require an additional CLD of similar length and complexity (e.g., in terms of the number of variables and links). However, the balance between pro-inflammatory and anti-inflammatory patterns also plays a crucial role in homeostatic regulation, allostasis and allostatic load, and from there, likely also in the development of T2D. In addition, we did not include the molecular feedback loops that exist between various receptors, and how their interactions could also modulate important processes, like glucose and lipid metabolism, immunity and inflammation, or stress responses themselves. Examples of such molecular mechanisms include the balance between MRs and GRs which can influence stress responsivity, inflammation, lipid metabolism and in more general terms, the physiological and behavioral adaptation to stress (Bender et al., 2013; de Kloet et al., 2018; Jia et al., 2021; Joëls et al., 2012; Thuzar and Stowasser, 2021). These short-term feedback loops also include related receptors, like CRH-1 and CRH-2, which could in turn, modulate the intensity and duration of the stress response, negative feedback, and the behavioral response to stress. This may also involve stress-induced feeding, and, as a result, such changes could mediate the role of stress in T2D onset (Bakshi et al., 2002; Dautzenberg et al., 2001; de Kloet, 2003; Raftogianni et al., 2018).

We also did not comprehensively investigate the literature relating

emotional and cognitive processes and psychological states associated with stress responses to the brain network regulating the activity of the HPA axis as specified in the scope of the CLD. In addition, in order to keep the CLD readable and tractable, we mainly focused on the possible role of HPA axis activity and its implication in pathways related to T2D pathogenesis. This choice was also motivated by the more detailed body of literature investigating the regulation and evolution of markers of HPA axis (re)activity in the context of chronic stress. Yet, an important body of literature on autonomic responses, their evolution after exposure to chronic stress and their relation to relevant factors for human health (e.g., health behaviors) may further inform a model such as the current CLD (Gianaros and Jennings, 2018; Gianaros and Wager, 2015). In particular, activity of the parasympathetic nervous system promotes glycogenesis in the liver, regulates hepatic lipid metabolism, promotes insulin secretion by the pancreas and amplifies the action of insulin in important target organs particularly in the postprandial state (Bruinstroop et al., 2013; Carnagarin et al., 2018; Güemes and Georgiou, 2018; Vosseler et al., 2021). The parasympathetic influence on the control of insulin secretion is, among others, mediated by arcuate nucleus NPY and POMC neurons (Diepenbroek et al., 2013; Güemes and Georgiou, 2018; Kalsbeek et al., 2010; Thorens, 2011). It is assumed that sympathetic overactivity, in parallel with parasympathetic defects, induces impaired glucose uptake, storage and utilization resulting in hyperglycemia, hyperinsulinemia and insulin resistance which results in metabolic imbalance and thereby constitutes a pathway for the development of T2D (Carnagarin et al., 2018; Vrijkotte et al., 2015). Chronic stress could directly (e.g., via the repeated activation of the sympathetic nervous system) or indirectly (e.g., by disturbing the function of NPY and POMC neurons) lead to a disturbed balance between the sympathetic and parasympathetic control of glucose metabolism and in this fashion increase the risk for T2D. In addition, a disrupted balance between the parasympathetic and sympathetic nervous systems may sustain high blood pressure, continued stimulation of the heart and inflammation (McEwen, 2006; Tracey, 2009; Woody et al., 2017) and through these mechanisms, further increase the risk for T2D.

Second, the model is relatively generic regarding other processes. We opted for an inclusion of neuroendocrine processes, with the aim of examining how different stress paradigms could influence health in a different manner. This choice was motivated by the assumption that uncontrollable stress might impact health more severely than controllable stress (Epel et al., 2018; Koolhaas et al., 2016). However, we could only describe possible mechanisms in a general manner and not make specific hypotheses as described in the scope of the CLD. For this reason the CLD does not necessarily respect "the rules" of causal loop diagramming (Kenzie et al., 2018). Specifically, regarding the neural mechanisms involved in physiological stress responses, certain nodes correspond to brain regions and not aggregate quantities and arrows between these nodes to functional connectivity between the regions in question rather than positive or negative effects.

Third, when evidence from non-human animal studies was informative on related topics and data from humans studies could be related to evidence obtained from non-human animal studies, we included these mechanisms in the CLD (Miller et al., 2009). However, they might remain hypothetical in humans. For instance, we included the effects of insulin on secretion of anorectic and orectic peptides in the hypothalamic NPY/AgRP while data on humans have not revealed this level of detail (Alkemade et al., 2012; Kalsbeek et al., 2020).

Moreover because of the need for integration of knowledge from multiple fields to reach our objective, a systematic review was not deemed suitable. Instead, we structured the review on recommendations from Miller et al. (2009). In addition, we compensated for the possibility that we had missed relevant information by consulting experts in both human and non-human animal research.

To conclude, we built a CLD describing underlying non-linear biological mechanisms that could link chronic stress to T2D pathogenesis. The CLD illustrates how multiple factors could affect relevant biological

systems and increase the vulnerability of individuals exposed to chronic stress to T2D onset through multiple pathways and temporal scales.

The CLD might be used to formulate novel hypotheses and serve as a basis for the identification of biomarkers of stress and the development of computational models. In particular CLDs can be extended into system dynamics models which enable to simulate the evolution of a system over time or can be used as platforms to integrate existing computational models. Computational models have for example been proposed to simulate the activity of the HPA axis or the circadian regulation of insulin secretion (Hosseinichimeh et al., 2015; Woller and Gonze, 2018). Integrated computational models could help to identify the most important pathways and feedback loops given specific inputs and drivers, further understand intra and inter-individual variability in biomarkers of stress, generate hypotheses and evaluate the risk of developing T2D.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yfrne.2021.100972.

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