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Molecular Docking of Gamma Amino Butyric Acid GABA on Rattus Norvegicus B-receptor as Antidiabetic

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Abstract: Earlier research reported that GABA had a correlation with diabetes in processes of glucose homeostasis. This study aims to identify the validity of B-receptor *Rattus norvegicus* as GABA protein target, modeling the structure and knowing the binding affinity between GABA and B-receptor *Rattus norvegicus* through molecular docking. The research was carried out using in-silico method. The interaction of GABA with the target protein was determined using SuperPred, followed by modeling the protein target using SwissadMe. Ramachandran Plot and Errat Procheck are used to determine the validity of the protein target. Molecular docking was determined using Pyrx and PyMol. The results showed that GABA binding to the B- receptor Rattus norvegicus has biological activity as glucose oxidase inhibitor and antidiabetic. The conclusion are: B-receptor Rattus norvegicus is a valid protein target for binding to GABA; there are four 3-dimensional models of B-receptor *Rattus norvegicus* and the best model has 98.43% sequence identity; the binding affinity of GABA (ligand) on B-receptor *Rattus norvegicus* from the best model is -3.4 kcal/mol energy, 1.773 RMSD lower bound, and 1.81 RMSD upper bound. It is suggested that this research might be used as an empirical basis to further investigate GABA as antidiabetic.

Keywords: Antidiabetic; GABA; GABA B receptor; Molecular docking; Rattus norvegicus

Introduction

Diabetes was the ninth biggest cause of death worldwide in 2019, according to the World Health Organization (WHO, 2020). This result is based on the rise in male mortality due to diabetes, which has increased by 80% since 2000. In coherence with the WHO, the International Diabetes Federation (2021) estimated, the number of diabetics will increase by more than 600 million in 2030 and reach 735 million in 2045. Research related to anti-diabetes needs to be conducted to address this global health issue.

Gamma Amino Butyric Acid (GABA) is an active compound that has potential as antidiabetic. In mammals, GABA is the main neurotransmitter in the central nervous system. Besides in central nervous system, GABA also exists in high concentration in pancreas β-cells with insulin (Nikmaram et al., 2017). Earlier research reported that GABA in pancreas had correlation with diabetes in regards with regulating glucose homeostasis condition and including insulin and glucagon in their regulation process (Taneera et al., 2012), effect on insulin expression in pancreas by IHC (Indrowati et al., 2017) and promotes β-cell proliferation (Untereiner et al., 2019).

Liu et al. (2017) reported GABA and sitagliptin individually improved glucose control, increased plasma insulin levels, and reduced plasma glucagon levels. Its related with stated from Choat et al. (2019) that GABA may protect β-cells from autoimmune destruction, reduce pancreatic inflammation, and potentiate the regeneration of new β-cells in the setting

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of type 1 diabetes mellitus (Choat et al., 2019). Rezazadeh et al. (2021) showed GABA and insulin treatments effectively lowered blood glucose levels, improved glucose tolerance, and reduced HbA1c levels in patients and their offspring. GABA also increased insulin sensitivity as measured by glucose infusion rates (GIR) and enhanced the expression of IRS1, Akt, and GLUT4 genes, which are crucial for insulin function. Furthermore, Soltani et al. (2011) found that GABA therapy has potential clinical application in treating T1D by regulating islet cell function and glucose regulation through both β-cell restoration and immunosuppression pathways.

GABA can function optimally when it encounters valid receptors. There are two kinds of receptors of GABA involves GABAA and GABAB receptors, which structures and functions were different. GABAA receptors are ligand-gated chloride channels formed up of pentameric arrangements of several subunits (Ghit et al., 2021). GABAB receptors are G protein-coupled receptors that activate Gαi/o-type proteins, providing slow and persistent inhibitory activity. GABAB receptors exert their inhibitory effects by activating positively rectifying K+ channels, inactivating voltage-gated Ca2+ channels, and inhibiting adenylate cyclase (Terunuma, 2018). The GABA-B receptor is found, among others, in Rattus norvegicus. The potential of GABA as an anti-diabetic agent can be more comprehensively understood if information about the binding of GABA to its receptor is validated.

