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Title

Impact of insulin and insulin resistance on brain dopamine signalling and reward processing – An underexplored mechanism in the pathophysiology of depression?

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ABSTRACT

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Type 2 diabetes and major depressive disorder (MDD) are the leading causes of disability worldwide and have a high comorbidity rate with fatal outcomes. Despite the long-established association between these conditions, the underlying molecular mechanisms remain unknown.

Since the discovery of insulin receptors in the brain and the brain's reward system, evidence has accumulated indicating that insulin modulates dopaminergic (DA) signalling and reward behaviour. Here, we review the evidence from rodent and human studies, that insulin resistance directly alters central DA pathways, which may result in motivational deficits and depressive symptoms. Specifically, we first elaborate on the differential effects of insulin on DA signalling in the ventral tegmental area (VTA) - the primary DA source region in the midbrain - and the striatum as well as its effects on behaviour. We then focus on the alterations induced by insulin deficiency and resistance. Finally, we review the impact of insulin resistance in DA pathways in promoting depressive symptoms and anhedonia on a molecular and epidemiological level and discuss its relevance for stratified treatment strategies.

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1. Introduction

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Insulin is a peptidergic hormone mainly produced by the beta-cells of the pancreas and was initially thought to regulate blood glucose concentrations only by binding to its receptor and promoting glucose uptake into cells in the periphery. However, when insulin receptors were identified in multiple brain areas, the essential role of central insulin signalling in the regulation of whole-body glucose metabolism was recognized. Amongst other regions, insulin receptors (IR) are highly expressed in the dopaminergic (DA) midbrain (Figlewicz et al., 2003; Jones et al., 2017; Milstein and Ferris, 2021; Pardini et al., 2006a), which encodes reward-seeking behaviour, so that a further role of central insulin signalling – the regulation of reward-related behaviour – has been progressively unravelled in recent years. Due to the alterations observed in DA-encoded reward-related behaviour, it has been proposed that impaired DA signalling in conditions of central insulin resistance might be causally related to depressive and anxious symptoms (Cai et al., 2018b; Dutheil et al., 2016a; Ho et al., 2012a; Kleinridders et al., 2015). In recent years, a wave of fundamental rodent studies has revived the old debate regarding the comorbidity, and causality, of diabetes and depression, offering new opportunities to investigate underlying mechanisms and use them to improve treatment efficacy.

In this review, we explore the role of insulin in regulating DA signalling in the midbrain - with a focus on the projections from the ventral tegmental area (VTA) (see 2.1) to the ventral striatum (see 2.2) – and consequently in reward-related behaviour encoded by the mesolimbic

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pathways (2.3 and 2.4). Further, we review how central insulin resistance affects DA signalling (3.1 and 3.2) and reward-seeking behaviour in rodents (3.3) as well as humans (3.4) and as an outlook discuss the clinical importance of (impaired) insulin signalling in depression and its therapeutical implications (3.5).

1.1. Encoding of reward-related behaviour in the DA midbrain

The DA midbrain including the VTA and the substantia nigra (SN) is the major source of DA neurons in the brain. DA neurons are organized in subpopulations, which are heterogeneous in their anatomical location, projection site, electrophysiological properties, and function (German and Manaye, 1993; Roeper, 2013). While DA neurons in the SN (pars compacta) mainly project to the dorsal striatum (nigrostriatal pathway) and are involved in movement control, different subpopulations of DA neurons projecting from the VTA to the prefrontal cortex (mesocortical pathway) and the ventral striatum (mesolimbic pathway), in particular the nucleus accumbens (NAc), encode multiple aspects of reward-seeking behaviour, such as reward-driven (reinforcement) learning and motivation to work for reward (Beier et al., 2015; Tobler et al., 2005). Palatable food, sex, and social contact are considered as primary rewards that are strongly encoded in this system. According to the currently dominant theory of reward learning, reward-driven learning is guided by reward prediction errors (PE), which reflect the discrepancy between an expected reward and the actual level of the obtained reward. These PEs function as learning signals and are encoded by dopamine (DA) cell spiking in the VTA causing phasic DA release in the NAc in case of a bigger reward obtained than expected (positive PE) and by a decrease of DA spiking if a smaller than expected reward is gained (negative PE) (Mohebi et al., 2019). As learning progresses, phasic DA release shifts from responding to the obtained rewards to responding to the perception of a learned cue predicting an upcoming reward (Schultz, 2001; Schultz et al., 1997). Both the cue and reward-associated DA signals are essential for consolidating learned associations so that inhibition of either cue- or reward-related DA signals impairs the expression of learned associative behaviour (Van Zessen et al., 2021). The reward PE theory has currently been challenged by Jeong et al. (2022), who developed an algorithm for retrospective causal learning and found that mesolimbic dopamine release conveys retrospective causal associations but not prospective reward PE. While these theories diverge conceptually and propose different biological frameworks of DA action, they both consolidate the relevance of DA signals in association learning, which guides adaptive behaviour.

Additionally, DA not only encodes learning signals but also motivates action initiation to obtain a reward. As such, DA release ramps up when we approach a reward, reflecting reward expectancy (Mohebi et al., 2019). The amount of DA released during this phase is locally controlled in the NAc without corresponding changes in VTA DA cell spiking (Mohebi et al., 2019) and provides information about the value of the anticipated reward, motivating the initiation of action to obtain it (Hamid et al., 2016; Howe et al., 2013; van Swieten and Bogacz, 2020). In this constant feedback circle, the actions initiated upon the perception of a potential reward shape future reward behaviour, as NAc DA release is attenuated unless a correct action to obtain the reward is initiated (Syed et al., 2016).

1.2. Dopamine signalling in the ventral striatum

Since DA ramping in the NAc is independent of VTA DA cell spiking, the magnitude and duration of DA signalling not only depends on the somatic firing of DA VTA neurons but also on the regulation of DA release from nerve terminals within the NAc (Fig. 2). DA release in the NAc is regulated by cholinergic interneurons within the NAc, which are tonically active and release acetylcholine (ACh). ACh binds to nicotinic and muscarinic acetylcholine receptors on DA nerve terminals to directly depolarize DA terminals increasing striatal DA release independently of somatic firing, which provides a distinct modulatory mechanism (Aosaki et al., 1995; Kramer et al., 2022; Shin et al., 2015; Zhou et al., 2001). Moreover, terminal DA signalling depends on DA

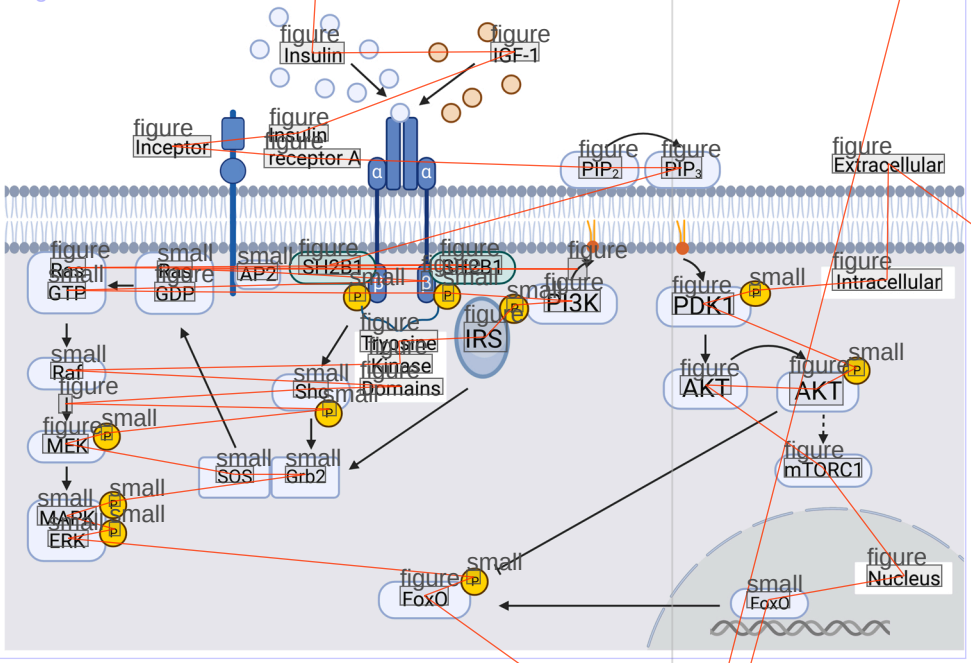

Fig. 1. Intracellular insulin signalling: Insulin and IGF-1 (with lower affinity) bind to the α-subunit of the IR and induce two signalling pathways by autophosphorylation of the IR ß-subunit. PI3K/AKT pathway: Phosphorylated IR leads to phosphorylation of IRS thus resulting in binding of PI3K to the IRS. This in turn leads to conversion of PIP2 into PIP3 which leads to phosphorylation of AKT via PDK1. AKT activates several proteins including mTORC1 and inhibits FOXO1. The latter is transferred to the cytoplasm thus inhibiting transcription of genes relevant in neuronal functions. MAPK/ERK pathway: Phosphorylated IR leads to Shc induction which in turn activates the Grb2/SOS-complex. Alternatively, or additionally, IRS can bind to that complex. In consequence, this leads to regulation of cell growth-related gene expression through activation of Ras which induces Raf thus resulting in a cascade of activating MEK and finally MAPK/Erk. (IR= insulin receptor; AKT=protein kinase B; PI3K=phosphatidylinositol 3-kinase; IRS=insulin receptor substrate proteins; PIP2 =phosphatidylinositol (3,4)-bisphosphate; PIP3 =phosphatidylinositol (3,4,5)-trisphosphate; PDK1 =phosphoinositide- dependent protein kinase 1; MEK = mitogen-activated protein kinase kinase, MAPK=mitogen-activated protein kinase, ERK= extracellular-signal regulated kinases). In the ß-cells of the pancreas the AP2-bound inceptor mediates the clathrin-mediated endocytosis of IR and promotes its degradation. The inceptor has also been identified in the brain, but its role is still unclear. Created with BioRender.com.

