

REVIEW ARTICLE

Potential role of insulin on the pathogenesis of depression

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Abstract

The regulation of insulin on depression and depression-like behaviour has been widely reported. Insulin and activation of its receptor can promote learning and memory, affect the hypothalamic-pituitary-adrenal axis (HPA) balance, regulate the secretion of neurotrophic factors and neurotransmitters, interact with gastrointestinal microbiome, exert neuroprotective effects and have an impact on depression. However, the role of insulin on depression remains largely unclear. Therefore, in this review, we summarized the potential role of insulin on depression. It may provide new insight for clarifying role of insulin on the pathogenesis of depression.

1 | INTRODUCTION

Diabetes is a metabolic disease characterized by hyperglycaemia due to the defect of insulin secretion or impaired insulin biological effect. A survey has shown that about 30% of people with diabetes also suffer from depression and 10% have severe depression, which suggests a close relationship between the two diseases.^{1,2} The mechanism of depression as a complication of diabetes is not completely clear, but studies have found that insulin deficiency or insulin resistance is the symptom that can also be observed in major depression disorder.³⁻⁵

Insulin is the only hormone in the human body that reduces the blood glucose level and promotes the synthesis of glycogen, fat and protein. Several studies found that insulin had the ability to affect the nervous system.⁶⁻⁸ Insulin receptors were distributed in other parts of the brain, except for the parts related to food intake and energy.⁹⁻¹¹ Experiments have gradually revealed other functions of insulin in the brain, for instance promoting memory, protecting neurons, regulating synaptic plasticity and maintaining HPA axis homeostasis.¹²⁻¹⁴ These effects of insulin may provide a background for its relationship with depression.^{15,16}

In this case, although there is no direct evidence supporting the link between insulin and treatment for depression, more and more researches support this hypothesis. Here, we review the relationship between insulin signalling and neurophysiological homeostasis, neurotrophic metabolism, cellular pathways and some survey statistics. The exploration of these links and the validation of more relevant mechanisms will develop a new impact on the way of the diagnosis and treatment of depression.

2 | INSULIN AND DEPRESSION

As early as 1980s, many evidences proved that insulin influenced depression and functional insulin receptors were widely present in the brain.¹⁷⁻¹⁹ Data from clinical and epidemiological studies demonstrate a two-way link between emotion and metabolic dysfunction. In young depression patients, insulin sensitivity is significantly decreased.^{20,21} Compared with "low insulin" (1.5 mU/kg × min), "high insulin" (15 mU/kg × min) induces a more pronounced of the ability to remember word lists in human being.²² Intranasal delivery of insulin in awake mice can transmit regulatory and metabolic

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hormones across the blood-brain barrier (BBB), significantly improve memory and downgrade anxiety levels in rats. Moreover, the insulin spray enters the nasal cavity through passages in the cribriform plate, thus olfactory bulb is the first region in the brain that receives insulin stimulation. Insulin does not cause damage to the olfactory neuroepithelium, nor does it affect the density and quantity of the olfactory nerve.²³ In human experiments, the use of insulin for intranasal treatment of patients with impaired memory is benefit to their memory without altering their peripheral blood glucose and insulin levels.^{24,25}

In addition to the direct effect of insulin on the nervous system, in recent years, some findings suggested that the association was related to the reduction of insulin receptor or the activity of receptor (ie, insulin resistance) in brain,²⁶⁻²⁸ and the insulin resistance was positively associated with depression.⁵ Long-term feeding of high-fat diet induces peripheral insulin resistance. The CA1 hippocampus of the peripheral insulin resistance is taken out for extracellular recording, and it is found that neuronal insulin resistance occurred here. At the same time, the levels of the neuronal insulin receptor, insulin receptor substrate 1 (IRSs) and phosphorylation protein kinase B (Akt) are reduced, which in turn leads to neuronal stress (increased neurocortical hormone).²⁹ Overnutrition and diabetes can selectively cause insulin resistance in different parts of the brain, disrupt homeostasis, affect the normal function of the brain and increase depression disease progression.³⁰

In the hypothalamic insulin receptor expression downregulation rat model constructed using a lentiviral vector,³¹ phosphorylation of Ser845 (Serine 845 of 3-hydroxy-5-methylisoxazole-4-propionic acid Receptor 1) was significantly reduced in rats. Phosphorylation of Ser845 is important for activity-dependent trafficking of 3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor glutamate receptor 1 (GluR1) to extrasynaptic sites for subsequent delivery to synapses during long-term potentiation (LTP) and is a "start" step of LTP by promoting expression of AMPA receptors at

extrasynaptic sites. Insulin regulates surface transport and phosphorylation of AMPA receptors to enhance synaptic transmission in LTP and increasing the extrasynaptic pool of AMPA receptors resulted in stronger LTP.^{32,33} At the same time, the activation of AMPA receptors leads to Ca^{2+} flood into the neurons, which mediates upregulation of mTOR and brain-derived neurotrophic factor (BDNF) and produces antidepressant effects,³⁴ on the other hand it subsequently produces NO. NO reduces intracellular ATP levels by inhibiting the mitochondrial respiratory chain, leading to neuronal dysfunction³⁵ (Figure 1).