This study aims to identify the validity of Rattus norvegicus B-receptor as GABA protein target, modeling the structure of GABA B receptor Rattus norvegicus and knowing the binding affinity between GABA and B receptor Rattus norvegicus. The research was carried out using the in-silico method through molecular docking analysis. The results of in silico research can become the basis for further research, including antidiabetics in vivo research.

This research is important because it provides specific information about the precise molecular basis of GABA binding to target proteins. The novelty of the research is presented by the absence of research results that provide specific information about the biological activity of GABA binding to the GABA-B receptor in Rattus norvegicus from a valid three-dimensional model structure review based on a molecular basis.

Method

The research was carried out using the in-silico method. The interaction of GABA with the target protein was determined using SuperPred, followed by modeling the protein target using SwissadMe. Ramachandran Plot and Errat Procheck are used to determine the validity of the target protein. Molecular docking of GABA with B-receptor in *Rattus norvegicus* was determined using software from Pyrx and PyMol. The workflow is presented in Figure 1.

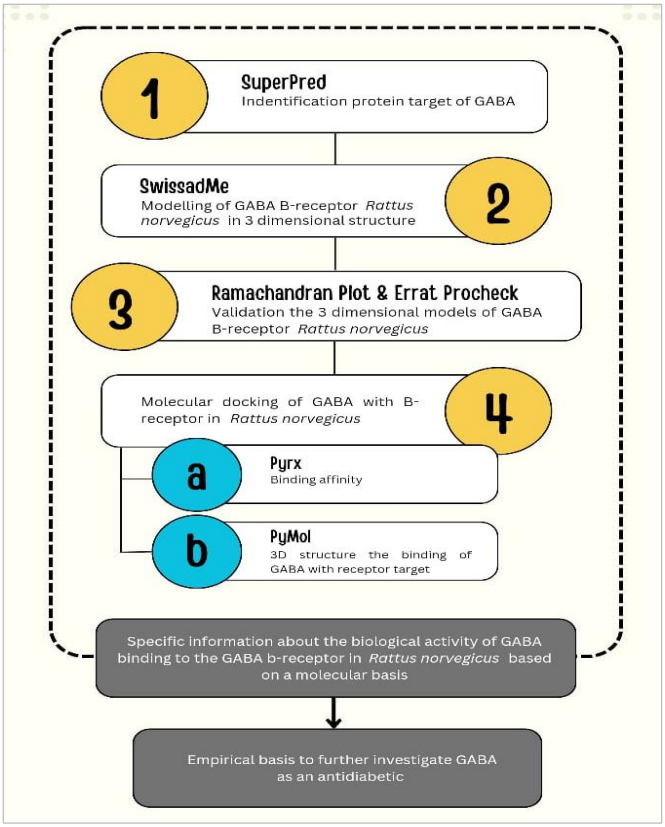


Figure 1. Workflow of molecular docking GABA B receptor Rattus norvegicus

Result and Discussion

The research was conducted in silico, starting with the identification of the GABA structure through the PubChem NCBI website. The identification results show GABA (mf C4H9NO2), Canonical smiles GABA C(CC(=O) O) CN and molecular weight 103.12 g/mol. GABA is also known by other names such as 4-aminobutyric acid, 4-Aminobutanoic acid, Piperidic acid, Piperidinic acid, Aminalon, 56-12-2, Gaballon, or Gammalon.

The computational prediction from PASSonline Way2drug indicates that in wet lab experiments, GABA has been strongly implicated in biological activity as a glucose oxidase inhibitor (Pa 0.938; Pi 0.003; Pa>Pi; Pa>0.7). However, its predicted biological activity as an antidiabetic agent remains weak (Pa 0.194; Pi 0.172; Pa>Pi; Pa<0.3). The computational results from SuperPred for identifying protein targets indicate that the GABA-B receptor is one of the protein targets associated with GABA, with visualization at 7C7S, activity at 530 nm, and EC50 type.

The protein target used for specific three-dimensional modeling is gamma-aminobutyric acid (GABA) B receptor 2 *Rattus norvegicus* justified with FASTA. FASTA is a text-based file format representing nucleotide sequences, originating from the FASTA software package, and it has become a standard in bioinformatics. Information from FASTA of GABA B-receptor 2 *Rattus norvegicus* are NC_086023.1:c66083695-65743073 Gabbr2; organism=*Rattus norvegicus*; GeneID 83633 and location at chromosome 5 locus. Besides GABA B-receptor 2, there's other targets in *Rattus norvegicus*, which is the CRA isoform of GABA B-receptor 1.

