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Insulin actions in the mesolimbic dopamine system

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ABSTRACT

As a major circulating feeding related hormone, insulin crosses the brain blood barrier and acts on the central nervous system to modulate both homeostatic and non-homeostatic feeding behaviours. The mesolimbic dopamine system is implicated in motivation and the reinforcement of food intake, and it can be delicately tuned in response to insulin. Studies have demonstrated differential effects of insulin in the ventral tegmental area (VTA) compared to the nucleus accumbens (NAc). This review summarizes current findings and discusses possible explanations for the discrepancies of insulin effects on the VTA and NAc in the normal and insulin resistant conditions.

1. Introduction

In addition to sensing and responding to changes in energy needs, food-seeking requires the encoding of environmental cues that predict the quality and availability of food as well as the motivation to obtain food. The ventral tegmental area (VTA) and its projections to the nucleus accumbens (NAc) are an important substrate for motivated behaviour as blockade of dopamine neurotransmission decreases responding for food on effort-based tasks (Nunes et al., 2013) and increased NAc dopamine enhances motivation for food (Pecina et al., 2004; Trifilieff et al., 2013). Furthermore, chemogenetic activation of dopamine neurons using Gq coupled designer receptors exclusively activated by designer drugs (DREADD) in the VTA, but not in the substantia nigra of TH:Cre rats selectively increased performance on a progressive ratio task for sucrose (Boekhoudt et al., 2018). It has been proposed that dopamine in the NAc provides a cost-benefit signal that translates incentive motivation into physical effort for food reward (Hamid et al., 2016; Salamone and Correa, 2012; Walton and Bouret, 2019). The excitatory neurotransmitter glutamate and the ability of glutamate receptors to undergo long-term synaptic changes play a central role in modulating the activity of dopamine neurons, such that long term potentiation (LTP) and long term depression (LTD) have been identified at excitatory synapses onto dopamine neurons (Bonci and Malenka, 1999; Overton et al., 1999). The strength of excitatory synaptic input onto VTA DA neurons, as well as their activity and output, contribute to reward-related behaviour. Indeed, transient excitatory synaptic plasticity onto dopamine neurons is required for learning of food-predictive cues (Chen et al., 2008; Stuber et al., 2008). Conversely, depression of excitatory synaptic transmission can reduce the intrinsic firing rate and excitability (Canavier and Landry, 2006), and likely reduces salience of reward predicting cues.

Multiple forms of LTD and LTP have been identified in the NAc. While LTD in the NAc is not modulated by dopamine (Kombian and Malenka, 1994; Manzoni et al., 1997; Pennartz et al., 1993), LTP can be modulated by dopamine under certain circumstances (Goto and Grace, 2005; Schotanus and Chergui, 2008). Interfering with excitatory synaptic transmission in the NAc decreases reward-seeking behaviour, including sensitized responding to drugs of abuse (Pierce et al., 1996; Vanderschuren and Kalivas, 2000) or natural rewards (Pitchers et al., 2010, 2012) as well as craving (Conrad et al., 2008) and relapse (Cornish and Kalivas, 2000). Notably, incubation of drug craving requires increased calcium-permeable (CP) AMPA receptor expression on medium spiny neurons (MSNs) of the NAc (Conrad et al., 2008). In contrast, the role of CP-AMPA receptors on MSNs is less clear in food-seeking. Immediately after sucrose seeking different studies have observed increases in AMPA receptors (Tukey et al., 2013), or no effect (Counotte et al., 2014; Dingess et al., 2017). A few weeks after sucrose or high fat seeking, incubation of food craving co-occurs with either decreased AMPA receptor expression (Counotte et al., 2014), no change (Tukey et al., 2013) or a rearrangement in AMPA receptor subunit composition (Dingess et al., 2017). Taken together, further study is required to fully elucidate how plasticity at excitatory synapses in the

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NAc may be associated with food craving.

Circulating peptides or hormones released in response to internal states, such as hunger or satiety, can promote or inhibit food intake respectively. The mesolimbic system is highly sensitive to peripheral metabolic factors that signal energy availability and may serve to gauge motivated behaviour in response to internal energy state. While ghrelin, leptin, amylin, glucagon-like peptide-1 and others modulate activity of the mesolimbic circuit (reviewed in (Liu and Borgland, 2015), this review is aimed to summarize the findings and discuss current perspectives on how insulin modifies the functions of mesolimbic dopamine circuitry.

