Estrogen – serotonin interaction and its implication on insulin resistance

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ABSTRACT

Introduction: Metabolic disease, including diabetes mellitus (DM), is a major burden worldwide. Obesity and insulin resistance (IR) are closely associated with DM. The action of estrogen and serotonergic neurons are known to improve insulin sensitivity and glucose homeostasis. Therefore, this report provides a comprehensive review focuses on the interaction between estradiol (E2) produced in the brain and serotonergic neurons in the development of IR.

Methods: A literature review. Relevant studies were thoroughly reviewed and summarized to review a possible association between neuroestrogen and serotonin signaling in the development of IR.

Results: DM is a common endocrine disease characterized by hyperglycemia. Evidence indicates that DM is strongly associated with IR. Previously, it has been reported that brain E2 modulates serotonergic neurons. Interestingly, both E2 and serotonergic neurons are known to regulate insulin secretion and sensitivity through the central mechanism. This review highlights the importance of understanding the possible mechanisms of neuroestrogen – serotonergic neurons in modulating insulin sensitivity.

Conclusion: Taken together, brain E2 possibly acts independently through estrogen receptor (ER) expressed in the hypothalamus or by stimulating serotonergic neurons to improve insulin sensitivity.

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has been rising rapidly, particularly in low and middle-income countries [1]. A recent report from WHO indicates the number of patients with T2DM is almost double in the last three decades [1]. Indeed, the incidence of T2DM linearly increases with obesity and aging [2,3], reflecting an increase of associated factors responsible for developing T2DM. T2DM is a chronic metabolic disease characterized by insulin insufficiency [4,5]. However, it is well documented that T2DM is closely related to severe IR [6]. IR is known as a poor predictive factor [7] and correlated with cognitive impairment in patients with T2DM [8,9]. Therefore, understanding IR mechanisms are the key feature in treating T2DM.

E2 is a sex steroid hormone with diverse actions, it is not only limited to the reproductive system but also responsible for regulating brain development and functions [10,11]. Besides, E2 is involved in glucose homeostasis, regulating insulin sensitivity and resistance [12,13]. A cohort study confirmed that prolonged E2 treatment in menopausal women may reduce the incidence of T2DM [14]. Consistently, menopausal women treated with E2 prevent the incidence of T2DM [15,16]. E2 mediates its effects through genomic and non-genomic pathways. Distribution of ERα in glucoregulatory tissues is more abundant than ERβ [17], suggesting that ERα plays a primary role in regulating insulin and glucose metabolism. Indeed, ERα knockout (KO) mouse displayed the imbalance of energy metabolism and IR [17,18]. On the other hand, membranes ER and G protein-coupled estrogen receptor (GPER) that activate downstream signaling pathways of E2 via protein kinases mediate rapid action in modulating glucose homeostasis [13,19]. However, by which mechanism E2 regulates insulin and glucose metabolisms are complex and remain elusive.

Serotonin (5-HT) is a neurotransmitter synthesized from tryptophan by the action of tryptophan hydroxylase (TPH) enzyme [11]. The role of brain serotonin is widely known in several physiological functions, including insulin and glucose metabolism [20,21]. Ablation of the brain 5-HT (Pet-1+) neurons in the mouse exhibited low insulin level and hyperglycemia [20], providing the information that defective central 5-HT functions may associate with the impairment of insulin signaling leading on the development of diabetes. Recently, it is reported that neuroestrogen regulates 5-HT neurons in zebrafish brain [11], suggesting a possibility that modulation of E2 on glucose metabolism is 5-HT-dependent or independent. Therefore, this short review will comprehensively discuss the interaction between E2 – 5-HT in...
regulating glucose metabolism, particularly focusing on the possible mechanisms E₂ – 5-HT influence on insulin sensitivity.

