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Review

Role of 5-HT2 receptors in diabetes: Swertiamarin seco-iridoid glycoside might be a possible 5-HT2 receptor modulator

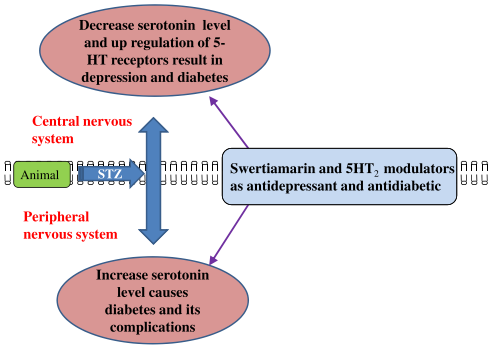
Rakesh Deelip Sonawane [a,c,*], Vijaykumar B. Deore [b,**], Savita D. Patil [d], Chandragouda R. Patil [a], Sanjay J. Surana [a,**], Ramesh K. Goyal [c,e,**]

[a] Department of Pharmacology, R.C. Patel Institute of Pharmaceutical Education and Research (RCPIPER), Karvand naka, Shirpur, Maharashtra 425205, India
[b] Medicinal Chemistry Department, Piramal Enterprises Limited, 1 Nirlon Complex, Off Western Express Highway, Goregaon (E), Mumbai, Maharashtra 400063, India
[c] Pharmacy Department, The M.S. University of Baroda, Vadodara, Gujarat 390001, India
[d] Department of Pharmacology, H.R. Patel Institute of Pharmaceutical Education and Research (HRPIPER), Karvand naka, Shirpur, Maharashtra 425205, India
[e] V ClinBio Labs, Sri Ramachandra University & Hospital, Porur, Chennai, Tamil Nadu 600116, India

HIGHLIGHTS

- Peripheral increase in 5-HT is a marker of diabetes and vice versa in the brain.
- 5-HT receptor expressions involved in pathogenesis of diabetes and depression.
- 5-HT2 modulators and SW ameliorate diabetes, depression and hyperlipidemia.
- 5-HT2 modulators and SW exhibit similar pharmacological profile.
- Similar signaling pathway indicates SW might be a 5-HT2 receptor modulator.

GRAPHICAL ABSTRACT



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ABSTRACT

In the present review, we are focusing on modulators of 5-HT2 receptors, swertiamarin and their role in diabetes. These drugs possess both central and peripheral actions in various animal models of depression, diabetes and obesity. Swertiamarin and 5-HT2 antagonist are reported antidepressant, hypolipidemic and beneficial in peripheral vasculopathy. In contrast to this, 5-HT2C selective agonist decreases hyperglycemia, hyperlipidemia and insulin secretogogue by action. Selective serotonin reuptake inhibitors (SSRIs) are known antidepressant having weight gain as an adverse effect. Swertiamarin has similar pharmacological actions as 5-HT2 antagonist and 5-

Abbreviations: DM, diabetes mellitus; 5-HT, 5-hydroxytryptamine; SSRIs, selective serotonin reuptake inhibitors; STZ, streptozotocin; 5-HTTLPR, serotonin transporter promoter polymorphism; 5-HTT, 5-HT transporter or serotonin transporter; SERT, serotonin transporter or 5-HT transporter; PCPA, chlorophenylalanine; LNAAs, large neutral amino acids; GG, genioglossus; GK, Goto–Kakizaki; KO, knockout; PFK, phospho fructo kinase; PLC, phospho lipase C; PKC, protein kinase C; ERK 1/2, extracellular signal-regulated kinase 1 and 2; JAK/STAT, janus kinases; p^{38} MAPK, phospho^{38} mitogen-activated protein kinases; PI_3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferator-activated receptor gamma; eNOS, endothelial nitric oxide synthase; PKB/Akt, protein kinase B; DOI, dimethoxy-4-iodoamphetamine hydrochloride; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA reductase; NF-κB, nuclear factor-κB; Glut 4, glucose transporter type **4**; SREBP-1c, sterol regulatory element binding protein-1c; LPL1, lipoprotein lipase 1; T2DM, type 2 diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; SD, Sprague Dawley; IDDM, insulin dependent diabetes mellitus; HSA, human serum albumin; AGEs, advanced glycation end products; GDM, gestational diabetes mellitus.

* Correspondence to: R.D. Sonawane, Department of Pharmacology, R.C. Patel Institute of Pharmaceutical Education and Research (RCPIPER), Karvand naka, Shirpur, Maharashtra 425205, India. Tel.: 91 2563 255189; fax: 91 2563 251808.
** Corresponding authors.
E-mail addresses: rakesh12283@gmail.com (R.D. Sonawane), vijaykumardeore@yahoo.co.in (V.B. Deore), sjsurana@yahoo.com (S.J. Surana), goyalrk@gmail.com (R.K. Goyal).