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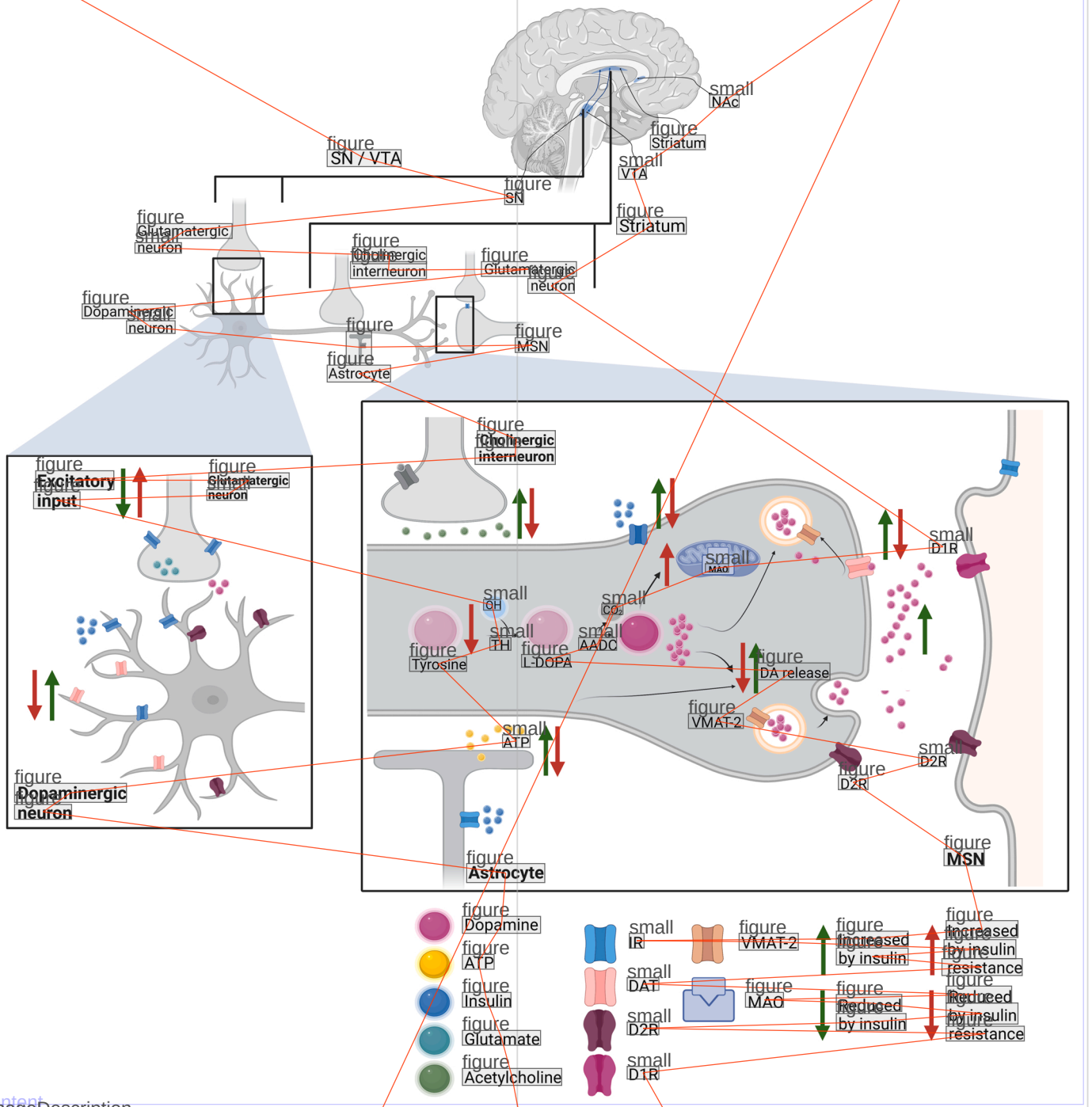

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Fig. 2. The effect of insulin and insulin resistance on DA signalling. Insulin has differential effects on somatodendritic (SN/VTA) and terminal (Striatum) DA turnover. In the SN/VTA, insulin induces DAT expression and diminishes the excitatory input of glutamatergic neurons resulting in decreased extracellular DA levels. In turn, insulin resistance diminishes DAT expression and increases the excitatory input of glutamatergic neurons resulting in increased extracellular DA levels. In the striatum insulin enhances DA reuptake by increased DAT expression. Here, insulin increases DA release by activating excitatory inputs of cholinergic interneurons and ATP-releasing astrocytes. Moreover, insulin directly binds to IR on MSNs, and activates excitatory projections to the MSN. In contrast, insulin resistance reduces DA reuptake by decreased DAT expression. Insulin resistance inhibits DA release by reducing excitatory inputs of cholinergic interneurons and ATP-releasing astrocytes. Moreover, insulin resistance inhibits direct binding of insulin to IR on MSNs, and reduces excitatory projections to the MSN. (SN=substantia nigra; VTA=ventral tegmental area; DA = dopamine; DAT=dopamine active transporter; NAc=Nucleus accumbens; TH = tyrosine hydroxylase; MAO=monoamine oxidase; D1R= dopamine D1 receptor; D2R= dopamine D2 receptor; MSN=medium spiny neuron) Created with BioRender.com.

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receptor availability and the efficiency of DA clearance, which is determined by the DA transporter (DAT) (Carvelli et al., 2002), the level of enzymatic degradation of DA (by COMT, mainly in cortex and less in DA midbrain), and its diffusion from the synapse. The inhibitory DA auto-receptor D2 modulates several of these regulatory steps: Upon binding of DA to axonal D2 receptors in the NAc, it reduces the

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exocytotic release of DA from axon terminals (Anzalone et al., 2012; Benoit-Marand et al., 2001, 2011; Kennedy et al., 1992; Palij et al., 1990; Phillips et al., 2002; Rougé-Pont et al., 2002; Schmitz et al., 2002), increases the activity of the DAT and consequently DA clearance from the synaptic cleft (Benoit-Marand et al., 2011; Cass and Gerhardt, 1994; Dickinson et al., 1999; Mayfield and Zahniser, 2001; Schmitz et al.,

2002; Wu et al., 2002). It also inhibits tyrosine hydroxylase activity (Kehr et al., 1972; Wolf and Roth, 1990) and therefore DA synthesis (Ford, 2014). Somatodendritic D2 receptors in the VTA also regulate DA signalling. Upon DA release from the soma and dendrites, DA binds to somatodendritic D2 receptors, which activates hyperpolarizing G protein-gated inwardly rectifying potassium channel (GIRK) currents resulting in reduced firing rate and excitability of VTA DA neurons (Beckstead and Williams, 2007; Lacey et al., 1987; Mercuri et al., 1997). While both axonal and somatodendritic D2 receptors reduce DA signalling onto medium spiny neuron (MSN) in the NAc, it is unclear how regulation of DA signalling via axonal and somatodendritic D2 receptors is intertwined and whether treatments, that change efferent axonal DA release, also cause similar changes in local somatodendritic DA release. Additionally, neuronal DA signalling is modulated by surrounding astrocytes, along with microglia and oligodendrocytes, which are important for the homeostasis of the brain microenvironment (Cai et al., 2018a).

1.3. Operationalization of dopamine-dependent reward behaviour

As a result, DA signalling between VTA and ventral striatum portrays two specific signals, both of which are affected by a plethora of regulatory influences equally important to guide reward-seeking behaviour and: 1) DA functions as a learning signal by encoding the difference between an expected and received reward guiding future reward-seeking behaviour and 2) it encodes motivation to approach a possible reward (Berke, 2018; Syed et al., 2016; Zolin et al., 2021). With both signals combined, DA conveys the decision variable "available reward for investment of effort", which is employed for both learning and motivational functions (Hamid et al., 2016). Studies assessing reward-seeking behaviour encoded by the DA midbrain in animals or humans employ many different tasks, each addressing a combination of the different aspects of reward-seeking behaviour guided by learned associations. In animals, food, in particular palatable food high in sugar (and fat), or addictive drugs are often used as rewards, the approach thereof, its retrieval and consumption as well as the effort exerted to obtain the reward (lever pressing) are measured to quantify motivation. Place preference conditioned by reward-predicting stimuli and learning of reward magnitude (such as indicated by size of lick bursts in a reward licking task) and reward retrieval (e.g. in a T-maze or three chamber arena) are widely used to analyze learning behaviour. In humans, self-report questionnaires, a variety of motivation and learning tasks in combination with functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) have been leveraged to disentangle the underlying mechanisms. While we here focus on DA-encoded reward-responsiveness, it needs to be kept in mind, that - apart from the difficulty of deciphering the many aspects of reward-seeking behaviour and the varied molecular regulators - reward-seeking behaviour is also affected by further cell types in the VTA and NAc, such as the VTA glutamate neurons, GABA neurons and local opioid signalling (Korotkova et al., 2004; Meier et al., 2021; Ohta et al., 2022; Zell et al., 2020).

