Early adversity and insulin: neuroendocrine programming beyond glucocorticoids

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Abstract

Exposure to direct or contextual adversities during one's early life programs the functioning of the brain and other biological systems, contributing to the development of physical as well as mental health issues in the long term. While the role of glucocorticoids in mediating the outcomes of early adversity has been explored for many years, less attention has been given to insulin. Beyond its metabolic effects in the periphery, central insulin action affects synaptic plasticity, brain neurotransmission, and executive functions. Knowledge about the interactions between the peripheral metabolism and brain function from a developmental perspective can contribute to prevention and diagnosis programs, as well as early interventions to vulnerable populations.

Brain-body connections shape developmental processes

Environmental conditions present during early developmental stages have a dramatic influence on an individual's health/disease trajectory over their life course. Exposure to direct or contextual adversities, such as violence or abuse, family dysfunction, socio-economic difficulties, malnutrition, or parental stress can hinder the development of the brain architecture and other biological systems, leading to increased risk for diseases later in life [1]. These changes, induced by early life adversity, have been commonly linked to alterations in executive functions (e.g., impulse control, cognitive flexibility, memory) [2, 3] contributing to the development of both physical and mental health issues in the long term. Advances in neuroendocrinology have established that there is a reciprocal communication between the brain and the body via hormonal and neural pathways. Hormonal feedback from neuroendocrine, immune, and metabolic systems to the brain regulates homeostatic functions in the hypothalamus. The same feedback affects emotions, behavior, and cognition in response to internal and external signals. These effects occur through direct signaling on brain receptors in cortical and subcortical structures, modifying genomic and non-genomic processes during development, and defining both the behavioral phenotype as well as influencing disease risk over the life course.

Among the many peripheral signals that act on the central nervous system, insulin merits attention considering the widespread distribution of its receptors in the brain [4]. Insulin has an essential role on peripheral glucose homeostasis and energy metabolism, but it is insulin's central action as a neuromodulator that is critically involved in the regulation of synaptic plasticity and **monoaminergic neurotransmission** (see **Glossary**). While the role of glucocorticoids in mediating the outcomes of early adversity has been explored for many years, less attention has been given to insulin. Glucocorticoids and the insulin axis interact with each other at different levels, in such a way that the well-known alterations in the **hypothalamus-pituitary-adrenal axis** induced by early adversity modify glucose metabolism, insulin secretion, and insulin signaling (**Table 1**). Acting on the adipose tissue, liver, skeletal muscle, pancreas and to a lesser extent on bone, gut, and brain, long-term glucocorticoid exposure leads to metabolic dysregulations with hyperglycemia, and insulin resistance, ultimately, contributing to the development of cardio-metabolic disease [5-8].

Despite this close relationship between glucocorticoids and the insulin axis on the development of chronic adult disease related to early life adversity (**Box 1**), insulin signaling has

many independent roles in the growing child's health and in the developing brain. Insulin influences physical health, neurodevelopment, behavior, and executive functions in physiological conditions and in response to early adversity. This review focuses on the function this hormone has on neurodevelopmental processes, as well as deviances from a healthy developmental trajectory induced by environmental adversity.

Central action of insulin

Insulin is one of the primary hormonal regulators of metabolism in animals. This hormone is composed of small polypeptides secreted by beta islet cells in the pancreas and regulates glucose uptake by cells in most peripheral tissues. The central nervous system uses non-insulin sensitive glucose transporters, **GLUT**-1 and GLUT-3, for the majority of glucose uptake, leaving insulin to play a neuroregulatory role in the brain [4]. Although most of the insulin in the brain comes from the periphery, a few studies suggest its synthesis also occurs in the brain (e.g., in rats [9]). Pancreatic insulin is transported into the brain via a specific, saturable carrier located on capillary endothelial cells [10], which has been suggested to be the insulin receptor (**IR**) itself [11].

The IR has two α-subunits, which are extracellular and include a ligand binding site and two cytoplasmic β-subunits. There are two isoforms of the IR: a long isoform called IR-B involved in the metabolic effects of insulin and predominating in adult peripheral tissues such as muscle, liver, kidney, and fat; and a short isoform called IR-A that binds to IGF-2, resulting in receptor activation and influencing hippocampal neurogenesis. While astrocytes express both IR-A and IR-B, neurons only express IR-A, even though IR density in general is much higher in neurons than in glia. Both IR isoforms are expressed throughout the brain in areas including the ventral tegmental area (VTA), striatum, hippocampus, hypothalamus, amygdala, and prefrontal cortex (PFC) [4].

IR central anatomical distribution overlaps with neurotransmitter systems [e.g., dopamine (DA), serotonin, γ-aminobutyric (GABA), glutamate] that are major players in the mechanism of neuronal communication. A wealth of studies demonstrate the importance of insulin signaling in many central nervous system functions, such as synaptogenesis, synaptic plasticity, neuroprotection, memory, and cognition, including **long-term potentiation and depression** (**LTP** and **LTD**) [12], attention, sensitivity to reward, inhibitory control [13], energy balance, and eating behavior [14]. Insulin and its receptor play a key role in the dynamics of dendrite formation,

spine density, neurite growth, and neuronal development [15]. Disruptions to their function, induced by early adversity, can have potent effects on neurodevelopment. When these changes occur during **critical periods** of development, they can have '**programming**' effects, leaving persistent marks in individuals' physiology and defining their health/disease patterns in the long term. Insulin can affect the development of different neurotransmitter systems, especially those with protracted developmental periods like the **mesocorticolimbic** dopaminergic pathway (**Box 2**), as well as modulate the function of these systems during one's life-course.