1.1. Insulin signaling in the brain

Circulating insulin rises after a meal and promotes glucose utilization by most tissues. Further, insulin is secreted from the pancreas in proportion to the amount of fat in the body and is thus considered an "adiposity" signal to the brain, relaying information about current energy balance (for a review see Woods and Seeley, 2001). The traditional view is that most insulin in the mature brain is transported there from the circulation (reviewed in Banks et al., 2012). Insulin gains access to the brain by a saturable transport process that was originally thought to involve transcytosis of insulin receptors across brain endothelial cells of the blood-brain barrier, similar to transferrin receptors (Banks et al., 1997; Duffy and Pardridge, 1987; Gray et al., 2017). However, recent evidence indicates that insulin can cross the blood brain barrier via non-receptor mediated process, such that peripherally-injected radiolabeled insulin was present in brain tissue of mice lacking insulin receptors on endothelial cells or in mice given the insulin receptor antagonist, S961 (Rhea et al., 2018). Insulin binds to a single-pass (spans the lipid bilayer only one time) tyrosine kinase membrane receptor, resulting in dimerization and activation of its intrinsic kinase domain. The kinase then phosphorylates insulin-receptor substrates (IRS2), which then mediate intracellular signaling cascades and transcription (Banks et al., 2012).

While most insulin in the CNS is derived peripherally, there is some evidence that insulin may also be synthesized in the brain. Early studies using an immunoassay approach suggested that insulin might be synthesized in the developed brain (Dorn et al., 1983). While some have reported that insulin is expressed at 100 times higher in brain than plasma levels (Havrankova et al., 1978), this experiment did not control for potential contamination of concentrated material in the acid/ethanol extraction techniques used to extract insulin from tissues (Eng and Yalow, 1981). Insulin mRNA has been reported in various regions of the brain, such as the olfactory regions, limbic regions, hippocampus and periventricular nucleus hypothalamus (Devaskar et al., 1993, 1994; Mehran et al., 2012). However, it should be noted that some studies used immortalized cell lines (Devaskar et al., 1994) and that the presence of mRNA does not always indicate the presence of functional proteins. Insulin synthesis has been demonstrated in neuroprogenitor cells from adult hippocampus and olfactory bulb (Kuwabara et al., 2011) as well as olfactory mucosa cells (Lacroix et al., 2008). Furthermore, functional evidence indicates that cortical GABAergic neurogliaform cells express insulin mRNA and can contribute to local insulin release in conditions when pancreatic insulin supply does not match demand and may modulate GABAergic effects in the cortex (Molnár et al., 2014). Therefore, in addition to circulating pancreatic insulin gaining access to the brain, insulin may also be synthesized in select neuronal populations although this idea remains somewhat controversial (see Figlewicz, 2003) and requires further study.

2. Cellular effects of insulin in the VTA

Insulin receptors, in addition to the intracellular substrates of insulin receptor activation, IRS2 and phosphatidylinositol (3,4,5)-trisphosphate (PIP3), are expressed on dopamine neurons of the VTA and substantia nigra (SNc) (Figlewicz et al., 2003; Liu et al., 2013; Pardini et al., 2006). Insulin increases phosphoinositol-3 kinase (PI3K) signaling (Mebel et al., 2012) and PIP3-immunoreactivity in the VTA (Figlewicz et al., 2003). Application of insulin (200 nM) to midbrain slices increases the firing rate of SNc neurons in half of dopaminergic neurons recorded. This effect is absent in mice lacking insulin receptors in tyrosine hydroxylase (TH) expressing neurons (Könner et al., 2011). While a mechanism has not been identified, one possibility may be due to insulin-induced PI3K activation (Carvelli et al., 2002; Garcia et al., 2005; Simon et al., 1997), and subsequent inhibition of A-type potassium channels leading to increased excitability as can occur with insulin-like growth factor on trigeminal neurons (Wang et al., 2014). VTA dopamine neurons are heterogeneous with respect to their molecular identity as well as their afferents and efferents (Lammel et al., 2008; Morales and Margolis, 2017). Therefore, future studies should assess if insulin modulates subpopulations of dopamine neurons depending on their projection targets.