2. Insulin signalling in the brain

Motivated behaviour – particularly food-seeking – critically depends on an organism's metabolic need and energy storage (e.g. an apple appears more valuable when we are hungry than when we just had lunch). Therefore, homeostatic information is integrated with external cues in the midbrain DA system through multiple pathways to ensure goal-directed adaptive behaviour. One of these pathways comprises metabolic hormones, which bind to their respective receptors in the DA midbrain to convey the current homeostatic state. In particular, insulin receptors are densely expressed in DA circuits.

Secreted in the pancreas, insulin reaches the CNS through the bloodstream and crosses the blood-brain barrier through a saturable transport system (Banks et al., 1997; Rhea et al., 2018). Rodent studies indicate that a small proportion of insulin is also directly synthesised in the brain, predominantly by neurons and neuronal progenitor cells of the olfactory bulb and the hippocampus (Kuwabara et al., 2011). In particular, GABA-ergic neurogliaform cells have been identified as potential producers of insulin in the CNS (Molnár et al., 2014). However, whether this CNS-derived insulin is physiologically relevant is still controversial and, so far, there is no evidence for local insulin production in the human brain.

In the brain, insulin receptors are ubiquitously expressed on neurons and glial cells, with the highest density in the olfactory bulb and the limbic areas. In contrast to adult peripheral tissues, where the long receptor isoform B (IR-B) predominates, neurons almost exclusively express the short isoform A (IR-A), lacking 12 amino acids within the C-terminus of the α-subunit (Gammeltoft et al., 1985; Heidenreich et al., 1983), but glial cells primarily express IR-B (Adamo et al., 1989; Milstein and Ferris, 2021). In contrast to IR-B, IR-A has a 2-fold higher sensitivity for insulin and can also bind IGF-1 (Denley et al., 2004; Milstein and Ferris, 2021; Mosthaf et al., 1990; Yamaguchi et al., 1991).

2.1. Intracellular pathways activated by insulin

Insulin unfolds its action by binding to the extracellular alpha-subunit of the insulin receptor, which causes dimerization and autophosphorylation of the intracellular ß-subunit.

This induces two canonical signalling pathways: 1) the PI3K/AKT pathway via tyrosine phosphorylation of insulin receptor substrate proteins (IRS) supported by the adaptor molecule SH2B1 (Morris et al., 2009) and 2) the mitogen-activated protein kinase (MAPK) pathways via phosphorylation of Shc (and/or IRS) (for details see Fig. 1).

The AKT pathway has a critical role in diverse biological processes including cell proliferation, differentiation, and metabolism (Chen et al., 2001; Scherer et al., 2021). On the one hand, it leads to the assembly of mTORC1, which is critical for regulating mitochondrial metabolism as well as lipid, fatty acid and protein synthesis (Sarbassov et al., 2005; Saxton and Sabatini, 2017; Wullschleger et al., 2006). On the other hand, the AKT signalling pathway inhibits the activity of the Forkhead box O (FoxO) transcription factor, which regulates glucose and lipid metabolism (Accili and Arden, 2004; Barthel et al., 2005). However, the exact role of FoxO in the brain is still unclear. IRS 1/2 in addition to or possibly competing with Shc can also activate the MAPK pathway, which plays a key role in many biological processes like cell proliferation, differentiation, development, transformation, and apoptosis (W. Zhang and Liu, 2002). Both Shc and IRS activate Grb2/Sos complexes, which, in turn, lead to the activation of Ras-Raf-MEK-ERC-cascade and further downstream substrates regulating cell growth-related gene expression (Siddle, 2011) and cell proliferation (Burotto et al., 2014). The relevance of IRS and Shc for activation of the Ras pathways may differ between cell lines and tissues (Pruett et al., 1995; Takahashi et al., 1997) as well as during different stages in brain development and function.

Very recently, a co-receptor called "inceptor" was discovered in the pancreas that is involved in the degradation of insulin receptors on ß-cells through clathrin-mediated endocytosis (Ansarullah et al., 2021). The inhibition of this co-receptor has been shown to be associated with higher insulin secretion and a lower peripheral glucose level, hence providing an interesting target for diabetes treatment. Whether this regulatory co-receptor has a relevant role in the brain is an area of current research.

2.2. Insulin action in the dopaminergic midbrain

For a very long time, hypothalamic nuclei have been considered the only central target of insulin to assure homeostatic control, which was assumed to be segregated from hedonic (food) reward seeking. However, a wave of fundamental studies has clearly shown that homeostatic

information is integrated into the DA midbrain since a) different neuron populations from the lateral hypothalamus and the arcuate nucleus of the hypothalamus project to the VTA inducing or inhibiting DA release in the VTA and its projection sites depending on the homeostatic state (Nieh et al., 2015; Qu et al., 2019; Reichenbach et al., 2022; Rossi et al., 2021; Zhang et al., 2022) and b) multiple metabolic hormones (including insulin) and nutrients also directly acts in the DA midbrain. Insulin receptors are co-expressed on DA neurons in the midbrain (Figlewicz et al., 2003) (see **Appendix,** Table 1). And indeed, key regulators of the intracellular insulin-signaling pathway such as IRS-2 and PI3K/AKT have been identified to play a critical role in DA signalling in VTA neurons (Lute et al., 2008; Pardini et al., 2006b).

2.2.1. Insulin increases DAT expression and function

Particularly, the PI3K/AKT pathway regulates DA clearance by modulating DAT expression and function (Carvelli et al., 2002). Acute application of insulin to the VTA in vitro reduced somatodendritic DA levels in fast-scan voltammetry through increased DAT clearance in a concentration-dependent manner by activating PI3K and mTOR signalling pathways (Figlewicz et al., 2007; Mebel et al., 2012). In line with this, increased DAT mRNA levels were detected in the VTA after chronic insulin application (Figlewicz et al., 1994). In turn, suppression of PI3K signalling, selective DAT inhibition with GBR12909 as well as DAT-knockout inhibited the DA-suppressing effect of insulin (Mebel et al., 2012; Williams et al., 2007).

Table 1
Rodent models of impaired insulin signalling used to investigate alterations in brain-DA signalling (see Appendix, Table S3 and S4).

Model	Primary mechanism	Phenotype
Otsuka Long-Evans Tokushima fatty (OLETF) rats	CCK receptor deficiency	hyperphagic, obese, prediabetic/diabetic with increasing age
Streptozotocin rat/mice	pancreatic islet ß-cell destruction	Hyperglycaemia, polydipsia, depressive-like behaviour
HF induced insulin resistance	excess calorie intake	hyperphagic, obese
NIRKO mice	brain/neuron-specific knockout of IR	hyperphagic, mild obesity, reduced fertility, decreased counter-regulatory response to hypoglycaemia
Zucker Fatty (fa/fa) rat	homozygous mutation of the leptin receptor	hyperphagic, obese, hyperinsulinemia, hypercholesterolinemia (substain: Zucker diabetic fatty rats – particularly males develop early diabetes)
Astrocyte specific IRKO mice	knockout of IR in astrocytes	normal body weight, fasting glucose level, glucose tolerance and insulin tolerance
		anxiety- and depressive-like behaviour
Goto-Kakizaki rats	spontaneously diabetic (resulted from a selective inbreeding of hyperglycaemic Wistar rats)	hyperglycaemia, insulin secretion deficiency, non-obese, non-hyperlipidemic
DA-specific IRKO	knockout of IR in DAT-expressing neurons	normal body weight, normal feeding behaviour, normal voluntary activity
hypo-IRAS	downregulation of hypothalamic IR through a lentivirus that produces antisense RNA selective for the IR	metabolic syndrome, deficits in neuronal plasticity, depressive-like behaviour
$IR^{\Delta TH}$ mice	Knockout of IR tyrosine hydroxylase-expressing cells	adiposity, increased fat mass, hyperinsulinemia, hyperphagia

2.2.2. Insulin modulates tyrosine hydrolase (TH) activity – the rate-limiting enzyme in catecholamine synthesis

Selective knockout of insulin receptors in TH-expressing neurons reduced the expression of TH-mRNA (Könner et al., 2011). Moreover, the acute application of insulin on VTA slices directly increases the firing rate of SN/VTA neurons in patch clamp recordings potentially through PI3K-signalling pathways (Könner et al., 2011). However, the exact signalling pathways are still unclear.