Selective downregulation of the hypothalamic insulin receptor was responsible for LTP deficiency in the CA1 region of the hippocampus, which also impaired synaptic plasticity in the hippocampus.³⁶ At the same time, the levels of BDNF in hippocampus and amygdala were decreased (Figure 1). In behavioural experiments, the fixed time of Hypo-IRAS rats increased significantly, the activity of forced swimming experiment decreased correspondingly, the sucrose intake of the sucrose preference test decreased, and the anxiety behaviour increased in the labyrinth test.^{36,37} Overall, these data support the hypothesis that downregulation or inactivation of insulin receptors increases the risk of mood disorders. Insufficient insulin receptor signalling may be a contributing factor to the development of depression. After using insulin sensitizers to alleviate insulin resistance, the depressive behaviour of obese animals was alleviated.^{38,39} However, in recent years, experiments have also shown that insulin receptor knockout has no effect on hedonic and anxiety behaviour in mice. The reason may due to the occurrence of compensatory.⁴⁰

As the only hormone in the body that lowers blood glucose, in addition to its receptor, the hypoglycaemic effect of insulin is closely related to its influence on the nervous system. There have been experiments showing that major depression is associated with glucose/insulin metabolism.⁴¹ Studies have continued to monitor blood glucose levels. After continuous subcutaneous insulin injections to control blood glucose, blood glucose levels were found to be

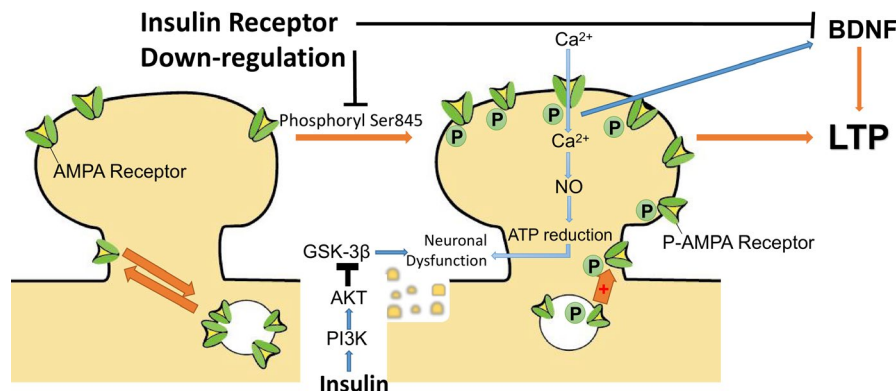


FIGURE 1 In general, phosphorylation of the 3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor Ser845 site and subsequent transfer of the receptor to the extrasynaptic site are the first steps in long-term potentiation (LTP). Phosphorylated AMPA receptors cause Ca^{2+} flow into nerve cells, which on the one hand leads to an increase of brain-derived neurotrophic factor (BDNF) levels and exerts an antidepressant effect, on the other hand leads to an increase of NO levels, decreases ATP levels and impairs neuronal function. Downregulation of the insulin receptor results in downregulation of phosphorylation of Ser845 site and decreases receptors transport, as well as causes decrease in BDNF levels, all of which inhibit LTP. Insulin activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway and inhibits the glycogen synthase kinase 3-beta (GSK-3 β) pathway, thereby inhibiting neuronal dysfunction

significantly related to the “tension” and “hedonic tone” scales. High blood glucose level has a negative impact on mood, and decreases the level of positive emotions and increases the level of negative emotions.⁴² Experiments have also shown that inducing low levels of blood glucose can benefit to human cognitive ability and allows them to remember more words.⁴³

Results measured by Seahorse XF extracellular flux analyzers extend the finding that abnormal glucose metabolism and abnormal mitochondrial function can be observed in patients with depression. High glucose (≥ 10 mmol/L) comparable to diabetic brain extracellular glucose level leads to inactivation of monophosphate-activated protein kinase (AMPK), which causes neuronal mitochondrial dysfunction,⁴⁴ and caused the hexokinase 1 (HK1) attached mitochondrial outer membrane (OMM) reduced HK1, an initial and rate-limiting enzyme of glycolysis. Binding to OMM greatly enhances HK1's own activity, couples cytosolic glycolysis to the function of mitochondrial oxidative phosphorylation and induces cells produce most of adenosine triphosphate (ATP). While powering the brain, it also prevents apoptosis and oxidative damage, protects neurons.⁴⁵ In the case of abnormal mitochondrial function caused by hyperglycaemia, the protection of neurons by HK1 disappears.

Imbalances in brain glucose metabolism often occur in patients with depression.⁴⁶ Glucose is the main energy source of brain cells, and its entry into brain cells is mediated by the glucose transporter (GLUT) family.⁴⁷ In the human brain, glucose transporter 1 (GLUT1) and glucose transporter 3 (GLUT3) are mainly transmembrane glucose transporters. GLUT1 is mainly expressed in endothelial cells and astrocytes, which is essential for brain maturation and normal brain function.⁴⁸ Compared to healthy comparison subjects, DNA methylation of the core promoter regions of GLUT1 was significantly increased in depression patients' brain cells, which reduced the efficiency of GLUT1 absorb glucose from blood vessels to cells, impaired brain metabolism. After treatment of depression patients, DNA methylation of GLUT1 promoter was significantly reduced. This may indicate that the successful treatment of depression is related to the increases of GLUT1.⁴⁹ And insulin could increase the expression of GLUT1 in an AKT-dependent manner and make GLUT have higher glucose transport activity.^{50,51} Acute stimulation with insulin on the plasma membrane of cells increases phosphorylation of AKT protein and levels of GLUT1 protein. Pre-treatment with AKT inhibitors can eliminate these effects. In addition, insulin stimulation did not affect GLUT12 protein levels on the plasma membrane of the cells.⁵¹

In addition to the effects of mitochondria on the nerves, the activation of the insulin-induced phosphoinositide 3-kinase (PI3K)/Akt signalling pathway increases cell viability (including nerve cells). Activation of Akt also results in the inactivation of glycogen synthase kinase 3-beta (GSK-3 β). GSK-3 β regulates mitochondrial biogenesis, bioenergy, permeability and apoptosis. The use of GSK-3 β inhibitors as drugs may be in the treatment of neurological diseases. Inactivation of GSK-3 β prevents nerve cell death^{52,53} (Figure 1).