Insulin also depresses excitatory synaptic transmission onto dopamine neurons at concentrations as low as 1–10 nM (Labouèbe et al., 2013). Insulin-induced LTD at excitatory synapses has been reported in other brain regions including the hippocampus (Man et al., 2000) and cerebellum (Wang and Linden, 2000), mediated by insulin-induced internalization of AMPA receptors. In contrast, insulin-induced LTD in the VTA occurs via activation of the Akt/mTOR signaling pathway and retrograde endocannabinoid signaling. This effect is selective to excitatory synapses as insulin did not alter GABAergic synaptic transmission on to VTA dopamine neurons (Labouèbe et al., 2013). Insulin-induced LTD is occluded during elevated plasma insulin levels post feeding (Labouèbe et al., 2013; Liu et al., 2016) or in a mouse model of hyperinsulinemia, even though both low-frequency stimulation-induced LTD and cannabinoid-induced LTD are unaffected, suggesting the disruption may be due to insulin resistance (Liu et al., 2013).

Excitatory inputs to the VTA promote burst firing activity of dopaminergic neurons (Grace and Bunney, 1984; Johnson et al., 1992). Midbrain dopamine neurons fire in a slow irregular fashion resulting in tonic release of dopamine. However, in response to salient environmental stimuli, spikes of dopamine neurons are clustered into bursts and the increase in extracellular dopamine in the projection areas is much larger than that observed for regularly spaced trains of action potential at the same frequency (Grace and Bunney, 1984; Overton and Clark, 1997). Transient increases in dopamine release enhance (or highlight) salient environmental signals while suppressing irrelevant signals, helping the animal pay attention to the environment and respond appropriately (Overton and Clark, 1997; Roitman et al., 2004). Thus, dopamine neuronal excitability states have profound effects on forebrain targets, such as the nucleus accumbens, to facilitate the expression of behaviours related to motivation. Because insulin suppresses excitatory inputs to the VTA yet increases firing rate, it is possible that insulin may have differential action on tonic versus burst firing in the VTA, such that tonic dopamine release may be increased whereas the ability to induce phasic bursts is suppressed. Presumably, the consequence of suppressed phasic burst firing is a decrease food-seeking behaviour (Roitman et al., 2004). Intra-VTA insulin effects on food seeking are discussed below.

2.1. Effect of insulin in the VTA on dopamine transporters and dopamine release

Insulin in the VTA can influence activity of dopamine transporters (DAT). Chronic intracerebroventricular injection of insulin (5 mU) elevates DAT mRNA in the VTA (Figlewicz et al., 1994). Furthermore, acute application of insulin to midbrain slices containing the VTA decreases somatodendritic dopamine concentration (Mebel et al., 2012) with an IC_{50} of 60 nM. This effect requires PI3K activation and increased trafficking of DAT, resulting in increased dopamine reuptake (Mebel et al., 2012). In mice lacking insulin receptors in TH-expressing

neurons (Könner et al., 2011) or in rats treated with streptozocin to destroy insulin secreting pancreatic beta cells (Figlewicz et al., 1996), midbrain TH mRNA expression is reduced. With streptozocin-treatment, the effects of altered peripheral glucose levels cannot be negated. This suggests that insulin receptor activation not only plays a role in modulating expression of DAT, but also TH.

While insulin decreases somatodendritic dopamine due to upregulation of DAT (Mebel et al., 2012), recent work indicates that intra-VTA insulin (1 or 100 nM) can suppress pedunculopontine nucleus (PPTg) -evoked dopamine in the NAc (Naef et al., 2018). This effect was blocked by intra-VTA S961 (Naef et al., 2018), implicating insulin receptor signaling in the VTA. Unlike stimulation of the medial forebrain bundle or the VTA, which directly evokes NAc dopamine release, stimulation of the PPTg induces burst firing of dopamine neurons (Floresco et al., 2003; Zweifel et al., 2009) to evoke NAc dopamine release. Therefore, intra-VTA suppression of NAc dopamine may require burst firing of dopamine neurons and insulin may act by inhibiting PPTg-evoked glutamate release. Because insulin suppresses presynaptic glutamate release onto VTA dopamine neurons (Labouèbe et al., 2013), one can speculate that decreased glutamate release probability of PPTg inputs to the VTA may result in decreased phasic dopamine release. This mechanism would likely fit with the long-lasting time course of insulin-induced suppression of dopamine release, such that the effect continues long after the likely metabolism or diffusion of insulin in the VTA.

