Antidepressant Effects of Anti-Hyperglycemic Agents

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Contributor: Young Sup Woo , Hyun Kook Lim , Sheng-Min Wang , Won-Myong Bahk

Close connections between depression and type 2 diabetes (T2DM) have been suggested by many epidemiological and experimental studies. Disturbances in insulin sensitivity due to the disruption of various molecular pathways cause insulin resistance, which underpins many metabolic disorders, including diabetes, as well as depression. Several anti-hyperglycemic agents have demonstrated antidepressant properties in clinical trials, probably due to their action on brain targets based on the shared pathophysiology of depression and T2DM.

insulin resistance depression anti-hyperglycemic agents

1. Introduction

Depression is a complex, heterogeneous illness associated with significant chronicity and considerable impairment of physical ability and psychosocial function [1]. Although antidepressants are the well-established first-line treatment for depression, current pharmacological therapies are often ineffective, yielding high rates of inadequate treatment response, reflected in recurrence or chronicity [2][3]. Furthermore, pharmacological therapy for depression is often associated with intolerance, with clinically substantive side effects including nausea, constipation/diarrhea, dry mouth, somnolence/insomnia, dizziness, sexual dysfunction, weight gain, increased appetite/anorexia, and with uncommon serious adverse effects including prolongation of corrected QT interval, increased risk of fracture, hyponatremia, and inhibition of platelet aggregation [4][5][6]. Therefore, there remains a need to elucidate novel targets that may yield improved efficacy, tolerability and, possibly, disease modifying effects.

The insulin signaling system has been proposed as a novel target in the treatment of depression [7][8][9]. Because a bi-directional association between diabetes/insulin resistance and depression has been described in many studies [9][10][11][12][13], an underlying shared pathophysiologic mechanism of depression and type 2 diabetes mellitus (T2DM) and anti-depressant effects of anti-diabetic agents have been explored in the field. Consequently, a growing body of evidence has suggested that altered insulin signaling, including insulin availability and/or sensitivity or availability of insulin receptors, is important to the underlying pathophysiology of depression [14][15].

Binding of the ligand to insulin receptors (IRs) generates intracellular signals via two main intracellular signaling pathways, the insulin receptor substrate (IRS)-phosphatidylinositol 3-kinase (PI3K)-Serine/threonine kinase (Akt) pathway and the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway,

which are known to be involved in depression pathophysiology [16][17]. Moreover, insulin signaling may act to regulate mood by modulating neurogenesis. Hippocampal neurogenesis is known to be impaired in both depression and diabetes [18][19]. In addition, recent studies have demonstrated that altered insulin signaling in the brain induces monoaminergic dysfunction [20][21]. Recent pre-clinical and clinical trials have also demonstrated relationships between insulin signaling and depression; knockdown of insulin receptors in the hypothalamus or astrocytes generated depressive behavior in mice [22][23], and insulin administration may have improved mood and cognition in a few human studies as well [14][24][25]. Additionally, several preclinical studies on animal models suggested that high fat diet induced metabolic dysfunction could induce depressive-like behavior [26] via dysregulation of synaptic plasticity and insulin signaling [27], serotonin mediated neurotransmission [28][29], brain indoleamine 2,3-dioxygenase (IDO) activity [30], and intestinal microbiome and brain metabolome [31]. Other trials examining the antidepressant effect of repurposed anti-hyperglycemic (anti-diabetic) agents including the insulin sensitizing agent pioglitazone [32] and glucagon-like peptide-1 (GLP-1) receptor agonists [33][34] also suggest that the attenuation of insulin resistance could be a plausible target for the treatment of depression.