The GABA's protein target was modeled using SwissadMe, with validation determined using Ramachandran Plot and Errat Procheck. The results from SwissadMe computation indicate there are four 3-dimensional models of GABA B-receptor *Rattus norvegicus* with varying sequence identity values. Those four models are shown in Figure 2.

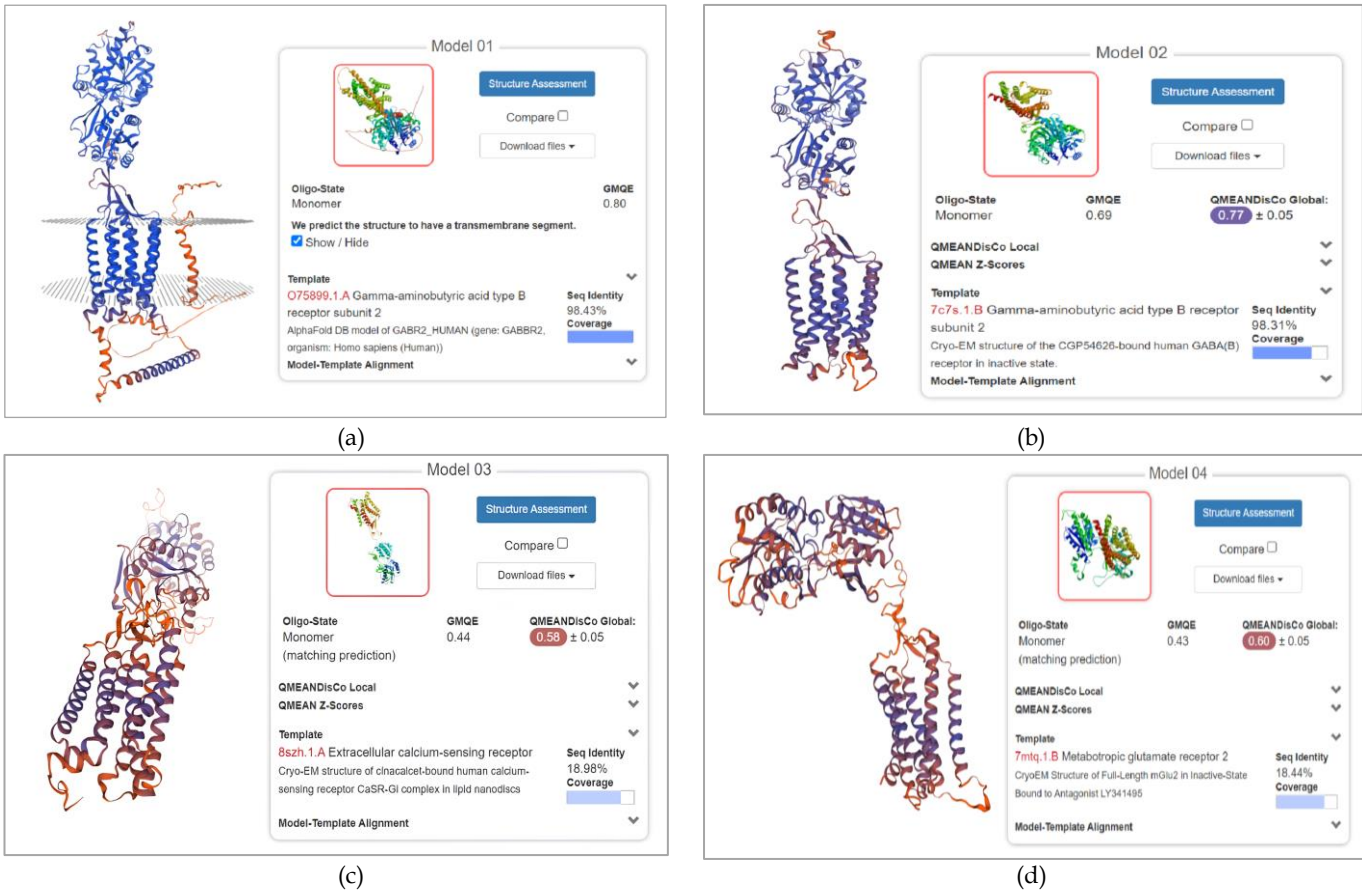
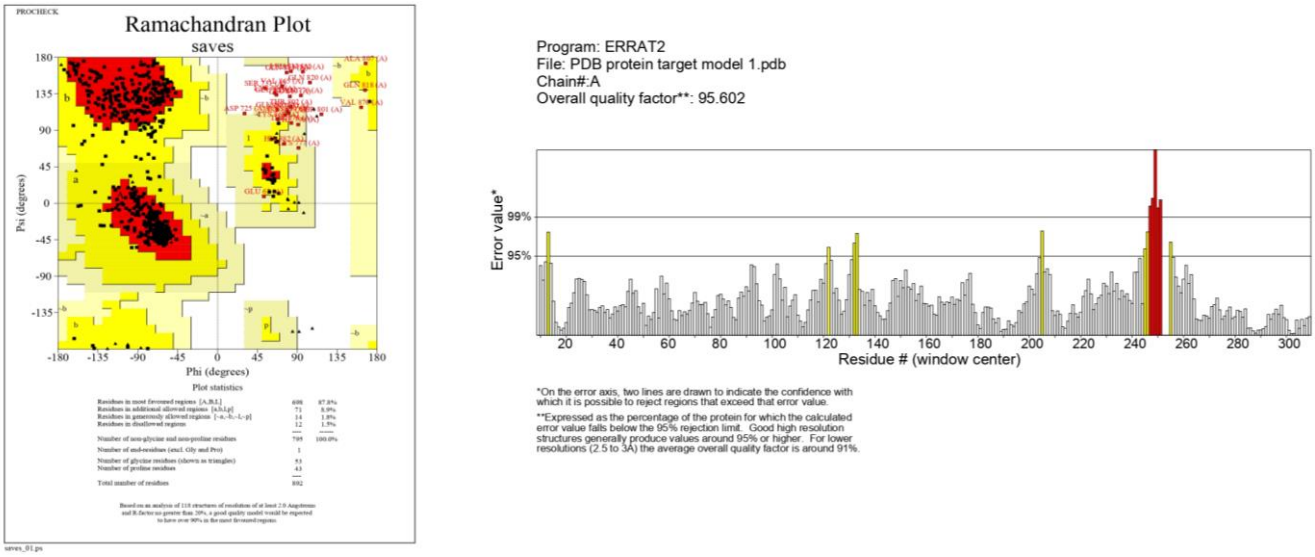