Therefore, there is a large range of adult disorders that could emerge from early adversity-induced dysfunctions in central IR-mediated processes, due to alterations in IR activation, diminished insulin availability, or malfunction of downstream intracellular signaling [4]. These include mood disorders [16], schizophrenia [17], and neurodegenerative processes such as Alzheimer's and Parkinson's diseases [18], suggesting a functional overlap between brain insulin dysfunction and altered brain neurotransmission in the pathogenesis of these conditions.

The modulation of central neurotransmission by insulin

Dopaminergic system

IRs are expressed by dopaminergic neurons in the midbrain, including the VTA and substantia nigra [19]. At the end of the 1970s, studies started demonstrating that glucose and insulin could modulate the number of DA receptors, the firing of DA neurons, and the release and turnover of striatal DA [20, 21], in addition to suggesting that this modulation was an important feature of psychopathologies like schizophrenia. A more recent postmortem gene expression study demonstrated that in individuals with bipolar disorder, major depression disorder, and schizophrenia, a lower expression of DA-related genes [**dopa decarboxylase (DDC)**, **tyrosine hydroxylase** (**TH)**, **vesicular monoamine transporter 2** (**VMAT2)** , DRD1, DRD2, DRD5, and **monoamine oxidase B (MAOB**)] was fully mediated by a lower expression of IR-related signaling genes [INSR, **insulin receptor substrate 1 (IRS1**), and IRS2], suggesting an impaired IR function in these cases [22].

Beyond gene expression, insulin seems to increase the capacity of DA reuptake through the dopamine transporter (DAT) by activating the **phosphatidylinositol (PI) 3-kinase (PI3K)** in rat synaptosomes and human cell cultures [23]. It was also shown that insulin reduces electrically evoked exocytotic [(3)H]DA release in rat nucleus accumbens (NAcc) slices and in medial PFC

slices [24]. Concomitantly, insulin reduces premature responses in the five-choice serial reaction time task and enhances the stimulatory effect of peripheral cocaine administration on impulsivity when injected directly into the NAcc [24]. This suggests that the presynaptic action of insulin regulates cocaine-sensitive monoamine transporter function in the NAcc and, consequently, impulsivity. Direct intracerebroventricular infusion of insulin results in an increase in DAT mRNA levels [25], suppressing DA-related behavioral outcomes such as sucrose intake and sucrose self-administration [26], which indicates that insulin modifies the rewarding value of sucrose. These studies in rats suggest that insulin can change the molecular response of DA within the mesocorticolimbic pathway, affecting the associated behavioral phenotype.

At the behavioral level, while insulin injection in the rodent NAcc shell leads to sweet flavor-preference conditioning [27], intra-VTA insulin inhibits food anticipatory behavior and conditioned place preference for food, suggesting that insulin may attenuate the salience of food-related contexts or cues in this brain area [28]. Moreover, as VTA DA neurons are heterogeneous [29], it remains to be established if insulin modulates subpopulations of VTA DA neurons depending on their projection targets. Finally, as insulin suppresses excitatory inputs to the VTA yet increases DA firing rate, it is possible that insulin has a differential action on tonic versus burst firing, such that tonic DA release is increased while phasic bursts are suppressed [30] (**Figure 1**).

A mouse model of brain-specific knockout of IR is linked to age-related anxiety and depressive-like behavior; this is due to altered mitochondrial function, aberrant monoamine oxidase (MAO) expression, and increased DA turnover in the mesolimbic system [31]. Loss of IR in astrocytes is associated with increased depressive-like behavior, which is accompanied by impaired DA release from brain slices, particularly in the NAcc [32]. These studies in mice suggest that the modulation of DA neurotransmission by insulin action on its receptor is linked to the development of phenotypes related to mood disorders such as depression and anxiety-like behaviors.

In humans, there is evidence for the modulation of DA by insulin. Insulin sensitivity index estimated from a glucose tolerance test was negatively correlated with ventral striatum D2 receptor availability measured by positron emission tomography (PET), whereas fasting insulin was positively associated with D2 availability in the right insular cortex [33]. Lower β-cell function (estimated using data from a glucose tolerance test) was related to stronger preference for an immediate and smaller monetary reward over delayed receipt of a larger one (greater delay

discounting), although no relationship was found with striatal D2 receptor binding [34]. Intranasal insulin administration can improve memory and mood in healthy men and women, behaviors linked to DA neurotransmission [35]. Intranasal insulin is also linked to differential resting-state activity in brain regions involved in reward processing [36], decreased food palatability ratings [37] and attenuation of visual processing of food images [38], without altering peripheral glucose sensitivity [39]. Taken together, these findings suggest that impaired insulin signaling in the brain, even in individuals who are non-diabetic, can have an important effect on behaviors that are associated with dopaminergic neurotransmission and with the development of different psychopathologies in the long-term including depression, anxiety, cognitive decline, and Alzheimer's disease [16, 18] as well as in the co-morbidity between these diseases and insulin resistance/type 2 diabetes [40].

Lastly, there is a tight connection between insulin and netrin-1, one of the guidance cues involved in the development of the mesocorticolimbic DA pathways [41]. Netrin-1 is involved in pancreatic morphogenesis and tissue remodeling, regulating fetal islet cell migration and stimulating in vitro insulin secretion by promoting β-cell Ca (2+) influx and **cyclic AMP (cAMP)** production [42]. Plasma netrin-1 levels are decreased in patients with type 2 diabetes and correlate negatively with insulin resistance measures [43]. In cultures of rat Schwann cells (glial cells that are part of the myelin sheath from peripheral nerve fibers), netrin-1 enhances migration through the activation of **PI3K**, an essential component of the cellular insulin signaling cascade [44]. Although not directly investigated to date, it is tempting to think that insulin could signal changes in the environment to the developing brain by modulating axonal guidance cues like netrin-1 and promoting neuroadaptations of the DA pathways. These could have noticeable consequences on discrete changes in executive functions, but also long-term effects on psychopathology risk.