2.2. Effects of insulin in the VTA on ingestive behaviour

Several lines of evidence indicate that insulin action in the VTA suppresses ingestive behaviour. While intra-VTA insulin (5 mU) infusion has no effect on short term (24 h) body weight and modest inhibitory effects on short-term feeding (Bruijnzeel et al., 2011), selective inactivation of insulin receptors in VTA/SN DA neurons ($IR^{\Delta Th}$ mice) increases body weight, fat mass and food intake (Könner et al., 2011). The VTA was the only sensitive site for insulin (5 mU) to block opioid-stimulated sucrose intake (Figlewicz et al., 2008), a model of hedonic feeding (Badiani et al., 1995). Consistent with this, intra-VTA insulin (0.3 μg) did not alter regular chow intake during the first hour or over a 4 h period, but decreased high-fat chow intake after mice were sated (Mebel et al., 2012). Infusion of a low dose of insulin into the VTA (15 ng) can increase the threshold for intracranial self-stimulation, suggesting decreased reward (Bruijnzeel et al., 2011). Thus, insulin in the VTA may decrease hedonic aspects of food intake.

Insulin in the VTA (5 mU) suppresses salience for food related contextual cues. While intra-VTA insulin does not alter effort for palatable food on a progressive ratio schedule (Labouèbe et al., 2013), intra-VTA insulin decreases food anticipatory behaviours and conditioned place preference for food (Labouèbe et al., 2013), suggesting that different aspects of food seeking are dissociable. These experiments were performed without food restriction, suggesting that insulin's effects on food seeking behaviour occur in positive energy balance. Consistent with this, intra-VTA insulin did not suppress food intake at the beginning of entrained feeding when animals were hungry, but suppressed food intake when animals were sated (Mebel et al., 2012). Thus, insulin may serve as a signal of high energy status in the VTA, and therefore reduce salience of food cues or the hedonic aspects of food intake when animals have replenished energy balance.

Palatable, energy dense food exposure over 24 h induces a food priming effect, such that even 2 days after food exposure, mice have increased food seeking (Liu et al., 2016). Immediately after palatable food consumption, plasma insulin levels are high and food approach behaviours are decreased. This decrease in food approach behaviours can be blocked by intra-VTA administration of an insulin receptor antagonist or by streptozocin inhibition of insulin release (Liu et al., 2016). Increased food approach behaviours were associated with increased number of excitatory, but not inhibitory, synapses onto VTA dopamine neurons leading to increased glutamate release lasting at least a week (Liu et al., 2016). Insulin (5 mU) suppressed the enhanced excitatory synaptic transmission as well as increased food approach behaviour 2 days after palatable food exposure (Liu et al., 2016). Thus, insulin in the brain may prove useful in decreasing food priming responses or food craving.

2.3. Effects of insulin in the VTA on drug-related behaviours

Chronic food restriction has historically been used to increase the rewarding, locomotor and motivating effects of food or drug seeking in a variety of models (reviewed in Carr, 2002; Carroll and Meisch, 1984). Food restriction decreases circulating insulin and leptin. Given that receptors for leptin and insulin are expressed on mesolimbic circuits underlying reward-seeking behaviour (Figlewicz et al., 2003), it has been proposed that low levels of these hormones might be associated with increased reward-seeking and higher levels of insulin or leptin, which reflect a positive energy balance, might suppress motivational drive to consume reinforcing substances (reviewed in Figlewicz and Benoit, 2009). In the context of survival, it is not surprising that circuits underlying the drive for motivated food-seeking are highly sensitive to low energy balance and that drugs of abuse can usurp this circuit to promote drug-seeking behaviour.

The psychostimulant drug, cocaine, induces its locomotor-activating and reinforcing effects by increasing NAc dopamine concentration (Di Chiara and Imperato, 1988). Because intra-VTA insulin can suppress dopamine in the NAc and suppress cocaine-evoked dopamine release (Naef et al., 2018), it was proposed that intra-VTA insulin might decrease cocaine-evoked locomotor activity. Indeed, intra-VTA insulin (100 nM) in the VTA remarkably decreased behavioural responsiveness to cocaine in mice (Labouebe, Liu et al., 2013) and rats (Naef et al., 2018). Intranasal insulin (5 μg/μl) also decreased cocaine-induced locomotor activity (Naef et al., 2018), an effect reversed by intra-VTA S961. In contrast, cocaine-induced locomotor activity is not changed after intra-NAc insulin treatment (Schoffelmeer et al., 2011). Intra-VTA insulin suppression of cocaine-induced locomotor activity involves insulin receptors and one of its substrate, IRS-2. Enhanced cocaine-induced locomotor activity was observed in rodents with IRS-2 overexpression, while blunted behavioural responses to cocaine in animals with IRS-2 deficiency or insulin receptor deletion in TH-expressing neurons (Iñiguez et al., 2008; Könner et al., 2011). Together, these results demonstrate that insulin signaling in the VTA can suppress cocaine-induced locomotor responses. Future experiments should test how intra-VTA or intra-nasal insulin can influence other drug-seeking behaviours.