Figure 2. Model of GABA B-receptor *Rattus norvegicus*: (a) Model 1; (b) Model 2; (c) Model 3; and (d) Model 4

Based on the four three-dimensional models of the GABA B receptor in *Rattus norvegicus*, the best model is model 1 with a sequence identity value 98.43%. The validation of 3 dimensions structure model Gaba B-receptor *Rattus norvegicus* using Ramachandran Plot and Errat Procheck. Results of validation model 1 are presented in Figures 3.

Next, molecular docking computational analysis was conducted using the Pyrx program to determine the binding affinity of four models from GABA B-receptor *Rattus norvegicus*. The result of Pyrx computation is presented in Table 1.

Based on the molecular docking analysis conducted using Pyrx, it was determined that model 1, which has a sequence identity of 98.43%, exhibits the highest affinity. Additionally, the results of molecular docking indicate that the binding affinity of GABA (the ligand) to the B-receptor of Rattus norvegicus is -3.4 kcal/mol energy, with lower and upper bound RMSD values of 1.773 and 1.81, respectively. The three-dimensional model depicting the interaction between GABA and the B-receptor of *Rattus norvegicus* was visualized using PyMol, as illustrated in Figure 4. The visualization results indicate that GABA as a ligand and B-receptor of *Rattus norvegicus* as its protein target can bind perfectly.