Serotoninergic system

The placenta produces serotonin that accumulates in the embryonic forebrain during the early phases of telencephalic development, until serotonergic raphe neurons progressively start to synthesize and uptake serotonin [45]. The brain expresses seven types of serotonin receptors (5-HT1-7) comprising a total of 14 subtypes [46]. Serotonin neurons from the dorsal and/or medial raphe nuclei innervate the entire forebrain and midbrain and are considered important in modulating several neurobiological functions especially those relating to emotional states [47].

Serotonin neurons express IR mRNA and peripheral injection of insulin increases both plasma and brain tryptophan levels, favoring serotonin synthesis [47, 48]. In humans, serotonin transporter binding is diminished in the diencephalon of insulin-resistant subjects [49]. Although the limited available data suggest that insulin directly increases serotonergic neuronal activity, there is a possibility that insulin modulates serotonin neurotransmission by acting on other neuronal subpopulations.

GABAergic system

GABA is the main inhibitory neurotransmitter in the adult brain. However, GABAergic synaptic transmission is excitatory in early life, exerting widespread trophic effects and undergoing a switch during development from being excitatory to inhibitory. There are two main types of GABA receptors: the ionotropic GABA-A receptor and the metabotropic GABA-B receptor. Heterogeneity on the distribution of their subfamilies and localization at the synaptic cleft, or extrasynaptically/perisynaptically, defines their role in tonic versus fast, phasic inhibition. GABAergic neurons develop early in the cortex during embryonic development, but in humans, the system continues developing into the first few years of infancy and possibly until adolescence. GABAergic cortical interneurons are the first neurons to generate network-driven activity in the developing brain. Interneuron-generated network-driven patterns modulate the proper development of synapses among cortical neurons, priming unorganized silent neurons to shift into functional circuits [50].

A recent hyperinsulinemic-euglycemic clamp study in mice showed that peripheral insulin upregulates the expression of multiple subunits of GABA-A receptors in the hypothalamus [51]. Insulin also regulates the tonic GABA-activated synaptic and extrasynaptic current density in hippocampal dentate gyrus granule cells and CA3 pyramidal neurons, reducing spontaneous neuronal firing during maturation of the young mouse brain as well as in a model of Alzheimer's disease [52]. Similar modulatory effects of insulin on GABA also occur in the rat amygdala [53] and PFC [54]. In patients with type 2 diabetes, a relationship between elevated medial PFC GABA concentrations (measured using magnetic resonance spectroscopy) and poorer episodic memory performance was observed, suggesting that abnormal GABA levels in the medial PFC are linked to the episodic memory decline that occurs in patients with type 2 diabetes [55].

Glutamatergic system

The neurotransmitters glutamate and GABA are involved in the balance between brain excitation and inhibition, having important roles in neuronal migration, synaptogenesis, synaptic plasticity, and modulation of memory and learning processes. Beyond their individual roles, glutamate and GABA receptors are colocalized in many brain regions and their steady interaction is a key factor for normal brain development. There are three types of ionotropic glutamate receptors: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartate (NMDA) [56]. In primary cultured neurons, acute insulin stimulation induces the expression of NMDA receptor subunits [51]. IR signaling enhances NMDA-mediated glutamatergic neurotransmission in the hippocampus and modifies AMPA receptor surface expression with effects on LTP/LTD depending on the activation of specific subunits [57]. Hippocampal-specific insulin resistance induced by a lentiviral vector leads to alterations in the expression and phosphorylation of glutamate receptor subunits, altering LTP and impairing hippocampal-dependent learning in rats [58]. IR are also expressed by NAcc medium spiny neurons in rats, where insulin influences glutamatergic excitatory transmission via pre- and postsynaptic mechanisms [59]. In cultures of rat cortical neurons, insulin modulates glutamate excitotoxicity [60]. In sum, the modulation of glutamatergic neurotransmission by insulin is involved in synaptic plasticity, memory formation, motivational systems, and excitotoxicity/neuronal survival.

Early life adversity, insulin, and brain neurotransmission

In pediatrics, a healthy childhood can be estimated by means of adequate age-appropriate growth and neurodevelopment [61]. Different aspects of the child's environment can affect these two parameters, such as the psychosocial context, the family function, or individual physiological or pathophysiological changes. From a biological perspective, insulin function is involved in both growth and development [62, 63] as well as in the adaptive responses to changes in the environment [64]. Stressful conditions or adversities happening early in life, either pre- or postnatally, can affect glucose homeostasis and insulin function in the short and long-term (**Box 1**).

Alterations in dopaminergic neurotransmission are seen in animal models of pre- and postnatal adversity, with varied impact on executive function-related behaviors. For example, in

rodents exposed to intrauterine growth restriction (IUGR, induced by malnutrition during pregnancy), there is systemic hyperglycemia/hyperinsulinemia [65], as well as alterations in the expression of genes or proteins related to dopaminergic signaling in the VTA, NAcc, and PFC (TH, pTH, D1, D2) [66-69]. These metabolic and neurochemical effects are accompanied by changes in cognitive flexibility, sensitivity to reward, and poor inhibitory control [66, 67, 69-71]. Chronoamperometric measures of DA release in response to sweet food were not affected in the orbito-frontal cortex, but were blunted in the medial PFC [70] and NAcc of IUGR animals, being completely reversed by a peripheral injection of insulin [68]. There is a decrease in suppressor of cytokine signaling 3 (**SOCS3**) protein in the VTA in these animals, which is a marker of altered insulin sensitivity in this brain area [68]. All these findings suggest that the modulation of DA by insulin is linked to the behavioral alterations in adult rats exposed to prenatal adversity. Prenatal stress in rodents also affects the development of serotonin raphe neurons as well as the long-term expression of serotonin receptors in limbic structures [45].