2.2.3. Insulin modulates the excitatory and inhibitory inputs on DA neurons

The VTA receives excitatory glutamatergic input from the prefrontal cortex, lateral dorsal tegmentum, pedunculopontine nucleus (PPTg), and lateral hypothalamus (Watabe-Uchida et al., 2012). Insulin administration in the VTA decreases the excitatory inputs on DA neurons and induces long-term depression (LTD) via AKT/mTOR signalling and endocannabinoid mediated presynaptic suppression of glutamate release (Labouèbe et al., 2013a), while the inhibitory GABA-ergic inputs remain unchanged (Labouèbe et al., 2013b). This effect could be driven by PPTg inputs to the VTA, as phasic DA release in the NAc evoked by stimulating PPTg inputs to the VTA is suppressed by intra-VTA insulin (Naef et al., 2019). This appears in contrast to the facilitating effects of insulin on the firing rate of VTA dopamine neurons. The spontaneous firing frequency was not different between control and insulin-receptor lacking DA neurons, suggesting that basal endogenous insulin signalling does not influence the firing of DA neurons. However, bath application of insulin increased the firing rate of DA neurons (Könner et al., 2011). This may occur via intrinsic mechanisms or through reduced inhibition of D2-receptors. It is possible that insulin has a differential impact on tonic and phasic DA release of VTA neurons: Higher firing frequency might increase tonic DA release in low concentrations in the NAc. And the insulin-mediated suppression of excitatory inputs could decrease the ability to produce phasic bursts, which are particularly relevant for the reward-seeking behaviour (Floresco et al., 2003; Tsai et al., 2009). However, these are only speculations and need to be systematically investigated in future studies.

To summarise the available data, insulin in the VTA reduces extracellular somatodendritic DA concentrations through increased DA reuptake, reduces LTD of excitatory inputs, and decreases PPTg-evoked DA release in the NAc.

2.3. Insulin action in the ventral striatum

In the NAc, DA-projections target GABA-ergic MSN, which form several subpopulations depending on the expression of D1 or D2 receptors (Soares-Cunha et al., 2019) (see **Appendix,** Table S1). The activity of MSNs is modulated by inputs from cholinergic and GABA-ergic interneurons as well as glial cells. All of these different cell types within the NAc express insulin receptors (Cai et al., 2018a; Warner-Schmidt et al., 2012). Hence, insulin can activate a complex signalling pathway in downstream DA target areas independent of its action in the VTA.

2.3.1. Insulin increases DA release and reuptake

Similar to its action on somatodendritic DA release in the VTA, insulin increases DAT surface expression and DA reuptake (Patel et al., 2019a; Williams et al., 2007) through PI3K-signalling in the DA terminals (Garcia et al., 2005; Patel et al., 2019b). Despite their role in reuptake, DATs are also known to mediate AMPH-induced DA-efflux through reversed transport. In line with this, insulin has been shown to facilitate AMPH-stimulated DA release mediated by DAT in hypoinsulinemic mice (Williams et al., 2007). In ex-vivo slices of the NAc and the dorsal striatum, Stouffer et al. (2015) demonstrated that insulin increases terminal DA release by acting on cholinergic interneurons. Furthermore, acute insulin administration has been shown to stimulate ATP release from astrocytes, which activates purinergic signalling cascades in DA neurons to facilitate DA efflux (Cai et al., 2018a). Due to the dynamic action of insulin on DA outflow and reuptake, the net effect is

difficult to predict. However, Stouffer et al. (2015) demonstrated that insulin-mediated DA release is higher than DA reuptake suggesting a positive net effect of insulin on extracellular DA concentrations in DA downstream targets. In line with this, systemic intra-peritoneal application of insulin has been shown to increase DA release in the NAc (30 min after the injection) and the dorsal striatum (80 min after the injection) in a dose-dependent manner (Potter et al., 1999). Likewise, ICV administration increased DA-release and DA content in the striatum (McCaleb and Myers, 1979). More specifically, while insulin application in the striatum has been shown to increase DA release, insulin administration in the VTA induces a long-lasting decrease of DA release in the striatum (Naef et al., 2019). Notably, the insulin release after food intake inhibits excitatory synaptic transmission in the VTA for 3 h – and hence considerably longer that the duration of the postprandial insulin spike itself - (Labouèbe et al., 2013b; Liu et al., 2016) likely underlying the long-lasting depression of DA release in the striatum (Naef et al., 2019).

2.3.2. Insulin modulates excitatory inputs on MSN

Besides, its direct effect on MSN, insulin has been shown to modulate excitatory transmission on MSN in a concentration-dependent manner. While low physiological insulin concentrations increased excitatory transmission on MSN neurons, high insulin concentrations suppressed excitatory transmission on MSNs (Oginsky and Ferrario, 2019).

In summary, the effect of insulin on terminal DA release in the striatum is dependent on the site of administration. While insulin applied in the striatum increases terminal DA release, insulin applied to the VTA suppresses phasic DA release by inhibiting excitatory inputs.

2.4. Impact of insulin signalling on reward behaviour in rodents

Unsurprisingly, the aforementioned effects of insulin on DA signalling within the mesolimbic pathway have been linked to changes in reward-seeking behaviour (see Fig. 3 for a brief description of the rodent tasks). The differential effects of insulin in the DA midbrain and the downstream targets result in different behavioural alterations depending on the site of insulin administration and the homeostatic status (hungry/sated) (see **Appendix,** Table S2).

2.4.1. The effect of insulin on food approach behavior

Injections of insulin into the VTA decreased food anticipatory behaviour (Labouèbe et al., 2013b) and food approach behaviour in a light-dark box (Liu et al., 2016). Insulin infusions in the VTA as well as in

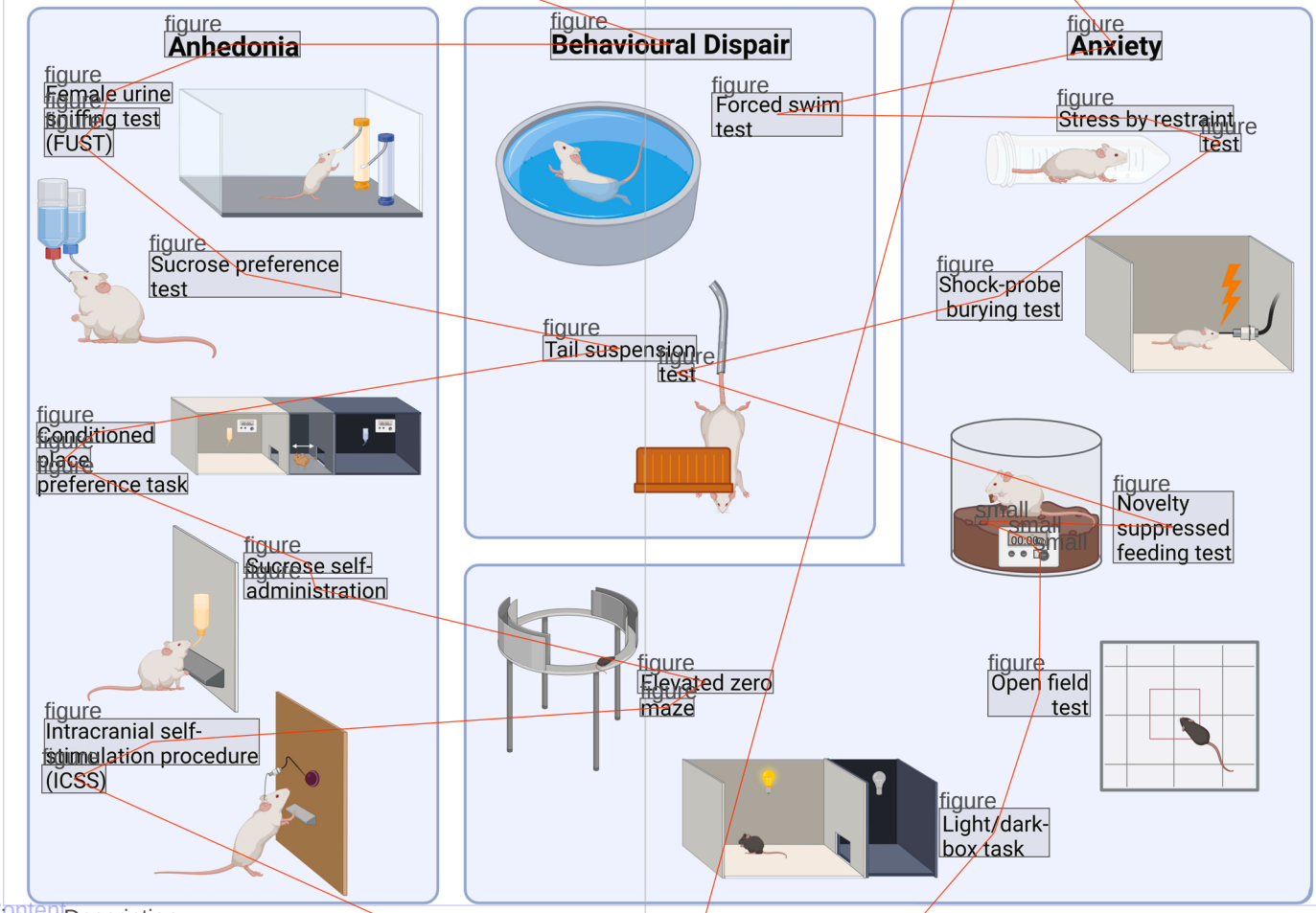

Fig. 3. Selected rodent tasks to assess depressive and anxious symptoms: Comprehensive frameworks for the analysis of depressive or anxious behaviour in rodent models are still missing. The currently available screening tools were developed to assess the efficacy of monoaminergic antidepressants. Anhedonia and behavioural despair are classically tested to describe depressive behaviour. Anhedonia— the loss of experiencing pleasure from usually enjoyable/rewarding activities—is operationalized by assessing reward sensitivity to food (sucrose preference test, conditioned place preference test using food stimuli) and non-food related stimuli (female urine sniffing test, intracranial self-stimulation, conditioned place preference using non-food stimuli) and motivational behaviour (sucrose self-administration, progressive ratio schedule). The immobility time when exposed to an unavoidable life-threatening situation (forced swim test, tail suspension test, learned helplessness) characterises behavioural despair. Antidepressants shorten the period of immobility and increase the number of escapes in the learned helplessness task. Anxiety is assessed by the animal's conditioned reaction to painful (shock-probe burying test) and stressful events (restraint stress) or its spontaneous reaction to a new environment or new stimuli that elicit a conflict between stress avoidance and exploratory drive (elevated zero maze, open field test, novelty suppressed feeding test, light/dark box task). Created with BioRender.com.