3. Cellular effects of insulin in the NAc

The NAc is primarily comprised of principal GABAergic medium spiny neurons (MSNs), while the remaining neurons are cholinergic tonically active neurons expressing choline acetyltransferase (ChAT) or GABAergic interneurons expressing parvalbumin, somatostatin/nitric oxide synthetase-1, or the calcium binding protein calretinin (Wilson, 2007). Insulin receptors are also expressed in the NAc (Kar et al., 1993). Insulin (30 nM) increases the firing rate of cholinergic neurons in the NAc, an effect blocked by intracellular application of HNMPA, an insulin receptor tyrosine kinase inhibitor (Stouffer et al., 2015). This suggests that insulin receptors are expressed on NAc cholinergic neurons and is consistent with insulin receptor immunoreactivity with ChAT-expression (Stouffer et al., 2015). Insulin can also bidirectionally modulate synaptic transmission onto MSN neurons. At low concentrations (10–30 nM), insulin increases excitatory synaptic transmission in the NAc core, an effect blocked by intracellular application of HNMPA suggesting that insulin receptors are also expressed on

MSNs (Oginsky et al., 2019). Insulin (30 nM) increased mEPSC frequency onto MSNs without changing mEPSC amplitude, implicating a presynaptic effect. However, at higher concentrations (100–500 nM), insulin suppresses evoked excitatory synaptic transmission onto MSNs via activation of insulin growth factor 1 (IGF1) receptors (Oginsky et al., 2019). This effect was likely mediated presynaptically as insulin decreased mEPSCs frequency and induced a paired-pulse facilitation. This effect was also blocked by an IGF1 receptor antagonist (Oginsky et al., 2019). Interestingly, insulin-mediated potentiation of excitatory synaptic transmission onto MSNs did not occur in obese animals, whereas IGF1 receptor-mediated suppression of excitatory synaptic transmission is intact (Oginsky et al., 2019). Taken together, physiologically relevant insulin concentrations can increase excitatory input onto MSNs.

Insulin receptors are expressed not only on neurons, but also on glial cells in the NAc (Cai et al., 2018). Loss of insulin receptors in primary astrocyte cultures also had a decrease in expression of GFAP, aquaporin 4, aldolase C, glutamine synthetase and glutamate transporter 1, with an increase in expression of ApoE (Cai et al., 2018), indicating that insulin receptors are important in regulating expression of other astrocyte markers. Furthermore, insulin receptors stimulate ATP release from astrocytes (Cai et al., 2018). Disrupted insulin signaling in NAc astrocytes reduced Munc18c phosphorylation and SNARE-dependent ATP exocytosis, which in turn decreased dopamine release and modulation of MSN activity (Cai et al., 2018). In addition to modulation of dopamine release, insulin-dependent astrocytic ATP exocytosis may also modulate other transmitter system in the NAc, which may need further investigation.

3.1. Insulin effects on dopamine release in the NAc

Insulin can indirectly modulate dopamine release in the NAc. As described above, insulin receptor activation on astrocytes increases ATP release and purinergic modulation of dopaminergic terminals to increase dopamine release in the NAc (Cai et al., 2018). Consistent with these findings, Stouffer et al. found that insulin (30 nM) increased dopamine release using voltammetry in striatal brain slices (Stouffer et al., 2015). However, the mechanism required insulin-mediated increased cholinergic activity at dopamine terminals rather than astrocytic ATP–induced dopamine release (Stouffer et al., 2015). Further studies should test if insulin-mediated purinergic and cholinergic induced release are synergistic or additive.

In contrast to insulin-mediated enhancement of striatal dopamine release, insulin can upregulate DAT in the striatum (Patterson et al., 1998; Speed et al., 2011; Williams et al., 2007). Application of insulin (1 μM) to DAT expressing HEK293 cells increased surface expression of DAT as well as dopamine reuptake via an Akt- and PI3K-dependent mechanism (Garcia et al., 2005). Furthermore, insulin (10 nM) application to NAc slices decreased electrically evoked tritiated dopamine release as well as cocaine-evoked dopamine release (Schoffelmeer et al., 2011). Patterson and co-workers used food deprivation as a model to decrease plasma insulin levels in rats and found decreased dopamine uptake in striatal synaptosome suspensions that was restored by direct in vitro insulin (1 nM) application (Patterson et al., 1998). Consistent with this, streptozocin-treated rats had decreased dopamine clearance (Owens et al., 2005) and decreased DAT surface expression in the striatum of hypoinsulinemic rats, an effect that could be reversed by striatal insulin (100 μM/100 nl) replacement (Williams et al., 2007).