Interference with the early postnatal experience in rodents also has effects on DA-related behaviors and neurotransmission, while leading to increased insulin resistance later in life [72, 73]. Both brief and longer periods of maternal separation events in the first few days of life are linked to alterations in sensitivity to reward in adulthood in rats [74, 75], as well as changes in DA metabolism in the NAcc [74, 75], in the expression of D1 and D2 receptor on projection neurons [76], and in the excitability and diameter of dendritic spine heads of dopaminergic neurons in the VTA [77]. In mice, stress early in life alters the transcriptomic patterns across the reward circuitry in males and females [78] and reprograms accumbal D2 medium spine neurons to increase the susceptibility to chronic social defeat stress in adulthood via histone methylation modifications [79]. Serotonin signaling is critically involved in long-term molecular adaptations related to the brain glucocorticoid programming effects in response to variations in the rearing conditions in rats [80]. Early life stress can also accelerate or delay critical periods of development, reflecting GABA circuit maturation and the brain's excitatory/inhibitory balance, which may be linked to the development of cognitive disorders [81].

Childhood maltreatment is a form of severe early life adversity, being a classical risk factor for developing adult cardio-metabolic diseases in humans, including insulin resistance and type 2 diabetes [1], and has been associated with several effects on brain and behavior. A study using PET described that severe physical or sexual abuse accompanied by unstable family arrangements

in childhood were associated with elevated DA function in the associative striatum in adulthood [82]. Another study using simultaneous electroencephalography-functional magnetic resonance imaging in young adults shows that early life adversity leads to hyporesponsiveness during reward anticipation and hyper-responsiveness when receiving a reward, a pattern that correlated with lifetime attention deficit hyperactivity disorder (ADHD) symptoms [83]. However, less extreme forms of early life adversity also elicit long-term effects [84], where even alterations in the maternal metabolic context can be seen as a form of adversity (**Box 3**).

Childhood contextual stress exposure is associated with differences in the serotonin receptor 2A gene methylation, which were also related to post-traumatic stress and depressive disorder symptoms in a sample of children [85]. A post-mortem study described decreased NMDA receptor binding in the dorsal prefrontal, dorsolateral prefrontal, and anterior cingulate cortex of individuals exposed to childhood adversity, suggesting that early life stress can cause glutamate excitotoxicity with NMDA receptor downregulation and/or neuron loss [86]. Methylation in a regulatory region of the ionotropic glutamate receptor NMDA type subunit 2B gene was associated with exposure to childhood adversity in a sample of adults, although no association was found between the epigenetic marker and depression status [87].

While a systematic review of the association between epigenetic modifications of the serotonin transporter gene and adverse exposures in humans seems to corroborate findings from experimental models in rodents, a wide heterogeneity in the revised literature prevents the establishment of a definite conclusion [88]. Dated candidate gene approaches have suggested that serotonin-related polymorphisms interact with early adversity modifying the risk for stress-related psychopathology [45]. A recent study [89] filtered the genetic markers identified in a genome-wide association study (GWAS) for adult high fasting insulin levels by selecting those most highly associated with peripheral insulin levels in children, to calculate a polygenic risk score (PRS). This fasting insulin PRS interacted with early life adversity and predicted childhood impulsivity at 3 years of age in an independent cohort. Interestingly, the markers composing the high fasting insulin PRS are mapped into genes associated with DA D2 receptor signaling, suggesting that individual variations in insulin function are related to differential effects of childhood adversity on executive functions, via DA-related mechanisms [89]. Finally, high fasting insulin genetic markers that predict childhood impulsivity in response to adversity were also significantly enriched in the accelerated cognitive decline GWAS, which may suggest that these genes are also important for

long-term effects on cognition [89]. This study is an example of novel functional genomics investigations, which carry the promise to illuminate these relationships from a genome-wide perspective [84, 90] (**Figure 2, Key figure**).

Concluding remarks

Metabolic factors (like insulin) acting on the brain very early in life can modify the development of different neurotransmitter systems and influence both executive functions and the risk of physical and mental diseases later in life. Basic science studies directly exploring these relationships at the molecular level in response to pre- or postnatal adversity are needed (see **'Outstanding Questions'**). Multilevel integration of models (animal, clinical, observational) and data modalities (gene expression, gene variants, neuroimaging, behavior, biomarkers) in the context of big data analysis from a life-course perspective is a promising avenue to identify the mechanisms involved in the response to adversity long-term consequences. For example, we have recently described that biologically informed polygenic scores reflecting individual differences in the mesocorticolimbic and hippocampal IR coexpression gene networks have a better prediction of child impulsivity and cognitive performance, as well as risk for addiction and Alzheimer's disease in comparison with conventional polygenic scores for ADHD, addiction, and dementia [91]. Insulin modulation of brain neurotransmitter systems may be the key to discover the impacts of early life stress on neurodevelopmental processes and executive function and consequences on the risk for psychopathology in adulthood. As we recognize the important roles that insulin has on the development of neuropsychiatric conditions like major depression, dementia, and Alzheimer's disease, it is essential to understand the role that these developmental aspects have on the establishment of risk for these diseases, as well as for the highly prevalent comorbidity between psychiatric and metabolic conditions. Knowledge about the interactions between the peripheral metabolism and brain function from a developmental perspective, can contribute to early prevention and detection as well as early intervention programs for vulnerable populations.