the NAc reduced regular chow consumption in rodents (Bruijnzeel et al., 2011a; Finnell and Ferrario, 2022a). The insulin action in the VTA is dose and time-dependent. While low doses of insulin (0.005–0.5 mU) do not modulate food intake behaviour, reduced food consumption can only be observed for high insulin levels (5 mU) in the first 24 h after the intervention. Mebel et al. (2012) investigated the influence of hunger and satiety status and demonstrated that 500 nM insulin applied to the VTA did not modulate regular chow feeding in hungry mice within the first four hours, but rather suppressed sweetened high-fat diet intake when applied in sated mice suggesting that insulin primarily suppresses "hedonic feeding" through modulating reward behaviour. Consistent with this, mice lacking insulin receptors in DA neurons had increased food intake, leading to increased body weight and adiposity (Könner et al., 2011).

2.4.2. Impact of insulin on reward sensitivity

In rats fed ad libitum intra-VTA application of low levels of insulin increased the threshold for intracranial self-stimulation suggesting reduced reward sensitivity (Bruijnzeel et al., 2011a). Opioid-stimulated feeding – a model for hedonic feeding – was only suppressed, when insulin was applied in the VTA (Figlewicz et al., 2008a, 2008b). Neither insulin application in the NAc nor in the hypothalamic nuclei showed a similar effect suggesting that this effect is specific to the VTA. ICV-insulin application combined with the D2-receptor antagonist raclopride reduced the lick rate in a sucrose-licking task (fixed-ratio), while insulin alone was not sufficient to induce this effect, confirming that insulin action is dependent on DA signalling (Sipols et al., 2000). Both ICV and intra-VTA insulin infusions have been shown to inhibit conditioned place preference to a high-fat diet or sweetened froot loops in a concentration-dependent manner in ad-libitum-fed rodents; again suggesting a reduced reward sensitivity (Figlewicz et al., 2004; Labouèbe et al., 2013b).

2.4.3. Role of insulin in learning and motivation

Insulin promotes learning of reward associations (such as nutritive value of food) and consequently forms preferences (Woods et al., 2016): Flavor-nutrient-preference learning in food-restricted and ad-libitum mice is dependent on insulin receptor activation in the nucleus accumbens. However, Figlewicz et al. (2004) revealed that in ad libitum-fed mice intra-ventricular insulin does not impair learning of the reward value of a high-fat diet. But, intra-ventricular insulin inhibits reward retrieval indicating an effect on motivation (Figlewicz et al., 2004). Finnell and Ferrario (2022b) systematically investigated the differential effect of intranasal insulin application in the core of the nucleus accumbens on cue-triggered food approach and motivation: while cue-triggered food approach remained unchanged by insulin the motivation to spend effort for food was reduced after insulin application.

For effort spending in progressive ratio tasks, the findings were inconsistent though: While (Labouèbe et al., 2013b) and Figlewicz et al. (2008a) reported no effect after intra-VTA and intra-NAc insulin application, others found reduced motivation after intra-NAc and ICV administration (Figlewicz et al., 2006; Finnell and Ferrario, 2022a). Findings from ICV-application have to be interpreted with caution, as the insulin effects cannot be attributed to specific brain areas or neuron populations. Here, insulin can either act directly on DA-circuitry or indirectly through other insulin receptive brain areas (e.g. hypothalamus) that modulate DA-signalling through multisynaptic connections. Moreover, it is important to note that most of the rodent studies used food stimuli to assess reward sensitivity, learning, and motivation. This is simply due to the fact that food stimuli are well-established in rodent assays and are easy to apply. However, Bruijnzeel et al. (2011b) leveraged an intracranial self-stimulation protocol and demonstrated a reward-suppressing effect, indicating that the action of insulin on the brain's DA system has implications far beyond food intake and metabolic regulation. These findings demonstrate conclusively that insulin has a reward-suppressing impact via its action on midbrain DA neurons, primarily under conditions of satiety. However, more research is required to delineate the receptors /cell subtypes involved and the different forms of rewarding stimuli such as drugs and social/sexual stimuli that are affected.

2.5. Impact of insulin on reward behaviour in humans

Recent human research has provided additional evidence for the insulin-mediated downregulation of reward-related processing (see **Appendix, Tables 7–10**). In humans, brain function is generally assessed using fMRI, which provides a surrogate marker for neuronal and glial activity through quantifying blood hemoglobin oxygenation (Ogawa et al., 1990). The standard procedure to study central insulin effects in humans is through intranasal insulin application, which enters the nasal mucosa and is transported to the CNS via diffusion and trans-neuronal transport via olfactory and trigeminal pathways bypassing the blood-brain barrier (Dhuria et al., 2010). The exact temporal dynamics of insulin's effect on neuronal signalling are unclear, however, there is increasing evidence that the main effect is achieved after 30 min in a dose-dependent manner (Born et al., 2002; Edwin Thanarajah et al., 2019; Kullmann et al., 2018).

2.5.1. Effect of intranasal insulin on mesocorticolimbic connectivity

Studies using fMRI have shown that intranasal insulin reduces not only the ratings of food palatability but also modulates the connectivity between the VTA and the NAc (Tiedemann et al., 2017), as well as the functional connectivity between the VTA and the ventromedial prefrontal cortex (Edwin Thanarajah et al., 2019). These findings align with several studies that reported alterations in regional activity and connectivity patterns of the reward circuitry after intranasal insulin application (Heni et al., 2012; Kullmann et al., 2012, 2018). These connectivity changes have been related to peripheral insulin sensitivity and measures of eating behaviour (Heni et al., 2012; Kullmann et al., 2015). Kullmann et al. (2021) performed a combined fMRI and PET study using the D2/D3-receptor ligand [11 C]-raclopride and directly assessed brain DA-signalling. They discovered that intranasal insulin decreased DA transmission in the ventral and dorsal striatum. Interestingly, insulin-induced effects in PET imaging were related to functional connectivity changes detected with fMRI 45 min after intranasal insulin intervention indicating that signal alterations, we observe in fMRI are indeed related to DA signalling.

2.5.2. Effect of insulin on food preference

Tiedemann et al. (2017) reported that after an overnight fast, blood insulin levels predicted food preference in insulin-sensitive participants: Higher blood insulin levels were associated with lower food liking. This suppressing effect was also evident after intranasal insulin application. In insulin-resistant participants, this association between food preference and blood insulin as well as central insulin was not detectable. Furthermore, the inhibitory effect of intranasal insulin on food preference seems to be sex-dependent: While in normal-weight men, insulin reduced food preference and food intake in the hungry state (Benedict et al., 2008), this effect was not evident in women neither in pre- nor postmenopausal stage (Benedict et al., 2008; Krug et al., 2010). In contrast, insulin reduced post-prandial snacking and food cravings in women (Hallschmid et al., 2012a). In line, the neuronal processing of food cues after intranasal insulin application has been demonstrated to depend on body weight and sex (Wagner et al., 2022).

2.5.3. Effect of insulin on motivation

The effect of insulin is not limited to food rewards. Glucagon-like peptide 1 (GLP1), which has an insulin-enhancing effect, modulates incentive **motivation** for both food and money (Hanssen et al., 2021). Of course, this effect is not solely attributable to insulin, since GLP1 has direct effects on DA neurons. Furthermore, food intake (elevating insulin levels among other factors) has been shown to reduce susceptibility to

non-food rewards and choices in the delay discounting task related to fluctuating blood glucose levels (Wang et al., 2017; Xu et al., 2015).

To conclude, human data provide clear evidence that central insulin modulates the activity and the connectivity of DA-pathways affecting reward behaviour.