(a) (b)

Figure 3. GABA B-receptor *Rattus norvegicus* model 1: (a) Result of Ramachandran Plot GABA B-receptor *Rattus norvegicus*; and (b) Result of ERRAT Procheck GABA B-receptor *Rattus norvegicus*

Table 1. Molecular Docking Result of GABA B-receptor *Rattus norvegicus* Computed by Pyrx

Model Ligand	Seq. Identity (%)	Binding Affinity (kcal/mol)	RMSD lower bound	RMSD upper bound
Model 1	98.43	-3.4	1.773	1.81
Model 2	98.31	-3.6	14.901	15.321
Model 3	18.98	-3.1	2.654	3.086
Model 4	18.44	-2.6	11.086	11.947

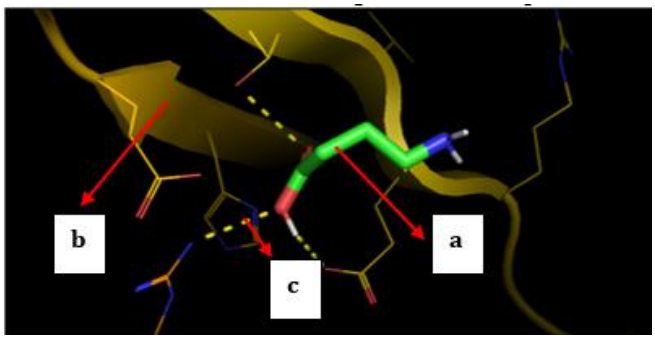


Figure 4. Molecular docking results of binding visualization between GABA and B-receptor Rattus norvegicus, computed by PyMol. (a) GABA as ligan. (b) GABA B-receptor Rattus norvegicus as protein target. (c) The binding of ligan and protein target

The comprehensive results of the study reveal that GABA holds substantial promise as an antidiabetic agent by targeting specific proteins. Gamma-aminobutyric acid (GABA) plays a pivotal role in both diabetes management and neuroprotection, particularly through its interactions with the GABA B-receptor of *Rattus norvegicus*. GABA serves as a crucial inhibitory neurotransmitter in the brain, where it modulates neuronal communication and maintains overall brain function (Shaye et al., 2021). Ngo et al. (2019) stated Gamma-aminobutyric acid (GABA) is a non-proteinogenic amino acid widely found in microorganisms, plants, and vertebrates. It has the potential to serve as a versatile therapeutic agent with applications in treating various diseases and promoting overall human health. Martin et al. (1998) reported the decrease in GABAergic activity due to the reduction of GABA B receptors on neurons may be a contributing factor to the resistance to antidepressants in rats with diabetes (Martin et al., 2022).

GABA also exerts significant influence on pancreatic hormone regulation. GABA regulates insulin and glucagon secretion, suggesting potential therapeutic avenues for enhancing beta-cell function in diabetes mellitus through activation of GABA(A) channels and modulation of GABA(B) receptors, it regulates. This dual action not only facilitates the maintenance of glucose homeostasis but also underscores GABA's role in metabolic regulation.

Moreover, GABA exhibits notable neuroprotective properties, including its ability to mitigate oxidative stress and preserve pancreatic health. These effects are crucial in reducing the risk of neurodegenerative diseases commonly associated with diabetes (Eltahawy et al., 2017). The intricate interaction between GABA and the GABA B receptor, as elucidated by Shen et al. (2021), highlights the receptor's critical role in mediating these effects. Specific conformational changes and intricate signal transduction mechanisms contribute to GABA's ability to modulate neuronal function and protect against cellular damage in diabetes.

Furthermore, insights from studies on differential protein profiles and immune modulation by Al-

Kuraishy et al. (2021) and Bare et al. (2018) underscore the therapeutic potential of targeting the GABA B receptor in diabetes management. Bare et al. (2018) noted differential protein profiles between type 2 diabetes mellitus (T2DM) and control rats, highlighting variations in protein bands across heart, liver, and kidney tissues. Al-Kuraishy et al. (2021) outlined the pancreatic GABA signaling system's role in hormone secretion regulation, immune suppression, β-cell survival enhancement, and potential conversion of α-cells to β-cells, proposing GABA as a promising oral treatment option for both type 1 and type 2 diabetes mellitus.