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Box 1

Stress and insulin – glucocorticoids and beyond

In response to stress, the HPA axis, the **sympathoadrenal** system, and the **proinflammatory cytokines** (TNF-α, IL-1 and IL-6) act synergistically to alter energy metabolism, resulting in an increase in gluconeogenesis, glycogenolysis, and insulin resistance. Long-term exposure to these mechanisms during chronic stress is implicated in the dysregulation of metabolism over time, as elevated glucocorticoids and prolonged sympathoadrenal activation promote visceral accumulation of adipose tissue and insulin resistance. At the same time, a systemic low-grade inflammation acts as an additional chronic stressor, prolonging the cycle.

Upon chronic stress exposure, glucocorticoids act on the adipose tissue reducing the expression of the glucose **GLUT1** transporter and the translocation of GLUT4 to the plasma membrane, diminishing the insulin-induced glucose uptake. They also decrease insulin receptor substrate (**IRS1**) phosphorylation and protein expression. In the liver, glucocorticoids dramatically decrease protein phosphorylation of important insulin signaling molecules like IR, IRS1 and PI3K, inhibiting insulin signaling and consequently stimulating the expression of its neoglucogenesis related target genes. In skeletal muscles glucocorticoids reduce PI3K activity and IR tyrosine phosphorylation, decreasing the level of **AKT** phosphorylation and diminishing insulin signaling. Glucocorticoids also affect insulin transport into the brain, as well as reduce IR activity, with reduced insulin-stimulated phosphorylation of the IR and decreased total AKT and total GLUT4 protein expression. Interestingly, glucocorticoids also severely impair insulin secretion by the pancreas, affecting the proliferation and survival of beta cells.

When stressful events occur during a **critical period** of development, they can have long-term **programming** effects, persistently modifying these molecular relationships between glucocorticoids and insulin, similarly to what happens in chronic stress. This is an important mechanism by which early life adversity leads to lifelong risk for chronic diseases like metabolic syndrome and psychopathology. Moreover, insulin itself also has long-lasting developmental programming effects on its target organs that are independent of glucocorticoid actions (see review main text). As opposed to initially thought, pancreatic beta cells have a dynamic development in terms of their capacity for insulin secretion and proliferation, with immature secretory function and a high rate of proliferation at birth, progressively increasing secretory capacity and reducing the ability to replicate. Like any other developmental process, pancreatic development can also be

affected by the conditions existent during early life. The primary role of pancreatic beta cells is to produce insulin and therefore, impairment of such cells hampers insulin secretion in the periphery and subsequent central insulin levels, given that the majority of central insulin comes from the periphery. In sum, insulin signaling acts both in conjunction as well as independently from glucocorticoids, having long-term programming effects on health and neurodevelopment in response to early adversity.

Box 2

The prolonged development of dopaminergic pathways

Dopamine (DA) is widely distributed in the central nervous system. There are multiple DA receptors separated into two families: D1 (which includes D1 and D5 receptors) and D2 (D2, D3 and D4 receptors). D1 stimulation activates adenylyl cyclase (AC) activity whereas D2 activation inhibits AC, increasing protein kinase A (PKA) activity. Enhanced PKA activity elevates synaptic plasticity, stimulates neuronal development, and increases DA synthesis. Low PKA signaling is known to be the cause of several brain degenerative diseases including Alzheimer's and Parkinson's disease, suggesting that PKA could play a neuroprotective role.

DA neurons are found in three main locations: First, the ventral midbrain, divided into a) substantia nigra pars compacta, that innervates the dorsolateral striatum and caudate putamen forming the nigrostriatal pathway, involved in the control of voluntary movement and body posture and b) the ventral tegmental area (VTA), that projects to the ventral striatum (NAcc, amygdala and olfactory tubercle) and the prefrontal cortex modulating cognitive and emotional/rewarding behaviors. Second, a group of cells on the diencephalon that projects to autonomic areas of the lower brain stem, spinal cord, hypothalamus, and to the pituitary gland and amygdala, playing a role in neuroendocrine functions (gonadotropin-releasing hormone and prolactin secretion). Lastly, a small group is found in the telencephalon (olfactory bulb periglomerular interneurons and retina amacrine interneurons) that makes local connections.

Studies in mice suggest that the first mesocorticolimbic DA neurons appear by mid gestation [92]. The different mesocorticolimbic DA cell groups have been reported to be generated at slightly different time points, with a rostrolateral to caudomedial gradient during neurogenesis. Right after these neurons are formed, they start extending neurites in the direction of their migratory pathways, beginning their long way towards their projection areas in the forebrain in a

unique developmental process that will be completed only by early adulthood [41], with final axon density levels and increase in dopamine synapses onto prefrontal pyramidal neurons. During neural development, growing axons find their targets by responding to the coordinated actions of proteins called guidance cues, that form signaling pathways that conduct growing axons to their intended targets [93]. The extent and organization of the mesocortical dopamine axon growth early in life determines the organization of the local PFC circuitry and cognitive function in adulthood [41]. As a result of this protracted developmental trajectory of the prefrontal cortex with progressive changes in dopamine innervation, the dopaminergic neurotransmitter system is especially vulnerable to the effects of environmental adversity during critical periods of development. This explains why the effects of early adversity often involve behaviors related to the function of dopamine signaling, such as inhibitory control, cognition, and sensitivity to reward, with long-term impact on the risk for diseases such as mood disorders, ADHD, addiction, and dementia.