Collectively, there have been many investigations about the effects of insulin and blood glucose on depression, but the results are not identical. Therefore, more research may be needed.

3 | EFFECT OF INSULIN ON DEPRESSION

3.1 | Insulin affects depression through hypothalamic-pituitary-adrenal axis

Under normal conditions, the negative feedback regulation of the hypothalamic-pituitary-adrenal axis (HPA) process is as follows: the corticotropin-releasing hormone (CRH, also known as CRF) secreted by the hypothalamus activates the CRH1 receptor and induces the secretion of pituitary adrenocortical hormone (ACTH). Then, ACTH causes the adrenal gland to release glucocorticoids (cortisol in humans, corticosterone in rodents) (GC), which activate the glucocorticoid receptor (GR) and mineralocorticoid receptors (MR) to activate the negative feedback loop and restore homeostasis.^{54,55} In major depression, the secretion of CRH is increased, and GC is overproduced, the sensitivity of GR is impaired, HPA negative feedback mechanism is damaged.^{56,57} Studies have been conducted through dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test and insulin resistance evaluated by the homeostasis model assessment of insulin resistance (HOMA-R) to demonstrate that HPA axis dysfunction is associated with insulin in patients with depression.¹⁴ Insulin has a certain degree of influence on hormones involved in HPA negative feedback.⁵⁸

In an *in vitro* study of the mHypoA-2 /12 β hypothalamic cell line, insulin leads to activation of the CRH promoter primarily through activation of the cyclic adenosine monophosphate/AMP protein kinase A (cAMP/ PKA) pathway and the PI3K/ AKT pathway,^{59,60} for CRH promoter contains cAMP response element-binding protein (CREB) binding site that binds to the major transcription factors to stimulate transcription of the CRH gene.^{61,62} After the use of PI3K inhibitors, insulin stimulation is reversed⁶⁰ (Figure 2).

Phosphorylated Akt/CREB and BDNF and other downstream molecules in hippocampal neurons are downregulated when insulin resistance occurs.^{63,64} In addition to affecting the CRF promoter, insulin can also affect the number of CRF neurons.⁶⁰ Three hours after injecting insulin *in vivo*, the presence of CRH neurons increased.⁶⁵ These evidences show the effect of excessive insulin on CRH may indicate its negative impact on depression.^{60,66}

CRF signals also play an important role in the physiological function of insulin. Rats exposed to chronic unpredictable mild stress (CUMS) have upregulated expression of the peptide urocortin 2 associated with corticotropin-releasing factor, increased cAMP production, and cAMP/CREB pathway activates rats arcuate nucleus cells overexpressed factor signalling inhibitor 3 (SOCS3). Then, SOCS3 leads to insulin signalling involving the STAT3 and PI3K-AKT-FOXO1 pathways damaged by inhibiting the activation of insulin receptor substrate 2 (IRS2) and PI3K. Insulin signal returns to normal after using antidepressants.⁶⁷

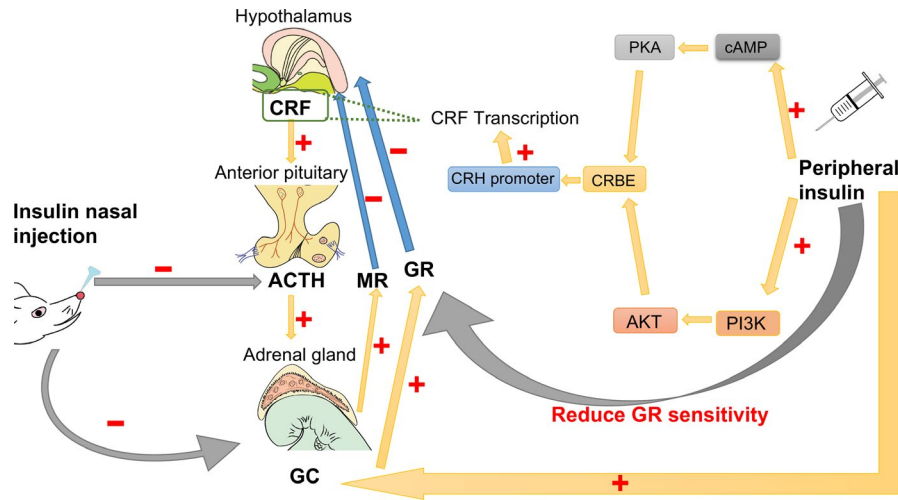


FIGURE 2 Peripheral injection of insulin can increase cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) levels through cAMP/protein kinase A system AMP protein kinase A (PKA) and PI3K/AKT pathways, and then affects corticotropin-releasing hormone (CRF) promoters, stimulates CRF gene transcription and increases CRF levels. At the same time, peripheral injection of insulin leads to an increase in glucocorticoids (GC) levels and a decrease in GC sensitivity. In contrast, insulin injection into the nasal cavity reduces adrenocortical hormone (ACTH) and GC levels