3. Impaired insulin signalling and the dopaminergic circuitry

Changes in diet are known to modulate both insulin and DA signalling in mesolimbic pathways. Chronic food restriction reduces circulating insulin levels and baseline DA levels in the mesolimbic circuitry leading to higher reward sensitivity and stronger DA release in response to refeeding (Carr and Weiner, 2022a; Heffner et al., 1980). In contrast, high fat diet (HFD)-induced obesity is associated with hyperinsulinemia but lower baseline and amphetamine-induced DA levels in the NAc compared to healthy normal weight controls (Geiger et al., 2009a). Interestingly, in diet-induced obesity (DIO) a chow meal is no longer able to induce a DA-response in the NAc, but a HFD meal is required to trigger this DA response (Geiger et al., 2009b). So while both food restriction and obesity are associated with reduced baseline DA levels in the striatum, there is a bidirectional effect on insulin-dependent DA release (Stouffer et al., 2015). These observations have sparked attention to the role of insulin in mediating these effects.

Several rodent models have been leveraged to investigate the effects of changed insulin transmission on midbrain DA neurons and their primary projection regions (Table 1). These models differ in their availability of insulin, the induction of downstream insulin signalling pathways upon binding of insulin to its receptor, receptor availability and specificity of the intervention.

3.1. The impact of insulin deficiency on DA signalling in rodents

Insulin deficiency and its impact on DA signalling are typically studied in a.) rodent models with damaged pancreatic beta cells due to the administration of beta cytotoxics such as streptozocin (STZ) (Furman, 2015) or alloxan, b.) hereditary models prone to type 1 diabetes (Li and Sun, 2010), or c.) rodents after prolonged fasting. Among these models, the STZ-model is most frequently used and involves repeated administration of low doses of streptozotocin resulting in partial damage to the pancreatic islets. This causes chronic inflammation, insulin deficiency and hyperglycaemia, which mimic the pathology of T1DM in humans. An alternative protocol is a single, high-dose administration of streptozotocin, which destroys beta cells completely and does not exhibit human T1D features such as pancreatic insulitis (Furman, 2021). However, all of these models except for prolonged fasting are generally associated with hyperglycaemia, which directly affects neuronal signalling and insulin receptor sensitivity. Therefore, insulin replacement cannot fully restore function in these models (Bellush and Henley, 1990). Moreover, there is growing evidence, that the effect of the beta cytotoxics is not solely attributable to the destruction of ß-cells since a direct ICV application of small doses of alloxan and STZ induced changes in the brain DA signalling comparable to the peripheral administration (Salković et al., 1995).

Insulin receptor knockout models allow the direct investigation of insulin downstream signalling (Table 1). Beyond general IR knockout models, targeted knockdown of IR in neurons, astrocytes, or in TH-expressing or DAT-expressing neurons have been leveraged to unravel the action of insulin in the central nervous system and particularly the DA circuitry. Moreover, customized inactivation of IR has also been investigated by administering antibodies into specific brain locations.

Insulin resistance secondary to obesity and metabolic dysregulation is typically investigated after HFD, or in rodent strains genetically prone to obesity or diabetes mellitus type 2 such as the Goto-Kakizaki (GK) rat or the spontaneously diabetic Torii and the Wistar rats (Islam and Loots, 2009; Li and Sun, 2010). HFD has a clear impact on insulin signalling in DA pathways as evidenced by reduced phosphorylation of AKT in striatal and nigral brain slices (Speed et al., 2011). Nonetheless, it is essential to note that both HFD and obesity result in a number of metabolic and inflammatory changes that can additionally affect DA signalling. Furthermore, HFD regimes differ in their duration and composition (e.g. 50 % of daily kcal requirements from fat vs. 60 % from fat; saturated vs. unsaturated fat) leading to heterogeneous findings and making it challenging to attribute findings solely to insulin changes (Hryhorczuk et al., 2016).

3.2. The impact of insulin resistance in the dopaminergic midbrain

3.2.1. Insulin resistance changes TH-activity

In the VTA, both lack of insulin (due to STZ-induced destruction of pancreatic beta cells) as well as impaired IR signalling (due to knock-out or inhibition in TH-containing neurons) reduce the expression of TH mRNA indicating reduced DA synthesis (Figlewicz et al., 1996; Könner et al., 2011) (see **Appendix,** Tables S3-S4). Similarly, TH activity in terminal fields of DA neurons is suppressed in diabetic rodents after HFD (Chu et al., 1986; Glanville and Anderson, 1986; Kono and Takada, 1994) and genetic models of diabetes (Do Nascimento et al., 2011).

3.2.2. Insulin resistance affects DA-turnover

Food restriction for 24–36 h leading to reduced insulin levels has been demonstrated to diminish DAT mRNA amounts in the VTA/SN, indicating decreased DA turnover (Patterson et al., 1998). Moreover, insulin fails to increase the firing frequency of DA neurons if the IR is inactivated (Könner et al., 2011) and neuronal IR-KO mice show increased levels of monoamine oxidase A and B (MAO A and B) leading to increased DA (and other monoamines) degradation in these areas (Kleinridders et al., 2015). In situations of transient (Labouèbe et al., 2013b; Liu et al., 2016) or prolonged hyperinsulinemia (Liu et al., 2013) insulin loses its ability to induce long-term depression (LTD) of excitatory synapses onto VTA DA neurons (Labouèbe et al., 2013b; Liu et al., 2016). Notably, 7 days of HFD were sufficient to induce insulin resistance in the VTA as demonstrated by reduced AKT phosphorylation in the VTA upon intracerebroventricular injection of insulin (Mizoguchi et al., 2021).

Collectively, insulin deficiency and insulin resistance reduce DA synthesis, DA reuptake, depression of excitatory inputs on DA neurons, and the firing frequency of DA neurons in the VTA.

3.3. The impact of insulin resistance in the ventral striatum

3.3.1. Insulin resistance changes evoked DA release

In the ventral striatum, impaired insulin signalling reduces DA release in response to stimuli (food, electrical or insulin) (see **Appendix,** Tables S3-S4); this effect is evident in neuron-specific IR knock-out (NIRKO) mice (Kleinridders et al., 2015) and HFD-induced insulin resistance (Chen et al., 2019a; Fordahl and Jones, 2017; Stouffer et al., 2015). However, it is important to note, that Fordahl et al. (2017) could not detect any change in evoked DA release in insulin-resistant rodents.

3.3.2. Insulin dysregulation impacts baseline DA levels

Equally to evoked DA release, reports about baseline DA concentrations in the NAc are heterogeneous: While Kleinridders et al. (2015) could not detect any differences in DA content (but only in DA release) between rodents with low insulin levels (prolonged fasting) and insulin resistance (HFD) compared to normal insulin sensitivity, Chen et al. (2019b) observed lower baseline DA levels in insulin resistance. As Oginsky et al. (2019) pointed out, a considerable source of heterogeneity in rodent studies might be caused by the various rodent strains and their susceptibility to weight gain, because intrinsic excitability of NAc core neurons differs between obesity-susceptible and -resistant rats. It is generally assumed that reduced excitatory synaptic transmission on MSNs (Oginsky and Ferrario, 2019) is a key mechanism by which insulin resistance abolishes the capability of insulin to increase DA release in the

ventral striatum (Stouffer et al., 2015). In line, the modulation of MSN activity was attenuated in NIRKO mice (Kleinridders et al., 2015) and DA release in the NAc is equally decreased if insulin signalling in NAc astrocytes is disrupted leading to reduced ATP exocytosis and purinergic signalling cascades in DA neurons (Cai et al., 2018a).

3.3.3. Insulin resistance reduces DA turnover

Insulin resistance reduces DAT expression, and DA reuptake via attenuated AKT signalling (Bellush et al., 1991; Cumming et al., 2015). Moreover, selective inhibition of the insulin receptor has been shown to attenuate DA reuptake (Fordahl and Jones, 2017). The observation that both lack of insulin due to prolonged starvation and prolonged hyperinsulinemia reduce dopamine reuptake indicates that hyperinsulinemia leads to a desensitization of the IR and impacts downstream signalling pathways, that control DAT expression (Bitar et al., 1987; Fukuhara et al., 2019; Kleinrok et al., 1983). This effect is time-dependent. While 2 weeks of HFD did not have an effect, 6 weeks of HFD reduced DAT levels in the synaptosomal membrane-associated fractions (Cone et al., 2013). Notably, the effects of insulin resistance are reversible. Eight weeks of aerobic exercise restored insulin AKT/GSK3-β signalling, baseline DA levels, and DA release after food intake (Chen et al., 2019b).

Taken together, reduced insulin signalling/insulin resistance in the NAc reduces DA release and DA reuptake in DA axon terminals.

3.4. Effect of insulin resistance on reward behaviour and food intake in rodents

To date, only a few studies have examined how compromised insulin signalling in the mesolimbic pathways affects reward behaviour and food intake (see **Appendix,** Tables S5 and S6).

3.4.1. Insulin resistance modulated food intake behavior

Selective inactivation of IR in VTA/SN DA neurons increases food intake, resulting in higher fat mass and body weight (Könner et al., 2011). In line, insulin depletion in STZ-treated mice and insulin resistance after HFD resulted in increased food approach behaviour (Liu et al., 2016; Speed et al., 2011). In fact, increased calorie intake after HFD was associated with impaired AKT signalling and reduced striatal DAT expression indicating an IR-dependent mechanism. In line with this, viral rescue of AKT signalling and striatal DA expression decreased calorie intake (Speed et al., 2011). However, there are also opposing findings. In congenital IR knockouts in DA neurons, there was no difference in daily calorie intake, body weight or energy metabolism (Evans et al., 2018), suggesting that the alterations in food intake and body weight by IR signalling are not solely attributable to the DA system.