Box 3

Maternal diabetes – when the mother's metabolism is the early adversity

Exposure to a non-optimal fetal environment can also be considered a form of early life adversity. An important example is maternal diabetes mellitus (gestational or pre-existing). In healthy pregnancies, there is a physiological expansion of the adipose tissue in early gestation, followed by insulin resistance and lipolysis in late pregnancy, promoting the use of fatty acids as energy substrates in the mother and saving glucose and amino acids for the growing fetus. These mechanisms are exacerbated in cases where the pregnant woman has had pre-existing obesity or diabetes, with consequent fetal overnutrition [94]. The excess of glucose from maternal blood being transferred by the placenta to the fetus leads to fetal adaptations including reactive fetal hyperinsulinemia and excessive oxidative stress.

The consequences of this exposure to the offspring are diverse and contemplate health, metabolic, and neurodevelopmental outcomes [95]. Common acute consequences are complications during labor due to macrosomia and difficulties in the physiological adaptation to life ex-utero, such as hypoglycemia, changes in heart rate variability, and respiratory distress. There are also long-term effects of maternal diabetes during pregnancy, including accelerated fetal cardiac growth and altered cardiac development and function, altered hypothalamic circuit

formation with elevated body weight and glucose intolerance later in life, and altered glial cell development [94, 96].

Normally, the fetus can cope with the excess of glucose, maintaining normal glycemia, but having higher levels of circulating insulin. Such increased exposure to insulin during prenatal period induces not only anabolic effects (growth leading to macrosomia and fat accumulation), but also programs the metabolism to function in an altered state, increasing the risk for diabetes in the long term [96]. This metabolic programming occurs in insulin-targeted tissues such as fat, liver, and pancreas. Since the brain is another target for insulin, it is also impacted, with increased risk for autism and ADHD [97].

It is important to note that the clinical presentation of maternal diabetes covers a wide range of phenotypes, from maternal gestational diabetes (altered glucose tolerance test in mid to late gestation), to different degrees of maternal type 1 and type 2 diabetes mellitus. While these presentations share most of the consequences described above, there are some specificities. For example, fetal malformations are less frequent in cases of gestational diabetes than in cases where diabetes preceded the pregnancy. Another example is fetal growth restriction as opposed to macrosomia in cases of severe maternal diabetes with vascular compromising and placental insufficiency. Insulin is an important modulator of fetal growth and alterations such as hyperinsulinaemia and hyperglycaemia dramatically affect fetal growth and development, as well as short and long-term offspring morbidity.

Figure 1. Cellular effects of insulin in the ventral tegmental area (VTA) and nucleus accumbens (NAcc).
Insulin acts on insulin receptors (InsR) in dopaminergic neurons from the VTA, reducing somatodendritic dopamine (DA) concentrations by upregulating dopamine transporter (DAT) in addition to suppressing excitatory inputs by increasing phosphatidylinositol 3-kinase (PI3K) signaling. In the NAcc, insulin also acts on cholinergic interneurons, increasing their burst firing and enhancing DA release from the presynaptic neuron originating from the VTA. Insulin can also bidirectionally modulate synaptic transmission onto NAcc core medium spiny neurons, increasing excitatory synaptic transmission at low concentrations and suppressing evoked excitatory synaptic transmission in these accumbal neurons at higher concentrations via activation of insulin growth factor 1 receptors. Insulin receptor action on astrocytes in the NAcc stimulates ATP exocytosis. This figure was created using BioRender (https://biorender.com/).