ACTH and GC levels increase after insulin injection at a rate of 1.5 mU/min/kg.⁶⁸ Insulin can acutely enhance the effects of ACTH on androgen and glucocorticoid pathways.⁶⁹ GC, a typical bi-directional hormone that maintains normal physiological functions at normal concentrations, can cause nerve damage under high levels or chronic exposure.⁷⁰ GC is also an important mediator of cognitive deficits caused by diabetes and impaired synaptic plasticity in the hippocampus. Elevated GC levels reduce insulin receptor signalling, including in the brain.⁷¹ The insulin signalling pathway mediates the symptoms of depression caused by GC disorders. Administration of exogenous GC can alter gene expression of insulin, leading to impaired learning and memory function.⁷² Glucocorticoid binds fully to MR and subsequently activates the c-Jun N-terminal kinase (JNK) in the hippocampus, which is associated with insulin receptor-mediated inactivation of the Akt/GSK3b pathway.^{73,74} The Akt/GSK3b pathway is the pathway required to induce long-term potentiation and is the basis of learning and memory. The inactivation of this process leads to depressive symptoms such as decreased cell viability and cognitive deficits.^{74,75} Insulin can also inhibit transient potassium currents by activating PI3K-mediated signalling pathways. However, after GC pre-treatment, insulin's effect on transient potassium channels disappears, leading to excitotoxicity and depression-like behaviour in hippocampal neurons.⁷⁶

After insulin is used to lower blood glucose, mRNA expression of hippocampal mineralocorticoid receptors, which is able to suppress HPA activity, is decreased. However, this condition is limited to normal animals. In animals with congenital hypoglycaemia, MR levels of mRNA remain at baseline levels after insulin administration. This may be because the animal's stress on insulin/glycaemia has disappeared. And not just for MR, in hypoglycaemic animals, insulin-induced activation of GC is higher than normal. With repeated insulin stimulation, the levels of GC no longer changes significantly.^{77,78} This may indicate that one of the mechanisms by which insulin affects the HPA axis is its effect on blood glucose. When insulin does not effectively lower

blood glucose, its effect on the HPA axis is diminished. The effect of insulin on the FKBP5 gene also leads to a decrease in GR sensitivity (Figure 2). FKBP5-encoded protein FKBP51 regulates GR function, reduces GC-GR binding and GR sensitivity, promotes AKT dephosphorylation and downregulates AKT signalling. Overexpression FKBP51 can cause GR to be insensitive, and the GC level is too high.^{79,80} Studies have shown that the expression of the FKBP5 gene is positively correlated with serum insulin and is associated with insulin resistance.^{81,82} This process leads to prolonged activation of the HPA axis, which may be a risk factor associated with depression.

However, the effects on the HPA axis are different by insulin administration via the central or peripheral. Insulin single intranasal injection effectively lowers stress-induced HPA axis responsiveness,⁸³ reduces the levels of ACTH and GC levels and improves the memory and mood⁸⁴ (Figure 2). Insulin is a benefit to the function of hippocampal and amygdala neurons, projecting directly or indirectly to the paraventricular nucleus and peritoneal region of the hypothalamus, inhibiting the HPA axis.^{85,86} After 8 weeks of insulin administration via the nasal cavity, memory was improved and anxiety symptoms were alleviated.²⁵ A decrease in the introversion and anxiety scores, as well as a decrease in depression and anger, confirms that intranasal insulin improves depression. This method does not involve the action of peripheral insulin.^{70,83,84} Interestingly, however, intranasal injection of insulin only reduces the weight of normal-weight men, not the weight of obese men or women. Whether it is related to the sensitivity of insulin receptors in the case of sex hormones and obesity requires more experiments to explore.^{84,87,88}

3.2 | Insulin affects depression through neurotrophic effect

A growing evidence suggests that synaptic plasticity disorders and neuronal atrophy may be the causes of depression, and many

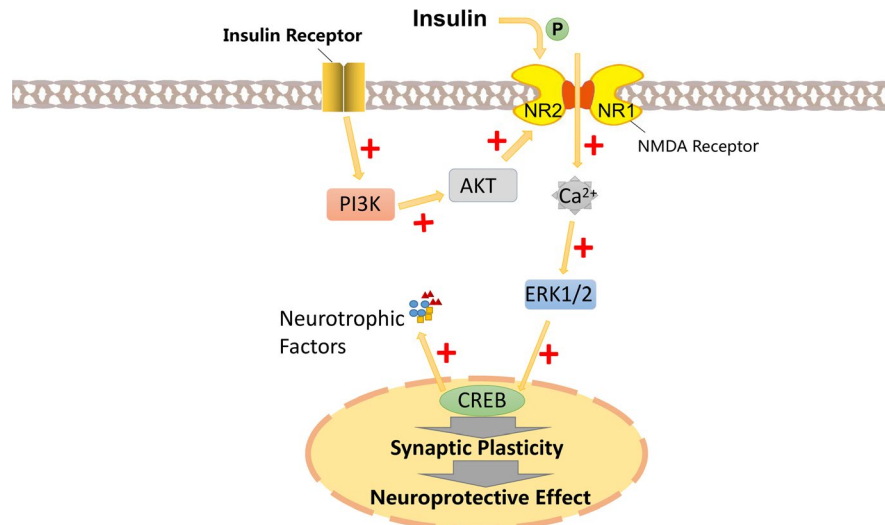


FIGURE 3 Insulin phosphorylates the N-methyl-D-aspartic acid receptor (NMDA) receptor subunit NR2 and enhances NMDA receptor activity. Activation of the NMDA receptor causes Ca^{2+} to enter the cell, and Ca^{2+} induces nuclear signal transduction mediated by extracellular signal-regulated kinase (ERK1/2) and then induces phosphorylation of CREB. At the same time, PI3K/AKT pathway, the downstream of the insulin receptor phosphorylates the NMDA receptor and then activates the CREB pathway to improve synaptic plasticity and promote learning and memory, produce neuroprotective effects, and produce neurotrophic factors