Data indicating insulin-induced increase DAT function resulting in increased dopamine reuptake appear to be at odds with that supporting an insulin-induced increase in dopamine release. It is possible that insulin modulation of dopamine release can outweigh effects of insulin on dopamine reuptake at transporters. Indeed, in the same system, insulin (30 nM) in the NAc shell increased the maximal rate of reuptake (Vmax) by 20%, but insulin-induced dopamine release was increased by 60% (Stouffer et al., 2015), suggesting that the releasing effects of insulin at dopamine terminals outweigh those at transporters.

A high fat diet can also influence the ability of insulin to modulate dopamine release. Similar to the loss of effects of insulin on modulation of excitatory synaptic transmission onto NAc MSNs of obese rats (Oginsky et al., 2019), insulin no longer increased dopamine release in the striatum (Stouffer et al., 2015). In support of these findings, mice fed a high fat diet for 6 weeks had systemic insulin resistance that correlated with deficits in DAT function, such that the maximal rate of dopamine reuptake was less in high fat fed mice (Fordahl and Jones, 2017). The effects of insulin on dopamine release were also abolished in the high fat fed mice due to a reduction in insulin receptor function (Fordahl and Jones, 2017). To sensitize the insulin signaling pathway, the investigators used a protein tyrosine phosphatase 1B inhibitor which restored the insulin-mediated increase in dopamine release (Fordahl and Jones, 2017). Taken together, high fat diet associated hyperinsulinemia desensitizes insulin receptors, which impairs insulin effects at dopamine release sites.

3.2. Effects of insulin in the NAc on ingestive behaviours

Because insulin increases dopamine release in the NAc, it has been proposed that insulin may mediate reward-seeking behaviours. Indeed, insulin antibodies administered to the NAc shell decreases preference for a flavor paired with sucrose, suggesting that insulin in the NAc reinforces preference for flavor stimuli that signals glycemic load (Stouffer et al., 2015). Supporting this, intragastric or oral glucose increases phosphorylation of insulin receptors as well as Akt and GluA1 AMPA receptor subunits in the NAc within 7 min after administration (Woods et al., 2016). Rodents with blocked NAc insulin receptor signaling during conditioning to flavors predicting sucrose concentration failed to acquire and express a preference for sucrose-predicting flavors (Woods et al., 2016), suggesting that insulin receptors in the NAc are signaling energy availability. Interestingly, this effect was gone in obese rodents (Woods et al., 2016). This may suggest that individuals with insulin insensitivity may inappropriately assess nutritive value.

3.3. Effect of insulin in the NAc on drug-related behaviours

Insulin (2 μM) administered to the NAc reduced premature responding in the 5-choice serial reaction time task, suggesting that insulin may reduce impulsive responding in this task (Schoffelmeer et al., 2011). However, NAc insulin had the opposite effect in the presence of cocaine, such that premature responses increased in the insulin and cocaine condition. This was not due to hyperactivity, as insulin in the NAc did not alter locomotor activity (Schoffelmeer et al., 2011). Because insulin increases DAT cell surface expression, the effects of amphetamine induced dopamine efflux are altered in the NAc (Owens et al., 2005). Insulin signaling via insulin receptors and PI3K works in tandem with dopamine signaling at D2 receptors to regulate DAT expression and function and therefore influence amphetamine-stimulated locomotor activity (Owens et al., 2005; Sevak et al., 2008).