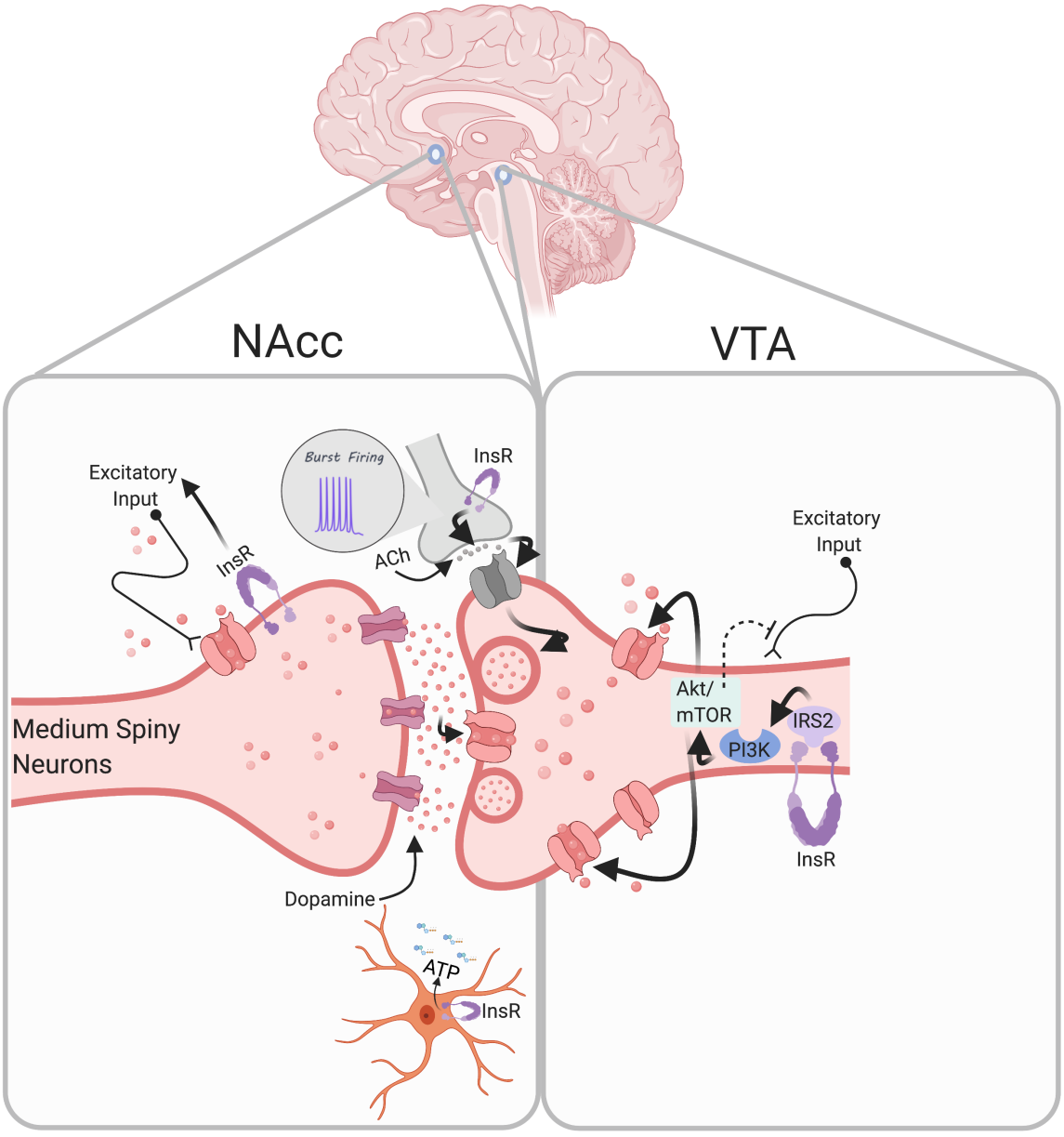

Figure 2. Key figure. Life-course perspective of the programming effects of insulin on neurodevelopment.
The interaction between early life adversity (pre- and/or postnatal) and the genetic background modifies gene expression and the effects of this interaction define the individual's health and disease trajectory over the life course. One of the main immediate effects of adversity occurring in a critical developmental period is the resulting impairment in optimal growth in general but also, specifically, pancreatic development, compromising insulin production and signaling. This triggers a cascade of adaptive metabolic and neurobiological mechanisms affecting behavior and the risk for mental and physical illness throughout the lifetime. This figure was created using BioRender (https://biorender.com/).

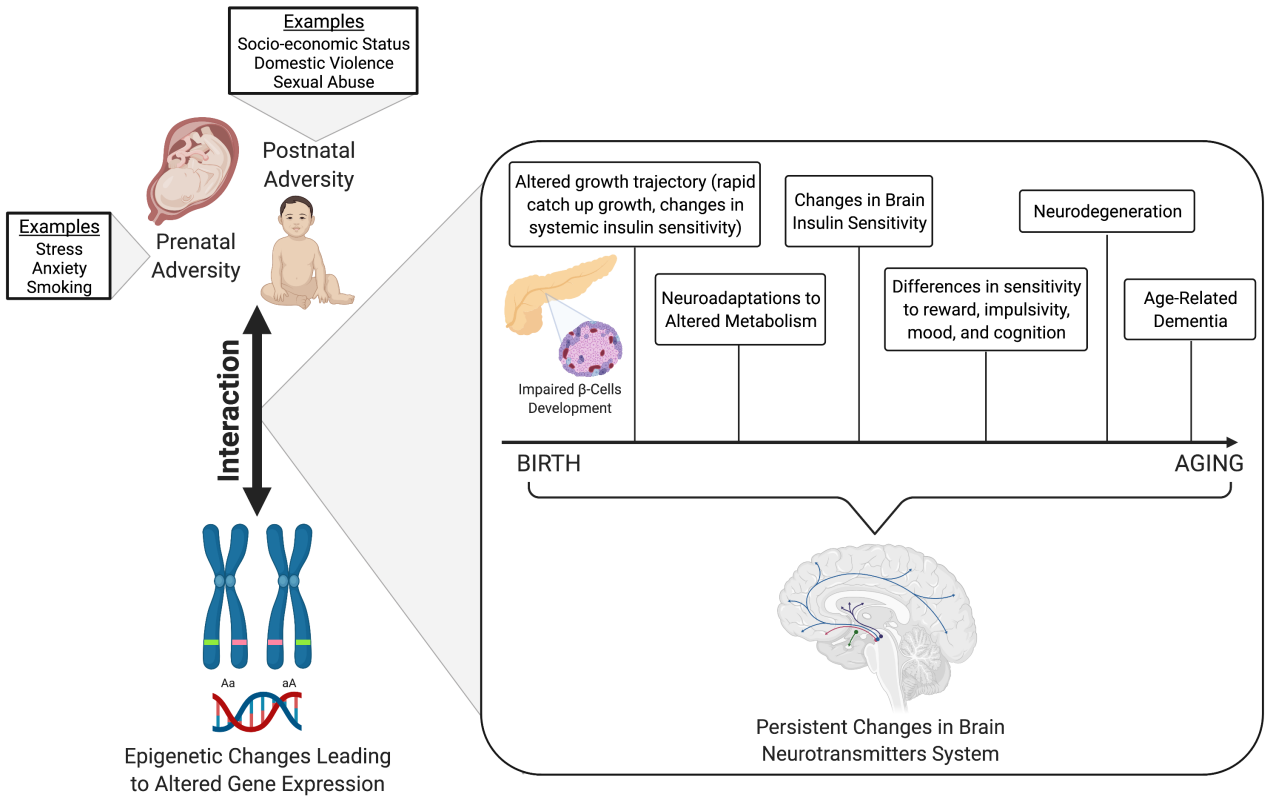

Table 1. Chronic glucocorticoid effects on glucose homeostasis, insulin secretion and signaling