antidepressants (such as ketamine) work by restoring synaptic plasticity and connectivity to key neural circuits.⁸⁹ The mechanism by which insulin improves memory and alleviates depression may be that insulin regulates synaptic plasticity in the hippocampus.^{90,91} It is generally believed that LTP and long-term depression (LTD) are synaptic mechanisms of learning in mammalian brains. Changes in both LTD and LTP may represent changes in synaptic plasticity.⁹² In hippocampal CA1, insulin inhibits the transmission of excitatory synapses and promotes LTP.⁹³ Insulin also regulates the endocytosis of AMPA receptors, which causes LTD of excitatory synaptic transmission.^{90,93,94} After reducing phosphorylation of the insulin receptor, the density of neuronal synapses decreased, the frequency of AMPA receptor minor excitatory post-synaptic current (mEPSC) reduced and the plasticity of experience-dependent dendritic arbour structural altered.⁹⁵

N-methyl-D-aspartic acid (NMDA) not only plays an important physiological role in the development of the nervous system, such as regulating the survival of neurons, promoting the dendrites of neurons, the development of axon structure, but also important in restoring synaptic plasticity. Now, NMDA receptor is an important development direction of antidepressants.⁹⁶ Insulin directly acts on the NMDA receptor, transiently phosphorylates the NMDA receptor subunit NR2 and enhances the current in the receptor to rapidly enhance NMDA receptor activity.^{97,98} Activation of NMDA receptors leads to Ca^{2+} entry into cells, and Ca^{2+} induces extracellular signal-regulated kinase (ERK1/2)-mediated nuclear signal transduction and then induces CREB phosphorylation.⁹⁹ At the same time, PI3K/AKT pathway in insulin downstream phosphorylates the NMDA receptor, then activates the CREB pathway to produce neurotrophic factors, improves synaptic plasticity, promotes learning and memory and produces neuroprotective effects.¹⁰⁰ NMDA mediates insulin-induced LTP and LTD, and this effect is specific. This process

is inhibited after the use of NMDA receptor antagonists. The PI3K pathway plays an important role in this process, PI3K signalling enhances the current in the NMDA receptor, and inhibition of PI3K also prevents LTD.^{98,101} After knocking out the insulin receptor, phosphorylation of the NMDA receptor subunit is reduced, and the downstream target PI3K and Akt are also reduced.^{101,102} In chronic stress-induced mouse models of depression (defined by reduced reward sensitivity), insulin receptor sensitizers restored their normal sugar-water preference and increased subunit expression of NMDA receptors in the hippocampus.¹⁰³ However, studies have also shown that injection of insulin into the lateral ventricle causes LTP deficiency, which indicates that local injection of insulin into the brain has an adverse effect on synaptic plasticity¹⁰⁴ (Figure 3). Discrepancies between different experiments may be the difference of insulin concentration, the difference of measurement time, the difference of experiments conducted in vitro or in vivo, and so on. In conclusion, the role of insulin in synaptic plasticity requires more experiments to explore.

In addition to regulating neural plasticity, insulin plays a role in regulating neuronal growth, survival, proliferation and differentiation. There is a specific binding site for insulin in the neural crest origin, which suggests a correlation between insulin and neurite formation in human neuroblastoma SH-SY5Y cells.¹⁰⁵ The way it enhances neurite growth including stimulates DNA synthesis¹⁰⁶ and increases the abundance of mRNA level of tubulin. Microtubules, cytoskeleton of axons and dendritic, the way insulin increases its mRNA is not covering all transcripts, but stabilized against degradation while increase the relative synthesis of tubulin. It has the same mechanism of how nerve growth factors act on microtubules and is common in the process of neurite elongation guided by neurotogenic polypeptides.¹⁰⁷ The survival of hippocampal neural stem cells in vitro depends on insulin,¹⁰⁸ and

insulin receptor/PI3K/AKT pathway induces neural stem cell reactivation.¹⁰⁹ The cessation of insulin causes autophagy-dependent cell death, a kind of regulated cell death that requires autophagy mechanisms without the need for other cell death pathways.¹¹⁰ Some experiments have been carried out to explore the mechanism of this phenomenon. In insulin-deficient hippocampal neural stem cells, GSK-3 β is an effector downstream of insulin, its inactivation reduces the level of autophagy-dependent cell death, its activation leads to cell death.¹¹¹ At the same time, the absence of insulin makes Ca²⁺ in the endoplasmic reticulum release, and elevated calcium levels activate AMPK.^{110,112} (Figure 3). AMPK phosphorylates autophagy-associated protein p62.¹¹³

Insulin is not only associated with autophagy-dependent cell death, but also with autophagy in organelles. Autophagy refers to the production of alternative energy sources by lysosomal lysing organelles (such as mitochondria and endoplasmic reticulum) during body in hunger, and insulin inhibits the process through the mammalian target of rapamycin mTOR- or/and AKT pathway after ingestion of food.¹¹⁴ The more important role of autophagy regulated by energy and insulin is to clear the aging and damaged organelles.¹¹⁵ When autophagy is reduced, mitochondria-derived oxidative stress increases and exacerbates insulin resistance.^{116,117} In patients with insulin resistance, the mitochondrial DNA copy number is reduced.^{118,119} In the streptozotocin model, which made by reducing insulin receptor phosphorylation and causes insulin resistance, adult hippocampal neural stem cells proliferate less, new neuronal formation is diminished, and GLUT and insulin-like growth factor (IGF) levels reduced.¹²⁰ The reduction of GLUT3 reduces the potential for neural stem cells to differentiate into neurons, as neonatal cells rely primarily on GLUT3 to transport glucose for energy.¹²¹ In this model, the content of reactive oxygen species (ROS) in hippocampal neural stem cells is greatly increased.¹²² Under normal circumstances, ROS mediates neuronal neurogenesis through PI3K/Akt signalling pathway. Whether in vivo or in vitro, reduced levels of ROS interfere with the function of normal NSCs and other progenitor cells.¹²³ Content of endogenous ROS in neural stem cells is high, but excessive ROS may produce cytotoxicity leading to neuronal cell death, or inhibit proliferation of neural precursors¹²⁴ (Figure 3).