3.4.2. Insulin resistance impacts the motivation to work for food

In line with increased food intake, the **motivation to work for food** increases with insulin resistance (see Fig. 3 for an overview of rodent tasks). Rats fed a high-fat diet for five weeks exhibited more lever presses in a progressive ratio task using sucrose reward, and ICV insulin was unable to suppress this effect (Figlewicz et al., 2006, 2008a, 2008b). Furthermore, obese insulin-resistant OLETF rats exhibited increased operant performance for sucrose reward (Hajnal et al., 2007). This is in contradiction, however, with evidence for reduced sucrose preference in insulin resistance (Cai et al., 2018b; Chen et al., 2019a). Moreover, McNeilly et al. (2016) demonstrated that 3–4 weeks of HFD, sufficient to induce insulin resistance, diminished the motivation to respond for sucrose pallets in Wistar rats. This deficit was ameliorated, but not totally reversed, by a dietary intervention (chow diet) that restored insulin sensitivity (McNeilly et al., 2016). However, it is significant to note that McNeilly et al. (2016) did not carry out a conventional progressive ratio task. They performed a delayed matching to place (DMTP) and a delay-non-matching to place operant task, that require cognitive flexibility and working memory, both of which are known to be impaired in obesity and insulin resistance without being related explicitly to DA-signalling.

3.4.3. Insulin resistance has an impact on reward sensitivity

The effect of insulin on motivation and reward sensitivity goes beyond food intake. Insulin deficiency due to fasting increased reward sensitivity in an intracranial self-stimulation task. This effect was reversed by insulin (Carr et al., 2000) and leptin administration (Fulton et al., 2000). Equally, insulin deficiency due to STZ-application increased reward sensitivity, but only in the first (three) weeks (Carr et al., 2000). Afterward, this effect was abolished (Carr et al., 2000) or even turned to the opposite showing reduced reward sensitivity (Ho et al., 2012b). In this case, insulin application improved reward sensitivity. Equally HFD for 15–17 weeks reduced the attraction of male rodents to female urine, that is normally perceived as rewarding (Dutheil et al., 2016a) indicating that insulin resistance over a longer period of time leads to anhedonia - the loss of experiencing pleasure from usually rewarding activities.

3.4.4. Insulin resistance leads to a depressive, anxious phenotype

Moreover, insulin resistance has been associated with behavioural despair (a core feature of depression) and anxious behaviour (Fig. 3). In life-threatening situations, insulin-resistant mice showed increased immobility in the tail-suspension test and the forced swim test and avoided exploratory behaviour in the open field task and during exposition to novel food stimuli indicating anxiety (Cai et al., 2018a; Gilak-Dalasm et al., 2021; Kleinridders et al., 2015).

3.4.5. Insulin resistance impairs preference formation

There is accumulating evidence that insulin plays an important role in learning and preference formation. During flavour-nutrient conditioning, a previously neutral flavour is associated with a positive post-ingestive consequence (e.g., intragastric glucose infusions) to form a preference for the flavour. While insulin-sensitive rodents fed ad libitum or after food restriction are able to establish flavour preferences, this effect is abolished in insulin resistance following HFD. Particularly, after HFD, there was less IR activation in the NAc after intragastric glucose infusion (Woods et al., 2016). Similarly, flavour-nutrient conditioning was inhibited after deactivating insulin bilaterally in the NAc via local administration of insulin antibodies (Stouffer et al., 2015). To differentiate whether this observation was driven by a change in motivation or indeed by a change in the learned reward value, Carr et al. (2022b) analysed the microstructure of licking for glucose: Insulin antibodies did not affect the number of lick bursts emitted (a measure of motivation and/or satiety), but decreased the size of lick bursts (a measure of reward magnitude). This effect was shown to depend on previous flavoured glucose consumption under insulin antibody treatment rather than on insulin antibody treatment per se, indicating that impaired insulin signalling in the NAc (shell) impairs learning by diminishing the estimated reward value rather than motivation per se (Carr and Weiner, 2022b).

3.4.6. The effect of insulin resistance on motor activity

Several models using insulin resistance after HFD or IR knockout in DA neurons or astrocytes (GIRKO) did not show any changes in voluntary motor activity (Evans et al., 2018; McNeilly et al., 2016). In STZ-diabetic mice, however, the results are very inconsistent, providing evidence for reduced, increased, and unaffected spontaneous locomotor behaviour (Ho et al., 2012b; Miyata et al., 2003), which might be related to the large variability in STZ-protocols in terms of timing, dosage and strains. These findings suggest that the shortage of insulin availability and the resistance of insulin receptors have differential effects on motor activity.

Collectively, impaired insulin signalling increases food approach, attenuates value formation and preference learning and promotes anhedonia and anxious behaviour. However, it is important to consider,

Content
that many aspects of reward-seeking behaviour, that are distorted by impaired insulin signalling, cannot be solely attributed to DA signalling in the VTA or NAc but are also related to their interaction with further brain systems (Fordahl and Jones, 2017; Patel et al., 2019c; Stouffer et al., 2015).

Headline
heading
3.5. Effect of insulin resistance on reward behaviour in humans

Content
There is no direct measure of central insulin resistance in humans (see **Appendix,** Tables S8-S10). Using [(18)F] fluorodeoxyglucose positron emission tomography (FDG-PET), Antony et al. (Anthony et al., 2006) discovered that glucose metabolism in regions subserving appetite and reward, including the mesostriatal system, is impaired in response to peripheral insulin administration in diabetes patients compared to healthy controls. This indicates that peripherally measured insulin resistance can be used as a surrogate for central insulin resistance. Since PET using radioactive ligands is limited in its accessibility, fMRI has emerged as a valuable tool for studying changes in brain signalling associated with insulin resistance. In fact, using resting state fMRI data, we demonstrated that the modulation of midbrain (SN/VTA) connectivity by intranasal insulin is compromised in participants with decreased peripheral insulin sensitivity (Edwin Thanarajah et al., 2019).

Headline
heading
3.5.1. Insulin resistance changes food preference

Content
Tiedemann et al. (2017) showed that non-diabetic participants with incipient insulin resistance have a lower preference for food items than healthy controls along with diminished activation of the NAc. At the same time, others reported that food-specific responses within the basal ganglia including the NAc are significantly greater in participants with insulin resistance or type 2 diabetes than in healthy controls (Chechlacz et al., 2009; Van Vugt et al., 2013). Stronger activation in the NAc was related to higher appetite ratings (Chechlacz et al., 2009). Besides the immediate response to food cues, the anticipatory response has also been shown to increase proportionally with BMI and insulin resistance (Simon et al., 2014). However, these studies have to be interpreted with care, because they included small sample sizes and differ in the fasting conditions and study populations (Alsaadi and Van Vugt, 2015; Chechlacz et al., 2009; Van Vugt et al., 2013). Studies assessing the modulation of the brain response to food pictures by insulin have been more consistent: both intranasal insulin, as well as a glucose challenge (which causes elevated insulin secretion), fail to decrease the brain signal to food pictures in insulin-resistant participants indicating that the ability of insulin to curb food intake by reducing the salience of (highly palatable) food cues may be impaired (Alsaadi and Van Vugt, 2015; Belfort-DeAguiar et al., 2016; Tiedemann et al., 2017). In line, during fasted conditions, intranasal insulin failed to decrease wanting for food in insulin-resistant participants (Kullmann et al., 2015; Tiedemann et al., 2017). However, a recent study demonstrated that in post-prandial conditions, a high dose of (160 IU) intranasal insulin reduced snacking in overweight women with insulin resistance (Hallschmid et al., 2012b; Schneider et al., 2022) suggesting that sufficiently high doses of intranasal insulin may enhance satiety signalling and compensate for reduced central insulin sensitivity.

Headline
heading
3.5.2. Impact of insulin resistance on learning and motivation

Content
As observed in rodent studies, the effects of insulin resistance on brain DA signalling are not limited to food intake behaviour. Lower ß-cell function and lower insulin sensitivity were related to increased delayed reward discounting indicating more impulsive choices preferring a small, immediate monetary reward, over a larger, delayed reward (Eisenstein et al., 2015). In line, more impulsive behaviour in the stop signal task of insulin-resistant subjects was mediated by striatal activation (Eckstrand et al., 2017). Furthermore, overweight and obesity, which can be concomitant with insulin resistance, are associated with impaired learning from negative feedback (Coppin et al., 2014; Mathar et al., 2017). Human studies reveal that insulin resistance also affects motivation. The influence of insulin on motivation highly depends on a person's satiety/hunger state of the organism: while hunger is associated with higher motivation for reward in insulin-sensitive humans, this effect gets lost in insulin-resistant humans (Hanssen et al., 2021). Interventions improving insulin signalling (such as GLP-1 analogues) restore the effect of hunger on motivation in insulin-resistant humans. Importantly, this holds true for both food and monetary reward, indicating that insulin resistance not only impairs food related behaviour but is relevant for pathological states characterized by generally diminished motivational behaviour.