2. Antidepressant Effects of Anti-Hyperglycemic Agents in Clinical Trials

2.1. Insulin

The antidepressant effects of subcutaneous insulin were investigated in two studies with T2DM patients. Reza et al. [35] reported significant improvements in depressive symptoms with subcutaneous insulin treatment in older (aged 65 years and over) type 2 diabetic patients. In this 12-week study, 30 consecutive patients advised to start insulin by the clinical diabetologist were treated with subcutaneous insulin, and 10 consecutive patients who remained on glucose-lowering drugs (combinations of gliclazide, metformin, and acarbose) were recruited as control subjects. Depressive symptoms at baseline, evaluated using the Geriatric Depression Scale (GDS) score, did not differ between the groups. Although the glycemic control remained relatively poor, with only a small reduction in Hemoglobin A1c (HbA1c) during the study in both groups, subcutaneous administration of insulin significantly reduced the GDS scores at both 4 weeks and 12 weeks compared to baseline; there was no change in the control group. However, in a follow-up study [36] of 57 older patients with poorly controlled T2DM, insulin was not associated with any change in depressive symptoms at the end of the 6-month study. The authors compared the effects of continuation of oral medication, change to isophane insulin, and basal/bolus insulin therapy. The results showed that the Hospital Anxiety and Depression Scale (HADS)-B (depression) scores were lower in the basal/bolus insulin group at 1 and 3 months compared to baseline, although the change at 6 months was not significant (p = 0.06). Moreover, insulin therapy did not improve depressive symptoms in a meta-analysis of diabetic patients [37]. Rather, diabetic patients on insulin therapy were significantly associated with the higher risk of depressive symptoms.

A few more clinical studies have investigated the effect of intranasal insulin on mood by studying subcutaneous insulin therapy in healthy or non-diabetic subjects. In an 8-week double-blind randomized comparison between intranasal insulin and placebo in 38 healthy subjects [38], intranasal insulin administration improved mood as well

as memory. In that study, the authors assessed mood using an adjective check list designed to assess actual mood on 15 dimensions and assessed cognitive function with a word list, word-stem priming, and the Stroop test. After 8 weeks of intranasal insulin, delayed recall was significantly improved, feelings of well-being and self-confidence were increased, and anger ratings were decreased in comparison with placebo. Intranasally administered insulin could attenuate the hypothalamic–pituitary–adrenal (HPA) axis response to psychosocial stress, which has been associated with depression in numerous previous studies [39]. A single intranasal dose of insulin, 5 min before being exposed to the Trier Social Stress Test (TSST), diminished the HPA axis response to the TSST as measured by cortisol taken from saliva and plasma [40]. However, in a double-blind study examining the effect of intranasal insulin administration on cognitive function and mood symptoms in patients with treatment-resistant depression [14], intranasal insulin did not result in statistically significant improvement in overall mood or cognition. No significant difference was found between the effects of intranasal insulin and placebo on changes in total Montgomery Åsberg Depression Rating Scale (MADRS) scores, the Positive or Negative subscales of the Positive and Negative Affect Schedule (PANAS), or a global index of neurocognition.

2.2. Metformin

The effect of metformin on mood has been investigated in four studies which included subjects with T2DM and impaired glucose tolerance in polycystic ovarian syndrome (PCOS). In a 1-year diabetes prevention study of subjects with impaired glucose tolerance, Ackermann et al. [41] investigated the association between changes in body weight and changes in health status among three intervention groups (intensive lifestyle intervention, pharmacotherapy with metformin, and placebo) using scores on the Beck Depression Inventory (BDI) as a covariate. BDI total score was significantly, but only slightly, decreased during the 1-year treatment period in all three groups. At 1 year, the changes in BDI total scores were −1.02 in the intensive lifestyle intervention group ($p < 0.001$), −0.71 in the metformin group ($p < 0.001$), and −0.58 in the placebo group ($p < 0.001$). However, it is not clear which intervention led to a greater decrease in BDI scores because the authors did not compare the treatment effects among the three groups. Moreover, as the baseline BDI scores were quite low (3.53 in the intensive lifestyle, 3.84 in the metformin, and 4.05 in the placebo group), the clinical significance of these results may be limited. However, in another randomized clinical trial (RCT), 24-week metformin treatment significantly improved MADRS and 17-item Hamilton Depression Rating Scale (HDRS) scores in patients with depression and T2DM [42]. The reduction in depressive symptoms was paralleled by improvement in HbA1c, but the correlation between HbA1c changes and changes in depressive symptoms was not reported. In that study, chronic treatment with metformin also improved cognitive performance as assessed by the Wechsler Memory Scale—Revised. The authors suggested that administration of metformin may improve depressive symptoms comorbid with T2DM through improvements in cognitive performance. In addition, in a 6-month study of premenopausal women (aged 30–45 years) with T2DM or prediabetes, administration of metformin reduced, albeit insignificantly, the BDI-II score ($p = 0.088$) as well as the number of patients with depressive symptoms (BDI-II score 14 or higher, $p = 0.056$) in women with diabetes but not in those with prediabetes [43].