Deficit of neurotrophic factors or disturbance of neurotrophic factor signalling pathways may be the primary cause of depression.^{125,126} As a member of the neurotrophin protein family, decreased levels of BDNF lead to pathophysiological symptoms of depression.¹²⁷ Normalized insulin signalling can both prevent and reverse BDNF transport defects.¹²⁸ Insulin also increases BDNF mRNA levels and phosphorylation levels of Akt and GSK3b in a concentration-dependent manner, thereby enhancing mouse memory in Y-maze experiments and reducing depression-like behaviour in forced swimming experiments.¹²⁹ Experiment used streptozotocin, which is toxic to insulin-producing B cells, to make a rat memory impairment model. Intranasal injection of insulin prevents STZ-induced cholinergic dysfunction and mitochondrial function degradation, restoring BDNF and CREB expression,¹³⁰ BDNF couple to CREB and is responsible for neurotrophic and neuroprotective role.¹³¹ In addition

to affecting the BDNF/ CREB pathway, insulin also mediates the troponin receptor kinase B (TrkB)/BDNF response and increases the expression of TrkB receptors and improves memory.¹³²

The BDNF gene is located on chromosome 11P13 and is widely expressed in the brain. When codon 66 of the BDNF gene was mutated from valine to methionine (Val66Met), BDNF transmembrane transport and expression level decreased, which made BDNF an independent risk factor for senile depression. It was verified that the Met allele of BDNF was significantly correlated with depression.¹³³⁻¹³⁵ Met/ Met genotype of the BDNF has a higher probability of depression than others.¹³³ BDNF Val/ Met and Met/ Met mutations are not only related to hippocampal volume and cognition, but also to obesity and type 2 diabetes.¹³⁶ In high-energy intake populations, Val/ Met is associated with increased insulin secretion and reduced prevalence of type 2 diabetes. People with Val/ Val alleles are more likely to develop diabetes than people with Val/ Met polymorphisms.¹³⁵

3.3 | Insulin affects depression through monoamine neurotransmitter

The hypothesis of monoamine neurotransmitter deficiency suggests that deficiency of monoamine neurotransmitters, namely norepinephrine and/or serotonin (5-HT), underlies clinical depression. Classical antidepressants that increase central monoamine levels according to this mechanism are very useful for the treatment of depression.¹³⁷

Monoamine 5-HT is a recognized neurotransmitter associated with the pathophysiology of depression, and the deficiency of 5-HT in certain areas of the brain can lead to depression. Tryptophan is converted to 5-hydroxytryptophan (5-HTP) under the catalysis of tryptophan hydroxylase (TPH), and 5-HTP converts to 5-HT by the catalysis of 5-HTP decarboxylase (5-HTPDC). The 5-HT not binds to receptor, partially reuptaked by plasma membrane serotonin transporters (SERT) or degraded to 5-hydroxyindolacetic acid (5-HIAA) by monoamine oxidase(MAO).¹³⁸ Rats with reduced insulin secretion have lower levels of 5-HT and dopamine (DA). And insulin administration lowers plasma glucose levels, which increases 5-HT levels.¹³⁹ Synthesis and conversion of 5-HT reduced by 44%-71% in diabetic rats with plasma glucose levels between 500 and 600 mg%.¹⁴⁰

Insulin affects 5-HT through a variety of pathways. First, insulin can increase the amount of 5-HT raw material tryptophan in the brain. Injecting insulin into the periphery affects the supply of tryptophan to the brain in two opposite directions: on the one hand, insulin promotes the binding of tryptophan to albumin in the blood, reduces the amount of free tryptophan in the circulatory system, thereby reducing the transport of tryptophan to the brain; and on the other hand, insulin removes some of other amino acids from the bloodstream, which would compete with tryptophan through the shared transport system of the blood-brain barrier, thereby increasing the influx of tryptophan into the brain. Because of these two effects, insulin increases the amount of tryptophan that enters the