Yeap et al. (2012) reported that the presence of increased levels of GABA and free amino acids in fermented mung bean and Mardi Rhizopus sp. 5351 extracts contributes to significant antihyperglycemic effects in alloxan-induced hyperglycemic mice, effectively lowering blood sugar levels without inducing hypoglycemia in normal mice. Hosseini et al. (2021) reported GABA administration improves liver function and insulin resistance in offspring of type 2 diabetic rats. These studies have shown variations in protein bands and immune responses between diabetic and non-diabetic conditions, emphasizing GABA's role in regulating these pathways.

GABA study was reported as role in episodic memory dysfunction (Thielen et al., 2019), ketosis management (Gaba et al., 2019), signalling in human pancreatic islets (Jin & Korol, 2023), metabolic stress (Ma et al., 2020), secretion in cytosolic beta cells (Menegaz et al., 2019), canine diabetes O'Kell et al. (2021) and insulin therapy (Rabinovitch et al., 2023). Fanisah et al. (2023) discussed the medicinal potential of natural plants, promoting their use in combination therapies with fewer side effects compared to conventional drugs. Jin et al. (2023) underscored GABA's presence in blood and its role in modulating interactions between immune and pancreatic islet cells, particularly relevant in type 1 diabetes. These insights further underscore GABA's broader physiological implications beyond its traditional neurotransmitter role, suggesting potential applications in immune modulation and integrative medicine approaches.

Studies of GABA in experimental animals show that GABA dramatically improves glucose tolerance in streptozotocin-induced diabetic rats fed with high-fat diet (Sohrabipour et al., 2018); has correlation with insulin-deficient diabetic mice (Sarnobat et al., 2022) and glibenclamide combination therapy in streptozotocin induced diabetes (Zhu et al., 2021).

Zhang et al. (2022) showed that GABA has effects on glycolipid metabolism, as well as intestinal flora in type 2 diabetic mice; GABA-Rich germinated Adzuki beans treatment has hypoglycemic effects on T2DM mice (Jiang et al., 2021) and triple drug therapy with GABA, sitagliptin, and osmeprazole prevents type 1 diabetes onset and promotes its reversal in non-obese diabetic mice (Lagunas-Rangel et al., 2022). Daems et al. (2019) reported treatment with empagliflozin and GABA improves β -cell mass and glucose tolerance in streptozotocin-treated mice.

GABA receptors have various roles that have been studied, including GABA receptor agonists in anesthesia and sedation (Brohan & Goudra, 2017); electrophysiology of ionotropic GABA receptors (Sallard et al., 2021); expression and function of GABA receptors in myelinating cells (Serrano-Regal et al., 2020) and structural basis of metabotropic GABA receptor (Shaye et al., 2020). Tian et al. (2023) also reported about the GABA and GABA-receptor system in inflammation, anti-tumor immune responses, and COVID-19. This shows that information about GABA B receptors, including those found in *Rattus norvegicus*, is an important study as a basis for research on GABA as an antidiabetic.

In conclusion, GABA emerges as a multifaceted molecule with significant implications in both diabetes management and neuroprotection. Its interactions with the GABA B receptor highlight its role in modulating neuronal function, regulating pancreatic hormone secretion, and protecting against oxidative stress. The therapeutic potential of targeting the GABA B receptor in diabetes management warrants further investigation, with potential implications for developing novel treatments to enhance metabolic regulation and mitigate the complications of diabetes. Future studies should continue to explore these interactions to advance our understanding and application of GABA in biomedical research and clinical practice.

Conclusion

The conclusion is B receptor *Rattus norvegicus* is a valid protein target for binding to GABA; there are four 3-dimensional models of B-receptor *Rattus norvegicus* and the best model has 98.43% sequence identity; the binding affinity of GABA (ligand) on B-receptor *Rattus norvegicus* from the best model is -3.4 kcal/mol energy, 1.773 RMSD lower bound, and 1.81 RMSD upper bound. It is suggested that this research might be used as an empirical basis to further investigate GABA as an antidiabetic.

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Author Contributions

Conceptualization, M, H, J, U, E; Methodology, M, H, U; Validation and formal analysis M, H, U, J, E; Resources M, H, J, E; Writing original draft preparation, M, U; writing, review and editing M, H, J, U, E.

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Conflicts of Interest

All the authors have no conflict of interest. All authors agreed to the published version of the manuscript.

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