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HT2C selective agonist. This warrants that swertiamarin might modulate 5-HT2 receptors rather than affecting the uptake of serotonin. In the light of present investigation, the mechanism of these drugs can correlate the role of central and peripheral 5-HT2 receptors in diabetes.

Contents

1. Introduction

Diabetes mellitus (DM) affects people from young to adult age of developing and developed countries. Diabetes is one of the major non-communicable disease that results in morbidity and mortality. Millions of Indians suffering from diabetes mellitus and soon India will become diabetic hub [1]. Diabetic complications such as cardiomyopathy, neuropathy, and vascular complications such as retinopathy and nephropathy are triggered by hyperglycemic condition which further affect normal metabolism of carbohydrates, proteins and lipids. Etiology of diabetes mellitus is much complex, a result of various factors such as genetic, neurohumoral, stressful lifestyle, junk food and auto immune infections [2–4].

Serotonin (5-hydroxytryptamine, 5-HT) receptors are G-protein coupled receptors. 5-HT2 receptor having subtypes 5-HT2A, 5-HT2B and 5-HT2C coupled with G-protein. Serotonin release correlates with insulin secretion in clonal insulin-secreting cells using ^{3}H-serotonin [5]. Serotonin negatively regulates beta cell differentiation [6]. Peripheral increase in serotonin level is a marker of diabetic complications [7] and positive correlation established in between plasma 5-HIAA (serotonin metabolite) level and coronary heart disease in Japanese diabetic patients [8] indicate peripheral serotonin plays important role in the development of diabetes and its complication. In streptozotocin (STZ) induced diabetic mouse model depressive behavior has been observed due to decreased 5-HT levels in the brain. Insulin action produced a reversal of depression in STZ diabetic animals and ameliorated brain 5-HT level [9]. STZ induced diabetic animals have shown changes in expression of serotonin receptors. Selective serotonergic functional alterations have therapeutic relevance to diabetic rats. 5-HT1A receptor activation mediated antidepressant effects decreased by induction of diabetes in a mouse model [10]. 5-HT transporter (5-HTT) gene expression studies in diabetic rats implicate a role for 5-HT receptors in diabetes [11]. The serotonin transporter promoter polymorphism (5-HTTLPR) might be a marker of type 2 diabetic progression, acting through different mechanisms rather than affecting food intake and obesity [12]. Overall, we come to the conclusion that depression, diabetes and 5HT2 receptor modulation is possibly pleiotropy. 5HT2 receptor modulators and seco-iridoid glycoside, swertiamarin, (Fig. 1) possess a similar pharmacological profile, which might explain the mechanism of swertiamarin.

2. Swertiamarin and 5-HT2 modulators as antidepressant

Swertiamarin was reported as an antidepressant in mice and rats [13]. 5-HT2 antagonists are reported as antidepressants with an effect on serotonin as well as on dopamine levels [14]. 5-HT2C receptor agonists exhibit the antidepressant action in a rat model [15].

3. Pharmacological actions suggesting swertiamarin as 5-HT2 modulators

In the present discussion, swertiamarin and 5-HT2 modulators possess similar central and peripheral actions as both are reported as antidepressants [13,16]. In the peripheral nervous system, 5-HT2 modulators and swertiamarin possess a hypolipidemic and anti-diabetic activity in various animal models (Fig. 2) while SSRIs exhibit similar pharmacological profile, but show weight gain as an adverse effect [17] which implies that swertiamarin does not affect serotonin uptake.

4. Serotonin and diabetes

Serotoninergic mechanism affects glycogen synthesis of hepatocytes due to phosphorus inactivation and countered by the atypical antipsychotic result in insulin resistance. 5-HT mediated hepatic dysregulation may induce type 2 diabetes by antipsychotic therapy [18]. Elevated plasma and whole blood serotonin levels are biomarkers of vascular complications and organ damage in patients at the early stage of diabetes mellitus [7]. In obese population having lower

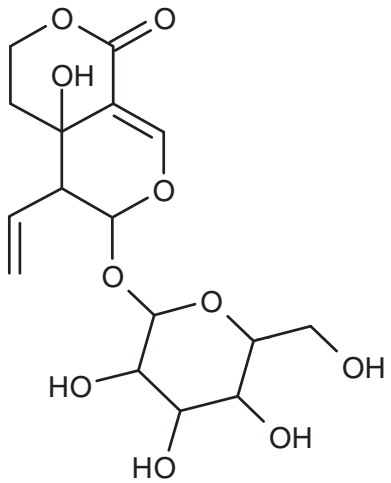

Fig. 1. Chemical structure of swertiamarin.