Metformin was included as an active control in three RCTs. In a study of women with PCOS, 12-week treatment with metformin (−0.3 ± 0.7) was marginally inferior to treatment with myo-inositol (−1.0 ± 1.7) in reducing

depressive symptoms as measured by BDI scores [44]. The study's clinical value in terms of improving depression outcomes is limited because the subjects were not selected for depression, and the baseline BDI scores were relatively low (15.1 ± 3.9 for the metformin group; 15.4 ± 5.2 for the myo-inositol group). Metformin was also inferior to pioglitazone at reducing depressive symptoms in patients with post-stroke depression and T2DM [45] and in patients with concomitant PCOS and MDD [46].

Recently, Moulton and colleagues conducted a meta-analysis of 19 published RCTs (five of metformin, two of peroxisome proliferator-activated receptor (PPAR)-γ receptor agonists, two of incretin-based therapies, and one of insulin) on the effects of diabetes treatments on depressive symptoms. They found that metformin had similar effects to placebo on depressive symptoms (pooled effect size = −0.49, 95% CI = −1.04 to 0.074, $p = 0.089$) and was inferior to active controls (pooled effect size = +1.32, 95% CI = 0.31 to 2.34, $p < 0.001$) [47].

2.3. PPARγ Receptor Agonists

Numerous studies have examined the antidepressant effects of PPARγ receptor agonists. PPARγ agonists such as rosiglitazone and pioglitazone have been evaluated in four open-label clinical trials [21][48][49][45] and six RCTs [50][46][51][52][53][54]. Majority of studies were conducted in subjects having metabolic or endocrinologic abnormalities such as T2DM, insulin resistance, obesity, metabolic syndrome (MetS) or PCOS [21][48][46][49][51][45], but some studies investigated antidepressant effects of insulin in subjects without metabolic abnormalities [50][52][53][54].

Rasgon and colleagues [48] tested the hypothesis that the addition of rosiglitazone, an insulin-sensitizing agent, would improve mood in prediabetic patients with unipolar or bipolar depression. The authors additionally administered rosiglitazone with treatment as usual for 12 weeks to eight patients, and the results showed a decline in the mean HDRS score. The improvement in depressive symptoms was not associated with improvements in insulin sensitivity as measured by the Matsuda Index. In open-label studies of another PPARγ receptor agonist, pioglitazone, among subjects with both depressive symptoms and metabolic risk factors, pioglitazone improved depressive symptoms in subjects with MDD and abdominal obesity/MetS [21] and with post-stroke depression and T2DM [45]. Kemp et al. [21] reported that total scores on the Inventory of Depressive Symptomatology (IDS) decreased from 40.3 ± 1.8 at baseline to 19.2 ± 1.8 at week 12 in 23 MDD patients with abdominal obesity or metabolic syndrome patients who received pioglitazone. Moreover, Hu et al. [45] compared the antidepressant effects of pioglitazone versus metformin as adjunctive with fluoxetine in patients with post-stroke depression and T2DM; pioglitazone decreased HDRS scores significantly more than metformin within 3 months of treatment, independently of depression severity.

Furthermore, in two double-blind randomized controlled trials with subjects with depression and comorbid conditions [46][51], pioglitazone showed significant antidepressant effects. Pioglitazone was superior to metformin in reducing HDRS scores at 6 weeks in patients with concomitant PCOS and MDD [46] and to placebo in reducing both depressive and anxiety symptoms, measured using the Hospital Anxiety and Depression Scale (HADS), in nondiabetic MetS patients [51]. Interestingly, the improvement in depressive symptoms was independent of the insulin-sensitizing effects of pioglitazone; in both studies, changes from baseline in homeostatic model assessment

of insulin resistance (HOMA-IR) values were not correlated with the changes in depressive symptoms. Meanwhile, Simuni and colleagues [55] reported the results of a phase 2 double-blind RCT of pioglitazone in early Parkinson's disease, which showed no significant difference between pioglitazone and placebo in changes in GDS scores over 44 weeks.