Collectively, and aligned with the preclinical findings, impaired insulin signalling in humans impairs food cue reactivity, learning and nutritional state-dependent motivation for reward.

Headline
heading
4. Clinical link to depression

Content
Given the influence of insulin and insulin resistance on reward behaviour, it is unsurprising that epidemiological studies have established a clear link between diabetes and depression and in particular anhedonia (Khaledi et al., 2019). Multiple meta-analyses showed a strong relationship between depression/anhedonia and obesity (which is associated with insulin resistance) (Abou Abbas et al., 2014; de Wit et al., 2010; Pereira-Miranda et al., 2017; Xu et al., 2011). Indeed, longitudinal studies demonstrated, that obesity increased the risk of experiencing depressive symptoms 1–5 years later (Frank et al., 2022), indicating a causal role on an epidemiological level. Interestingly, this association was not explained by socio-demographic, lifestyle, or illness-related factors, including systemic inflammation suggesting that metabolic dysregulation (and potentially insulin resistance) may play a direct role in the pathophysiology of depressive symptoms. Indeed, recent meta-analyses bridge the link between obesity and depression showing that insulin resistance increases the risk for depression: The prevalence of depression is increased to 19.1 % (range 6.5–33 %) for people with type II diabetes compared to 10.7 % (range 3.8–19.4 %) in people without diabetes. This is further supported by genetic studies, that report a genetic overlap between obesity, type II diabetes, and depression (Fanelli et al., 2022).

The link between insulin resistance and depression is bidirectional. In depressed patients, both insulin levels and the Homeostatic Model Assessment for insulin resistance (HOMA-IR) – a proxy for peripheral insulin resistance - are elevated during the acute episode but not during remission (Fernandes et al., 2022). Insulin resistance is associated with increased disease severity (Watson et al., 2021) and compromised antidepressant' treatment efficacy (Jeremiah et al., 2020; Lin et al., 2015). In a sub-analysis, Fernandes et al. (2022) revealed that in particular "atypical depression" is linked to increased insulin resistance. Although the concept of "atypical depression" (mood reactivity, hyperphagia, hypersomnia, interpersonal difficulty) is still under debate, notably increased appetite and weight gain belong to the core features of this subtype. In fact, about 35 % of MDD patients report increased appetite during a depressive episode, and about 20 % of MDD patients gain weight (Maxwell and Cole, 2009). Moreover, weight gain across depressive episodes is highly correlated within patients, suggesting a trait-like character (Stunkard et al., 1990). Therefore, it is unclear whether increased food intake results in reduced peripheral insulin sensitivity, or rather insulin resistance leads to mesolimbic dysregulation that is known to drive food intake (see 3.3). Supporting the latter hypothesis, Simmons et al. (2020) discovered that increased appetite in MDD patients was related to insulin resistance and low-grade inflammation (IL-1RA and IL-6) although the BMI was not different from patients with reduced appetite. In fact, the extent of insulin resistance correlated with the insular cortex response to food cues. In a large sample of 400 MDD patients, Kroemer et al. (2022) confirmed that the direction of appetite change is characterised by a specific neuronal signature. In resting state fMRI data, they found different NAc functional connectivity patterns between patients with increased and reduced

appetite; this study however did not consider metabolic parameters. Beyond appetite changes, anhedonia was found to be strongly linked with poor glycaemic control (OR 1.29, 95 % CI 1.09–1.52) in 5772 MDD patients (Nefs et al., 2012), but in a smaller sample of 604 participants with type 1 and 382 participants with type 2 diabetes, Ehrmann et al. (2017) could not replicate this finding.

4.1. The molecular mechanisms linking diabetes and depression

Despite the clear link between diabetes and depression on an epidemiological level, the molecular mechanisms remain unknown. Given the aforementioned evidence on DA-insulin interaction, impaired DA signalling in conditions of central insulin resistance has been proposed as a potential mechanism between depressive and anxious symptoms. In the last few years, a wave of fundamental rodent studies has provided evidence that insulin resistance in brain DA pathways can lead to depressive and anxious symptoms. This has been shown across different models of insulin resistance including HFD-induced insulin resistance (Dutheil et al., 2016b; Sharma and Fulton, 2013), STZ-induced diabetes (Ho et al., 2012b; Roostaei et al., 2018), and insulin receptor knockout in neurons (Kleinridders et al., 2015) or glial cells (Cai et al., 2018a).

Kleinridders et al. (2015) reported that brain/neuron IR knockout (NIRKO) mice, show age-dependent depressive and anxious behaviour due to impaired mitochondrial function and increased DA turnover by MAO, which is normally suppressed by insulin. Insulin receptor knock-out in glial cells, in turn, reduces ATP exocytosis, resulting in decreased purinergic signalling on DA neurons and subsequently anxiety- and depressive-like behaviour (Cai et al., 2018a). Mechanistically, a subsequent hyperdopaminergic state within the amygdala is probably responsible for the increase in anxiety observed in insulin-resistant and diabetic rats (Rebolledo-Solleiro et al., 2016). Interestingly, down-regulation of the IR in the hypothalamus can also induce depressive-like behaviour in rodents (Grillo et al., 2014) indicating that insulin signalling in the hypothalamus might also affect DA signalling in the midbrain.

4.2. Therapeutic approaches targeting insulin pathways

Based on the molecular evidence for the role of (impaired) insulin signalling in the development of depressive and anxious symptoms, these behavioural changes (see Section 3.3.) respond to treatments altering metabolic state and/or DA signalling: In NIRKO-mice depressive and anxious behaviour is reversed by MAO inhibitors (Kleinridders et al., 2015). In STZ-induced diabetes, depressive symptoms were reduced by insulin therapy, with some (but not all) studies indicating the same impact on anxiety (Gupta et al., 2014; Ho et al., 2012b). Furthermore, physical activity and food restriction, as well as the insulin sensitizers rosiglitazone or pioglitazone alleviated depressive-like behaviour in insulin-resistant rodents (Gilak-Dalasm et al., 2021; Parashar et al., 2018; Shimomura et al., 1990). Despite these promising animal results, the therapeutic link between insulin, DA and depression has hardly been examined in humans. Mansur et al. (2019) demonstrated, that being overweight moderated the association between reduced effort spending (which is DA-dependent) and MDD. Moreover, a single intranasal insulin administration has been shown to improve mood in overweight/obese women (n = 17) without psychiatric conditions (Schneider et al., 2022). Equally, repeated administration of intranasal insulin across eight weeks improved mood in obese (n = 15) and normal-weight participants without depression (n = 19) (Benedict et al., 2004; Hallschmid et al., 2008). Furthermore, diabetes and overweight attenuate the responsiveness to classical antidepressants (Miyata et al., 2003; Rizvi et al., 2014) and adjunctive therapies that enhance insulin sensitivity including both lifestyle (exercise) and dietary intervention improve antidepressant treatment response, even if peripheral insulin resistance is not used for treatment stratification (Jeremiah et al., 2020). A similar effect has been reported for adjunctive therapy with insulin sensitizers (Colle et al., 2016; Lin et al., 2015; Rasgon et al., 2010). Moreover, in the state of insulin resistance, different classes of antidepressants show distinct treatment efficacy and suppressing or enhancing effects on blood glucose levels and body weight (Anderson et al., 2002; Srisurapanont et al., 2022) indicating that the choice of antidepressant therapy should be influenced by the metabolic state. However, clinical trials targeting this question are still lacking. Overall, current data regarding the association between antidepressant-specific mechanism-of-action and effects on metabolic state and depressive symptoms, remain inconclusive but imply that SSRIs might have the best anti-depressive effect in the state of insulin resistance and have a beneficial effect on insulin sensitivity (Markowitz et al., 2011; Silva et al., 2012).

Notably, altered DA signalling is only one potential pathway that links insulin resistance and depression. There are several other factors, that contribute to this bidirectional link including impairments in serotonergic transmission, HPA-axis, neurogenesis, (neuro-)inflammation, opioid-mediated pathways, gut microbiome and gut-brain signalling (Carr, 1994; Zou et al., 2020), which are important, but beyond the scope of this review. Nevertheless, these presented findings are collectively of high (pre)clinical relevance as they point toward a metabolic subtype of depression, in which increased insulin resistance might function as a state marker. Targeting insulin resistance in depression might serve as an important avenue toward a personalized medicine approach in psychiatry.

5. Conclusions

Overall, DA signalling in the midbrain and consequently the DA encoded reward behaviour is modulated by insulin signalling. The effect of insulin on DA release, turn-over, and firing rate might seem contradictory at first glance, but this is due to the differential effects of insulin on the somato-dendritic spines in the midbrain and the axonal terminals in the striatum. Different rodent models of insulin resistance have provided clear evidence that insulin resistance leads to altered DA signalling and impaired reward behaviour. This might represent one critical mechanism in the bidirectional link between insulin resistance and depression. Hence, a detailed molecular understanding of the regulation of DA signalling by insulin will lay the basis for therapeutic advances in the metabolic treatment of depressive disorders.

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Appendix A. Supporting information

appendix

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105179.

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