2. Relationship of estrogen and serotonin on insulin and glucose homeostasis

Estrogen is a female sex steroid hormone that plays important roles in both reproductive and non-reproductive functions [22]. E₂, as a predominant form of estrogen, is synthesized by P450 aromatase (Aro) enzyme from testosterone (T) [11,22]. Early ontogeny of Aro is detected as early as embryonic day 9 (E9) with the optimal peak at E13–14 in mouse brain [23]. Similarly, high expression of brain aromatase (AroB) is detected at 48 hours post-fertilization (hpf) in zebrafish, indicating that locally produced E₂ in the brain is necessary for brain development and functions [24]. Expression of Aro in the brain is mainly localized in the amygdala, preoptic area, and hypothalamus [25,26]. While Aro is detected in the neuron and glial cells in mammals [27], fish Aro (brain type, AroB) only detected in glial cells, which later able to differentiate into neurons [28].

Previously, it is reported that healthy male treated with anastrozole (aromatase inhibitor, AI) for 6 weeks with 2 weeks washout periods exhibited a reduction of peripheral insulin sensitivity [29]. Indeed, homeostasis model assessment-insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) confirmed that the administration of E₂ improved insulin sensitivity in male patients with aromatase deficiency [30]. However, it seems that the low level of E₂ is not the only factor in developing IR, rather than the ratio between E₂ and T [30]. Similarly, mice lacking Aro (ArKO) displayed glucose intolerance and IR [31] and E₂ enhanced insulin sensitivity by stimulating phosphorylation levels of protein kinase B (Akt), downstream signaling pathways of insulin [32].

E₂ signaling effects are mediated by ERs, which are broadly distributed throughout the brain [33]. Both ERs (ERα and ERβ) are detectable in the mouse brain from E10.5–16.5 [34]. Hypothalamus as central of energy metabolism mainly expressed ERα, especially in the arcuate nucleus (ARC) and the ventromedial nucleus of the hypothalamus (VMH) [35]. A genetic study utilizing ERαKO and ERβKO shows that IR is observed only in mouse losing ERα but not ERβ [36–38], although administration of WAY200070 (ERβ agonist) improved glucose and insulin sensitivity by stimulating endogenous insulin secretion and pancreatic β-cell mass [39]. Further, several studies provide an important finding that non-nuclear ERs (GPER and membrane ERα) also determine the development of IR [40,41]. Collectively, these results suggest that there is a complex mechanism of E₂ regarding IR, which remained to be elucidated.

5-HT is synthesized in serotonergic producing cells from tryptophan by tryptophan hydroxylase (TPH) in both peripheral tissue and brain [42]. There are two isoforms of TPH, TPH1 and TPH2, which are exclusively expressed in the enterochromaffin cells and raphe, respectively [43,44]. The physiological actions of 5-HT are mediated by numerous 5-HT receptors (5-HTRs) and its transporter (5-HT transporter, SERT) [45]. Such various types of 5-HTR, only 5-HT₂A-R and 5-HT₂C-R are mainly expressed in the central nervous system (CNS) [45]. Raphé serotonergic neurons are generated during E11–E15 in rodents [46]. Because 5-HT does not cross the blood-brain barrier [42,47], locally produced 5-HT seems to have a specific function in those tissues. Although both peripheral and central 5-HT contributed in modulating metabolic homeostasis [42]. However, several lines of evidence indicate that central 5-HT system predominantly controls glucose homeostasis [21,48,49].

Fat pad and food intake reduction are observed in Tph2−/− [50], although high-calories food intake is reported by other investigators [51]. On another hand, obese mice are documented in Tph2−/− [50], suggesting that the effects of 5-HT deficiency on body weight and food intake vary. Nonetheless, these changes implicating dysregulation glucose turnover. Mutant mice slc6a4−/−, which exhibited a low level of brain 5-HT content displayed obesity, hyperglycemia, decreased glucose tolerance and insulin sensitivity [52–54]. Interestingly, such effects are caused by the suppression of cyp19a1 (aromatase gene) and insulin-induced-AKT activity [53,54]. Involvement of 5-HTR in regulating energy metabolism is well documented. Heisler et al reported that stimulation of 5-HT₁B-R promotes satiety [47], while treatment with 5-HT₂C-R agonist improves glucose homeostasis by upregulating pro-opiomelanocortin (POMC) neuron [55]. In agreement, deletion of the gene encoding 5-HT₂C-R induced the development of IR and T2DM [55].