Two RCTs have been performed in subjects with MDD but without metabolic abnormalities [50][52]. Pioglitazone adjunctive therapy for moderate to severe (17-item HDRS total score ≥22) MDD patients was superior to placebo in reducing the HDRS total score during the course of the 6-week trial [50]. Moreover, the frequency of treatment response, remission (HDRS score ≤ seven), and early improvement (≥20% reduction in HDRS score within the first 2 weeks) was significantly higher in the pioglitazone group than in the placebo group. However, Lin et al. [52] reported no significant difference in the mean decline in HDRS scores between the adjunctive pioglitazone group and the placebo group when subjects both with and without insulin resistance were included. The difference in HDRS score change was only significant in subjects with insulin resistance. Another remarkable finding from this study was the age effect; pioglitazone was more effective in younger patients.

Studies of patients with bipolar depression have also been conducted [49][53][54]. In their proof-of-concept study, Kemp and colleagues [49] reported that adjunctive pioglitazone treatment significantly decreased the total IDS-C30 and Quick Inventory of Depressive Symptoms (QIDS) total scores at the end of an 8-week study in 34 patients with bipolar depression and MetS or insulin resistance. More than three-quarters of these patients, it should be noted, were experiencing treatment-resistant bipolar depression, having already failed two mood stabilizers or the combination of a mood stabilizer and a conventional antidepressant. Additionally, the improvement in depressive symptoms was associated with a reduction in the inflammatory biomarker interleukin (IL)-6. Zeinoddini et al. [53] also reported antidepressant effects of adjunctive pioglitazone relative to lithium in their double blind, placebo-controlled RCT. That study included 48 patients with bipolar I depression and without diabetes or MetS, who had previously failed to respond adequately in the current episode to a trial with lithium plus antidepressant. The total HDRS score was decreased significantly more in the pioglitazone group than in the placebo group over 6 weeks, and the difference was significant onwards from week 2. However, another double-blind placebo-controlled RCT failed to show the antidepressant efficacy of pioglitazone in patients with bipolar depression [54]. Adjunctively administered pioglitazone with concomitant mood stabilizers, antipsychotics, and antidepressants with 38 bipolar depression patients showed significant differences in IDS-C30 and MADRS changes relative to the placebo control group during the 8-week study. However, there was a borderline significant difference between the two groups (p = 0.056) in the IDS-C30 score favoring the placebo. The authors noted that the discrepancies between these results and those of previous studies may have stemmed from characteristics of the subjects, including the higher heterogeneity, lower depression severity, and higher concomitant hypomanic/mixed symptomatology of their study population compared with Zeinoddini's study [53]. In addition, in the pioglitazone group, but not in the placebo group, leptin level was increased in subjects who showed a decrease in depression score, and this correlation was significant [54].

In any case, pioglitazone's antidepressant efficacy has been supported by meta-analyses [32][47]. In a meta-analysis of four double-blind RCTs [50][46][52][53], pioglitazone induced higher remission rates than control treatments (27%

versus 10%, odds ratio (OR) = 3.3, 95% CI = 1.4 to 7.8, p = 0.008). Subgroup analysis showed that the OR was even higher in MDD patients (23% versus 8%, OR = 5.9, 95% CI = 1.6 to 22.4, p = 0.009) and in the patients without metabolic comorbidities (33% versus 10%, OR = 5.1, 95% CI = 1.5 to 17.9, p = 0.01). The reduction in HDRS score was also significant in pioglitazone treatment compared with control treatments (mean difference = 3.3, 95% CI = 2.6 to 4.0, $p < 0.0001$). Another meta-analysis [47], which included four more RCTs [51][45][55][54] than the meta-analysis by Colle et al. [32], also showed a significant treatment effect of pioglitazone (pooled effect size = −0.68, 95% CI = −1.12 to −0.24, p = 0.003). Interestingly, being female was significantly associated with improvement in depression, but age, baseline severity of depressive symptoms, baseline HOMA-IR, and baseline fasting glucose were not associated with changes in depressive symptoms.

2.4. GLP-1 Receptor Agonists (GLP-1RA)

An open-label, short-term study with liraglutide reported significant reduction in depressive symptoms [33]. In this 4-week study, which included 19 subjects with MDD or bipolar disorder with impaired executive function, administration of liraglutide significantly reduced HDRS scores as a secondary outcome measure, as well as improving executive function. The change in HDRS score did not moderate the improvement in cognition. However, liraglutide failed to show a significant effect on depressive symptoms in an RCT [56]. Treatment with liraglutide for 26 weeks reduced body weight and HbA1c significantly more than standard therapy, but it reduced BDI scores by only one point, which was not significant when compared with the control group.