3.4. Reconciling opposing effects of insulin in the VTA vs NAc

Insulin has opposing effects on dopamine in somatodendrites compared to terminal release. Application of insulin to striatal slices increases terminal dopamine concentration via action at insulin receptors on cholinergic interneurons to promote dopamine release (Stouffer et al., 2015). In the VTA, insulin reduces somatodendritic dopamine concentration by upregulating dopamine

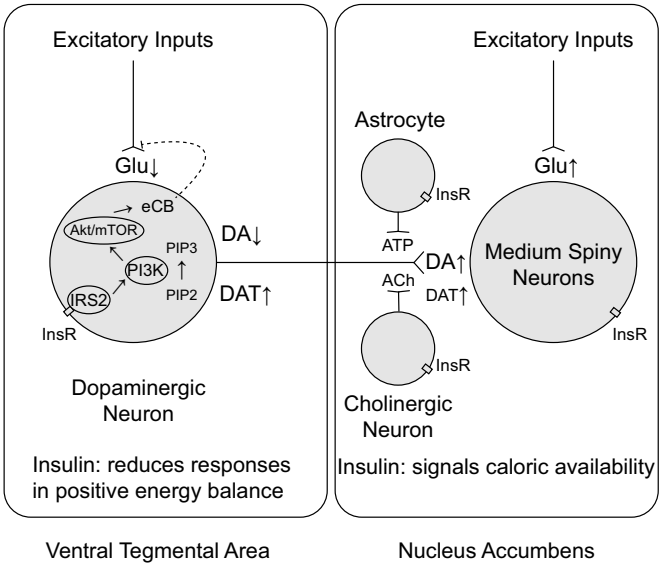

Fig. 1. Cellular effects of insulin in the VTA and NAc. Insulin in the VTA decreases efficacy excitatory inputs onto dopamine neurons and decreases somatodendritic dopamine. Insulin in the NAc increases excitatory synaptic transmission onto MSNs, increases firing of cholinergic interneurons and increases terminal DA release onto MSNs.

transporters (Mebel et al., 2012), an effect that has also been demonstrated in the striatum (Patterson et al., 1998; Speed et al., 2011; Williams et al., 2007). Insulin (1–100 nM) in the VTA suppresses PPTg-evoked dopamine release in the NAc reaching a maximal effect 30 min after delivery (Naef et al., 2018). Furthermore, CSF-administered insulin (4 mU/μl) initially increases dopamine release in the NAc, but after 30 min suppressed dopamine concentration measured with push-pull perfusion techniques (McCaleb and Myers, 1979). Systemically administered insulin at high concentrations (400–600 mU) increased NAc dopamine outflow (Potter et al., 1999), however this effect was likely due to a significant disruption in peripheral glucose homeostasis, an effect known to increase dopamine release (Carr et al., 2003). Taken together, the time course is important for how insulin may modulate dopamine in the mesolimbic circuit, such that there may be short term increases in NAc dopamine and then a suppression of dopamine concentration 30 min after insulin exposure.

Insulin has opposing effects on excitatory synaptic transmission in the VTA and NAc (Fig. 1). Insulin (10–500 nM) in the VTA induced an LTD (Labouèbe et al., 2013), whereas insulin (10–30 nM) in the NAc increases excitatory synaptic transmission (Oginsky et al., 2019). Similar to effects of insulin on dopamine concentration, the time course may be important. While the potentiation of mEPSCs occurred rapidly after insulin application to NAc slices, the insulin-induced LTD in the VTA was greatest 15–25 min after insulin application. These effects may be due to differences in perfusion rates on the slices. Alternatively, these processes may underlie the biphasic changes in CSF-administered dopamine outflow. Interestingly, in hyperinsulinemic states, the effects of insulin in the VTA or the NAc are abolished (Fordahl and Jones, 2017; Liu et al., 2013; Oginsky et al., 2019; Stouffer et al., 2015), suggesting that insulin receptors in the VTA and the NAc can be desensitized during hyperinsulinemia.

Insulin infused into the VTA decreased food anticipatory behaviours, preference for contextual food cues(Labouèbe et al., 2013), food priming (Liu et al., 2016), and sucrose self-administration (Figlewicz et al., 2008). In contrast, blocking the actions of insulin in the NAc decreases preference for a sucrose solution (Stouffer et al., 2015) and impairs conditioning of flavors predicting energy density (Woods et al., 2016). Notably, intra-ventricular insulin suppresses sucrose self-administration (Figlewicz et al., 2006). Thus intra-VTA insulin may provide a satiety signal to indicate meal termination, while intra-NAc insulin may signal the availability of energy density. Consistent the time course of effects of insulin on dopamine release, one may speculate that early in a feeding bout, factors such as energy availability may drive an animal to continue eating. Low levels of brain insulin early in the feeding bout may signal energy availability and contribute to enhanced feeding. However, 30–60 min past the onset of a feeding bout, with sufficient food ingested, brain insulin levels may be sufficiently high to decrease feeding or food approach behaviours.