How brain E₂ and 5-HT influence insulin and glucose homeostasis? As Aro is expressed in the brain, particularly in hypothalamus, E₂ produced in the brain likely controls glucose homeostasis through central mechanism (Figure 1). A subset of neurons in the hypothalamic arcuate nucleus (ARC), POMC and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons are a target of E₂ signaling, as these neurons expressed ERs [18,56]. Although a study by Olofsson et al showed there is no co-localization of ERα within NPY/AgRP neurons [57]. α-melanocyte stimulating hormone (α-MSH) and NPY/AgRP secreted by POMC neurons and NPY/AgRP neurons, respectively [18]. Administration of E₂ has been shown to upregulate POMC expression [58], and at the same time, E₂ increases α-MSH and decreases NPY immunoreactivity in ARC [59]. Also, activation of ER in POMC neurons enhanced the release of glutamate.
to facilitate inhibitory action on NPY/AgRP neurons [60]. The anorexic effect is observed when melano-
cortin receptor type 4 (MC4R) in paraventricular hypothalamus (PVH) is stimulated by α-MSH, while
the orexigenic effect is mediated by NPY/AgRP [18,61]. Thus, E2 appears to modulate POMC and
NPY/AgRP neurons to control satiety.

It seems direct actions of E2 on MC4R expressing
neurons are observed in PVH, as single-minded-1
(SIM-1) neurons expressed the abundant level of ERα
[62]. In fact, deletion of ERα from SIM-1 neurons
induced obesity [63]. However, another study con-
firmed that disruptions of MC4R did not influence the
effects of E2 on food intake and energy expenditure [62].
Activation of PVH area by E2 mediates peripheral symp-
pathetic activity, probably directly through MC4R
expressing neurons or indirectly through POMC and
NPY/AgRP neurons [64–66]. As POMC neurons pro-
jected its axons to sympathetic and parasympathetic
preganglionic neurons in intermediolateral nucleus
(IML) and dorsal motor vagal nucleus (DMV), respec-
tively, E2 possibly at the same time increases peripheral
insulin sensitivity through sympathetic pathways and
decreases insulin secretion through parasympathetic
pathways [67].

Similar to E2, the serotonergic neurons are also con-
sidered as one of the factors regulating glucose metabo-
lism [20,21]. 5-HT axons are projected from raphe to
hypothalamus [48], and it has been reported that 5-HT1B
R is detected in NPY/AgRP and mouse hypothalamic-2/
30 (mHypoA-2/30), expressing a PVN-speci-
car marker [47,68], while 5-HT2C-R expressed in POMC neurons
[47]. 5-HT agonist, D-fenfluramine (d-FEN), is known
to stimulate the release of 5-HT and activate 5-HT2C
R located on POMC neurons, which in turn could med-
iate anorectic effects through MC4R [69]. In parallel, the
administration of selective 5-HT1B agonists CP94253
showed that 5-HT mediates the inhibition of AgRP
release, but also at the same time decreases inhibitory input onto POMC neurons, as consequence 5-HT facilitates the release of α-MSH [47]. Furthermore, through 5-HT₂C-R, 5-HT stimulates sympathetic preganglionic neurons via MC4R resulting in the improvement of glucose tolerance and insulin action [55]. Thus, the central action of 5-HT is an important factor in modulating insulin and glucose metabolism. Recently, it has been documented that E₂ produced in the brain modulates serotonergic neurons in developing zebrafish [11], which is possibly mediated by ERβ as previously reported in mammals (Figure 1) [70,71]. On another hand, upregulation of cyp19a1 by 5-HT₃,R is observed in BeWo and JEG-3 choriocarcinoma cells [72], indicating that there is a close relationship between Aro and serotonergic neuron, although the effect of 5-HT on the brain Aro is yet to be reported. Therefore, the action of central 5-HT in modulating insulin and glucose metabolism might be dependent on E₂. Taken together, E₂ in the brain contributes to the regulation of glucose homeostasis independently through ERs or dependent on central 5-HT. Combination of E₂ and 5-HT treatment might be useful to provide a novel treatment for T2DM, though more detailed examination needs to be verified.

Disclosure statement
No potential conflict of interest was reported by the author.

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