Tissue	Glucose homeostasis	Insulin secretion	Insulin signaling	References
Adipose tissue	Inhibit glucose uptake and utilization	-	Increase insulin sensitivity in subcutaneous adipose tissue	Review in [5-8]
	Stimulate gluconeogenesis via increased lipolysis		Increase lipolysis contributing to adipose tissue redistribution and insulin resistance in muscle and liver	
Skeletal Muscle	Inhibit glucose uptake and oxidation	-	Reduction of insulin signaling at different points of the insulin receptor intracellular cascade	
	Reduce glycogen storage		Accumulation of triglycerides in fibers, increasing insulin resistance	
	Increase protein degradation to favor gluconeogenesis			
Liver	Stimulate gluconeogenesis	-	Increase insulin-stimulated hepatic lipogenesis leading to steatosis and insulin resistance	
	Increase glycogen storage		Decrease insulin binding to its receptor	
			Impairment of insulin receptor function and signaling cascade	
Pancreas	Decrease β-cell sensitivity to glucose	Inhibit insulin secretion from β-cells	-	
	Decrease upstream oxidative glucose metabolism	Induce β-cell hyperplasia		
	Reactive oxygen species generation, β-cell damage			
	α-Cell stimulation with enhanced glucagon			

	action and consequent hyperglycemia			
Brain	Abnormalities in cerebral glucose metabolism	-	Decrease insulin uptake/transport into the brain	
			Decrease insulin receptor expression in certain regions like the hippocampus and hypothalamus	

Glossary

Akt: Serine/threonine-specific protein kinase involved in cellular processes such as glucose metabolism, cell migration, cell proliferation, apoptosis, and transcription.

cAMP: Cyclic adenosine monophosphate is a second messenger used for intracellular signal transduction, such as transferring effects of hormones like glucagon and adrenaline into cells which cannot pass through the plasma membrane.

DDC: Dopa Decarboxylase is the encoded protein that catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine (DOPA) to dopamine, L-5-hydroxytryptophan to serotonin and L-tryptophan to tryptamine.

GLUT (1,3, 4): Glucose transporters are membrane proteins that facilitates the transport of glucose across the plasma membrane through facilitated diffusion. GLUT1, in adults, can be found in the endothelial cells of the blood-brain barrier. GLUT3 is mostly expressed in neurons where it is the main glucose transporter isoform. GLUT4 is expressed in adipose tissues and striated muscle.

HPA Axis: The hypothalamic-pituitary-adrenal axis describes the interaction between the hypothalamus, pituitary gland, and adrenal glands. Its main function is to respond to stress by secreting corticotropin-releasing hormone and adrenocorticotropic hormone into the bloodstream.

IR: Insulin receptor is a transmembrane receptor activated by insulin, IGF-1, and IGF-II. Neuronal IR signaling has been linked to energy homeostasis, reproduction, and the development of neurodegenerative diseases.

IRS1: Insulin receptor substrate 1 is a gene that encodes a protein which is phosphorylated by insulin receptor tyrosine kinase. Mutations in this gene are associated with type II diabetes and susceptibility to insulin resistance.

Long-Term Potentiation and Depression: Patterns of synaptic activity that produce a long-lasting increase (potentiation, or LTP) or decrease (depression, or LTD) in signal transmission between two neurons.

MAOB: Monoamine oxidase B is a protein that catalyzes the oxidative deamination of biogenic and xenobiotic amines and involved in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues.

Mesocorticolimbic: A system, extending from the ventral tegmental area to the nucleus accumbens and prefrontal cortex, which comprises a dopamine projection implicated in reward, motivation, and reinforcement learning.

Monoaminergic neurotransmission: Describing a relation to the monoaminergic system, which is composed by the neurotransmitters dopamine, noradrenaline, and serotonin.

Phosphatidylinositol (PI) 3-kinase: Central enzyme in a signaling pathway that mediates cellular responses to insulin and other growth factors. This enzyme phosphorylates the **3** position of phosphatidylinositol-4,5-bisphosphate to produce phosphatidyl-inositol-**3**,4,5-trisphosphate (PIP_3) at the plasma membrane.

Proinflamatory Cytokines: Signaling molecule secreted from immune cells to initiate the inflammatory response against pathogens mediating the immune response.

Programming: Programming effects leave persistent marks on the individuals' physiology and define his or her health and disease patterns in the long term as shown through studies which explain that fetal exposure to maternal depression during pregnancy has persistent effects on the metabolism of the young adult offspring.

SOCS3: Suppressor Of Cytokine Signaling 3 is a cytokine-inducible negative regulators of cytokine signaling. Studies of the mouse counterpart of this gene suggest that it plays a role in the negative regulation of fetal liver hematopoiesis and placental development.

Sympathoadrenal Axis: The sympathoadrenal system is a physiological connection between the sympathetic nervous system and the adrenal medulla and is involved in an organism's physiological response to outside stimuli.

TH: Tyrosine hydroxylase is the rate-limiting enzyme of catecholamine biosynthesis; it uses tetrahydrobiopterin and molecular oxygen to convert tyrosine to DOPA.

VMAT2: Vesicular monoamine transporter 2 is an integral membrane protein that transports monoamines, such as dopamine, norepinephrine, serotonin, and histamine from cellular cytosol into synaptic vesicles.

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