In humans, intranasal insulin can modulate resting state imaging of activity in brain regions involved in reward processing (Heni et al., 2016; Kullmann et al., 2013) and attenuates visual processing of food images (Guthoff et al., 2010). Intranasal insulin administration can access deeper brain parenchema via several pathways including the olfactory- and trigeminal-associated extracellular pathways, the cerebrospinal fluid and the perivascular pathway, however does not alter peripheral glucose sensitivity (Dhuria et al., 2010). In individuals with normal peripheral insulin sensitivity, intranasal insulin decreased food palatability ratings while the valuation of non-food related stimuli remained unchanged (Tiedemann et al., 2017). Reduced food palatability ratings were directly correlated with decreased food value signals in the VTA and NAc (Tiedemann et al., 2017). Taken together, similar to rodent experiments, intranasally administered insulin suppresses food valuation and food-related activation of the mesolimbic pathway.

Because postprandial insulin decreases dopaminergic output from the VTA, but increases dopamine release at terminals, insulin resistance likely impairs dopamine responses in each region in response to a meal. Impaired dopamine uptake was also observed in rodents without diet induced obesity after 6-week high fat food treatment (Cone et al., 2013), or in obese rodent (Fordahl and Jones, 2017). This effect is reversed with intra-NAc insulin (Fordahl and Jones, 2017). Because NAc insulin signals energy availability, it is possible that in the obese state, there is a failure to appropriately register and respond to glycemic load resulting in enhanced food consumption.

4. Conclusions

It must be noted in that many of the studies described, exogenous insulin was applied at saturating concentrations at its receptors given that the affinity of insulin for its receptors is approximately 1 nM (or 14.3 μU/ml), although this will vary in different tissues and which insulin receptor isoforms are expressed (Boucher et al., 2014). Furthermore, binding of insulin to its receptors is complex with co-existence of high- and low-affinity binding sites (De Meyts and Whittaker, 2002). Higher than physiological concentrations are sometimes required as it takes time for insulin to penetrate a slice, in the case of in vitro experiments, or to distribute through a volume of tissue in intra-cranial administrations. Because insulin can act at IGF1-receptors at higher concentrations, it is important to test if observed effects are mediated via IGF receptor signaling (Siddle, 2012). There have been few reports of insulin action at receptors other than insulin, IGF, or peripherally located insulin-related receptors, therefore off target effects of insulin are unlikely.

Mesolimbic dopamine system plays a critical role in the reinforcing and motivating aspects of food intake. A growing body of literature has shown that insulin can act on mesolimbic system to influence dopaminergic signaling and alter feeding behaviours. Insulin in the VTA suppresses contextual cue related feeding behaviours by selectively inhibiting excitatory inputs onto dopamine neurons and elevating somatodendritic dopamine clearance, while insulin in the NAc enhances dopamine release and DAT activity by acting on cholinergic interneurons and astrocytes (Table 1). While the opposing effects of insulin

Table 1
Cellular and behavioural effects of insulin in the mesolimbic dopamine circuit.

Insulin effects		VTA	NAc
Cellular	Receptor expression	DA neurons	Cholinergic neurons/ MSNs / Glial cells
	Excitatory transmission	mEPSCs ↓	mEPSCs ↑
Dopamine release		Somatodendritic ↓	Terminal ↑
Dopamine transporter		DAT ↑	DAT ↑
Ingestive behaviours		Hedonic feeding ↓	Reward seeking ↑
		Salience of food cue ↓	Impulsivity ↓
		Food priming/craving ↓	
Drug-related behaviours		Cocaine induced locomotion ↓	Cocaine induced locomotion?
			Cocaine induced impulsivity ↑

↑: increase; —: no change; ↓: decrease.

in the VTA and NAc are not fully understood, it is likely that insulin actions on dopamine dynamics are brain region specific to optimize the animal's response to the external environment and internal energy status. When an animal is sated, insulin in the VTA reduces immediate food value by switching neuronal firing patterns, while insulin in the NAc induces astrocytic ATP exocytosis to indicate current energy increment and increases dopamine release in response to the reinforcement of energy-rich foods. Therefore, insulin may act in the mesolimbic dopamine system to convey energy status and thus appropriately reinforce energy-rich foods and post-prandially decrease salience of food-related cues. Deciphering the discrete roles of insulin in the mesolimbic dopamine system would be of importance for developing more efficient therapeutic strategies for metabolic syndromes, substance use disorder and eating disorders.

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