2.5. Safety and Tolerability

The use of insulin could be limited by the risk of hypoglycemia, which is an important adverse effect of insulin therapy. Owing to the risk of hypoglycemia of intravenous insulin infusion, and the fact that high systemic doses would be needed to achieve functionally effective insulin concentrations in the CNS, this mode of administration is not viable for the psychiatric patients [57]. However, intranasal administration allows a non-invasive, direct delivery of insulin to the brain, by bypassing the blood–brain barrier (BBB) and thereby avoiding potential systemic side effects of lowering blood glucose levels [58][59]. In a clinical trial of intranasal insulin, it was well tolerated, and no subject exhibited hypoglycemia or other safety concerns [60].

There are also some adverse reports on the use of metformin. Abdominal pain and other gastrointestinal (GI) symptoms are not uncommon adverse effect of metformin. About 10% of patients stopped taking metformin due to its GI adverse effects [61]. Despite its rarity, lactic acidosis could result in a serious or lethal complication. Furthermore, metformin could be associated with CNS adverse effects. In an animal study, metformin therapy promoted neurodegenerative process by altering tau phosphorylation-dependent pathways in *ApoE* knockout mice [62]. Metformin also impaired cognitive function and increased the risk of Alzheimer's disease in patients with diabetes [63]. However, there was a contrary report suggesting that metformin use was not related to adverse outcomes of brain structures and cognitive function [64]. These discrepancies suggest that further studies are needed to determine whether metformin truly has a potential role in the prevention or treatment of neurodegenerative disorders [65].

Adverse effects of PPARγ receptor agonists on neuronal function were also noted in both animal and human studies [65]. Rosiglitazone was associated with neuronal apoptosis in the hippocampus of rats [66], and cognitive complications in patients with T2DM [67]. Although the use of PPARγ receptor agonists in T2DM is declining due to its adverse effects, a meta-analysis suggested a relatively favorable safety in MDD patients [32]. There were no deaths, major adverse events, and clinically significant weight gain or weight change [32]. However, caution needs to be exercised because some adverse effects such as increased appetite (15–25%), headache (5–26%), nausea (8.7–25%), sexual dysfunction (20%), abdominal pain (20%), muscular pain (10–17.4%), blurred vision (13–15%), irritability (11.7%), and edema (11.7%) were common after pioglitazone administration [32].

GLP-1RA including liraglutide is commonly associated with GI adverse effects including nausea and vomiting [68]. However, they were all well-tolerated, and no severe adverse events or severe hypoglycemia were reported in an RCT [56]. Moreover, a pooled analysis of phase 2 and 3a trials of liraglutide for weight management showed liraglutide was generally safe with no clinically significant neuropsychiatric safety concerns [69].

3. Conclusions

Disappointingly, evidence suggest that treatment of anti-hyperglycemic agents to depression have shown limited success. Although the antidepressant effects of PPARγ receptor agonists were supported in multiple clinical trials and meta-analyses, the antidepressant efficacy of anti-hyperglycemic agents so far has been equivocal. Since a bidirectional relationship between insulin resistance and depression is supported by several bodies of evidence, it is important to clarify the potential association of these two conditions and explore their common pathophysiological basis. Evidence from investigations of the antidepressant properties of repurposed anti-hyperglycemic agents may provide new insight into the role of brain insulin signaling in the pathophysiology of depression. In the present article, we reviewed the antidepressant properties of anti-hyperglycemic agents including metformin, PPARγ receptor agonists, and GLP-1RA and addressed the underlying mechanisms of these properties. However, although clinical trials have offered some encouraging results, few studies have addressed a sufficient number of biomarkers to enhance our understanding of the molecular and cellular mechanisms involved in the pathophysiology of depression and the antidepressant properties of anti-hyperglycemic agents. Additionally, other important issues are not addressed in this review. Insulin-sensitizing agents may improve the response to antidepressant drugs. Differential impact of changes in central versus peripheral insulin signaling system during pathological conditions and pharmacotherapy with agents targeting insulin receptor should also considered to gain a better understanding of the antidepressant effects of anti-hyperglycemic agents. Unraveling the relationships between depression and impaired insulin signaling could be a matter of great importance as we pursue an understanding of the associated pathophysiology and explore alternative treatment options. Further studies focusing on this issue are warranted.

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