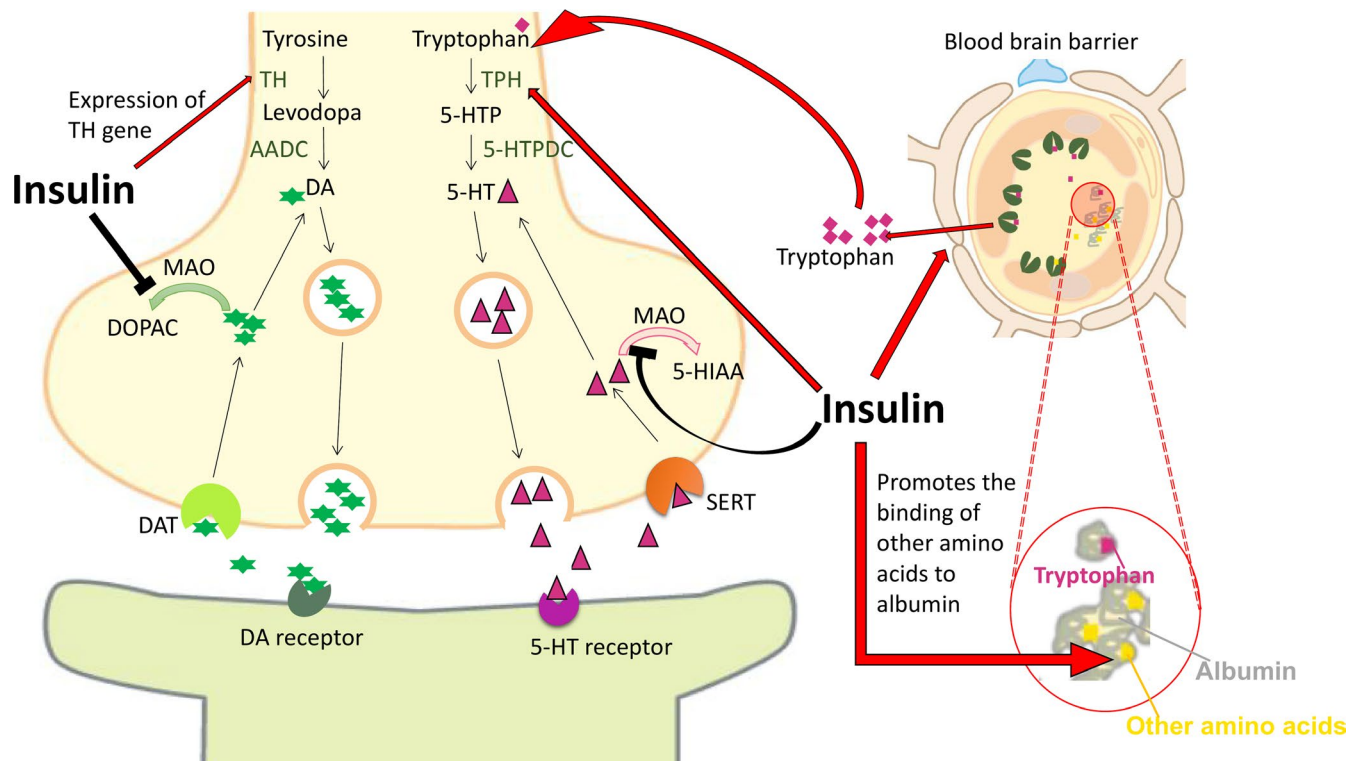


FIGURE 4 Insulin increases the supply of tryptophan to the brain. Although it promotes the binding of tryptophan to albumin, it also increases the binding of other amino acids to albumin, which increases the binding rate of tryptophan to the blood-brain barrier transport system. Except increases tryptophan, raw material of 5-HT synthesis, insulin also enhances the activity of 5-HT synthetase tryptophan hydroxylase (TPH) and inhibits the activity of monoamine oxidase (MAO) which degrades 5-HT. Insulin also activates the promoter of dopamine synthase tyrosine hydroxylase (TH), increasing the mRNA level of TH, and reduces the activity of dopamine degrading enzyme MAO, preventing the decomposition of dopamine

brain.¹⁴¹ Except increases the tryptophan intake, insulin increases the rate of neuronal serotonin synthesis.¹⁴² In the pineal body cultured in vitro, insulin enhances tryptophan hydroxylase activity¹⁴³ (Figure 4).

Insulin could also contribute to the regulation of mood by influence the emotion modifier dopamine, an important monoamine neurotransmitter that is primarily responsible for delivering excitement and pleasure. One of the principles of antidepressant monoamine oxidase inhibitors is to inhibit dopamine metabolism and increase its level in brain.¹⁴⁴ Destruction of the DA system is the basis for the lack of pleasure in several mental illnesses, including depression.^{145,146}

Tyrosine is transported to dopamine neurons by low- or high-affinity amino acid transport system, then catalysed by rate-limiting enzyme tyrosine hydroxylase (TH) in the cytoplasm and converted to levodopa. Under the catalysis of aromatic amino acid decarboxylase (AADC), the levodopa converts to dopamine and dopamine released from the monoamine transporter (VMAT) to the synaptic gap.¹⁴⁷ The dopaminergic neuron terminal has dopamine transporter (DAT), an absorption device, and is a membrane protein located in the presynaptic membrane of central dopaminergic neurons. Under normal circumstances, dopamine releases into the synaptic cleft, and then DAT pumps dopamine back to the nerve endings. After part

of dopamine returns to the synaptic terminals, some dopamine degraded to dihydroxyphenylacetic acid (DOPAC) in the synapse under the oxidation of MAO.^{148,149}

Dopamine neurons in the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) express the insulin receptor.¹⁵⁰ Experiments have shown that after peripheral injection of insulin, dopamine release increases in the nucleus accumbens, whereas in the striatum, 200,400 mU of insulin causes an increase in dopamine release, but dopamine release is inhibited in the group treated with 600 mU insulin. These data suggest that peripheral insulin injections cause changes in dopamine release in NAC and striatum.¹⁵¹ In autopsy results, decreased expression of insulin receptor-associated signalling genes (ie, INSR, IRS1 and IRS2) resulted in genes that regulate dopamine neurotransmission in dlPFC and hippocampus (ie, DDC, TH, VMAT2, DRD1, DRD2, DRD5 and MAOB). The gene expression is reduced, which in turn leads to lower dopamine metabolism.¹⁵² This result is basically consistent with relevant clinical data.^{150,153,154}

Insulin uses a biphasic manner to stimulate the cis-regulatory element associated with the TH promoter, for instance the hypoxia-inducible factor 1- α ,¹⁵⁵ specific protein 1,¹⁵⁶ and increases the level of TH mRNA,¹⁵⁷ increases the expression of the TH gene.^{154,155} Deletion of the insulin receptor on dopamine neurons

reduces the rate-limiting enzyme TH expression¹⁵⁸ (Figure 4). Insulin signalling affects dopamine utilization and turnover. Insulin-activated insulin receptors cause an increase of DA uptake by DA transporter (DAT). This process involves the PI3K/AKT signalling pathway and causes DAT to be inserted into the plasma membrane.^{159,160} The level of DAT mRNA expression in the VTA/SNC of rats treated with insulin injected into the third ventricle (i.c.v.) was significantly elevated.¹⁶¹ While insulin increases dopamine uptake, its primary role in NAC and CPu is to enhance dopamine release. This dynamic regulation from dopamine of insulin release is primarily involved in the excitatory insulin-dependent increase in striatal cholinergic interneurons (ChIs), which leads to dopamine release increased through activation of nicotinic acetylcholine (ACh) receptors (nAChRs). The effect of insulin on ChIs and DA release is mediated by the insulin receptor. In the striatum sections of food-restricted rats, the effect of insulin on DA release was amplified, while in obese rats, the effect of insulin was diminished.¹⁶²

In neurons, insulin is able to reduce the activity of monoamine-degrading enzyme: MAO-A and MAO-B, thereby reducing monoamine clearance and increasing 5-HT and DA signalling and prolong the monoamine half-life after it released.¹⁶³ Insulin receptor knockout mice have elevated levels of monoamine oxidases A and B, resulting in increased dopamine conversion and age-related anxiety and depression-like behaviour.¹⁶⁴ However, the increase in MAO and the increase in DA metabolic breakdown caused by downregulation of insulin receptors only occurred in the striatum and NAC, which was not detected in the prefrontal cortex. This may indicate that different brain regions respond differently to insulin or insulin resistance.^{164,165} MAO A and B also degrade serotonin, which affects the signal transduction of serotonin. Since serotonin signalling is also associated with depression, this pathway may also be associated with the pathogenesis of mood disorders¹⁶⁶ (Figure 4).

3.4 | Interaction of the gastrointestinal microbiome and insulin in depression

The accumulating knowledge of the correlation between gastrointestinal and depression gives rise to the microbiota-gut-brain (MGB) axis. The prevalence of depression in irritable bowel syndrome is reported to be 84%.¹⁶⁷ In view of this situation, gut microbiota targets may be a new research direction. A few of gut microbiota genera and their metabolites can synthesize neurotransmitters and neuropeptides and essential amino acids and participate in immune and endocrine functions.^{47,168,169} For example, eating bifidobacterium longum could reduce anxiety in mice with colitis by improving hippocampal BDNF mRNA levels.¹⁷⁰ In another study, administration of lactobacillus helveticus increased serotonin concentrations in the hippocampus and alleviated depression and anxiety.^{171,172} Induction of diet-induced obesity mice exhibits insulin resistance and a variety of depression-like and anxiety-like behaviours. Oral

antibiotics metronidazole or vancomycin can enhance insulin signalling in the brain and relieve depression. Gut microbiota regulators could improve the balance of microorganism to ameliorate glucose metabolism defects and insulin secretion disorders by adjusting the microbiota-gut-brain axis. Then, gut microbiota reduces depressive behaviour through changes brain insulin signalling, inflammation, neurotransmitters and other neuroactive molecules (such as BDNF).^{173,174}

Gut microbes and insulin interact with each other. Increasing insulin secretion and reducing insulin resistance could improve glucose regulation, restore intestinal microbiome disorders and maintain the homeostasis of the gut microbiota.^{169,175,176} Under the premise that the flora remains stable, probiotics secrete a variety of signal molecules, which work through different pathways, thereby exerting antidepressant, immune regulation or regulating neurotransmission.¹⁷⁷ Low levels of two major probiotic bacteria (lactic acid bacteria and bifidobacteria) are usually found in depression individuals.¹⁷⁸ In the case of gut microbiota homeostasis, ingestion of lactobacillus rhamnosus increases the central mRNA expression of γ -aminobutyric acid (GABA) receptors, while reducing depression and anxiety-like behaviour in mice.¹⁷⁹ Supplementation with lactobacillus helveticus can improve memory and cognitive ability in chronically stressed rats. This improvement in memory is associated with increased level of hippocampal norepinephrine and decreased levels of plasma corticosterone and adrenocorticotrophic hormone.¹⁷¹ Previous studies have also shown that ingestion of lactobacillus helveticus can enhance memory and reduce intestinal inflammation in rats induced by neural inflammation.¹⁷⁸ Understanding the interaction of the gastrointestinal microbiome with insulin provides some treatments that may be superior to standard antidepressants and shows the potential of regulating the gastrointestinal microbiome to treat depression.

4 | CONCLUSION

The incidence of depression has gradually increased in recent years, and the effects of insulin on depression are widely studied. Therefore, it is important to clarify the potential association of depression and diabetes and explore the common physiological and pathological basis of their pathogenesis. In this article, we outlined the role and possible regulatory mechanisms of insulin, which plays an important role in the course of diabetes, in depression and depression-like behaviour. These include the different effects and mechanisms of peripheral and intranasal insulin injections on the HPA axis, the effects of insulin on neurogenesis, synaptic plasticity and neurotrophic factors, and the positive effects of insulin on depression through monoamine neurotransmitters and gastrointestinal microbiome. Therefore, this review may provide new insight for clarifying the role of insulin on the pathogenesis of depression.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

XHZ and BJL wrote the first draft of the manuscript; LHS and WY wrote sections of the manuscript; RC provided the critical revisions. All authors revised the manuscript and approved the submitted version.

DATA AVAILABILITY STATEMENT

Data available on request.

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