Evidence for Central Regulation of Glucose Metabolism

Two abbreviations are used: T2DM, Type 2 diabetes; T1DM, Type 1 diabetes.

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Evidence for central regulation of glucose homeostasis is accumulating from both animal and human studies. Central nutrient and hormone sensing in the hypothalamus appears to coordinate regulation of whole body metabolism. Central signals activate ATP-sensitive potassium (K\textsubscript{ATP}) channels, thereby down-regulating glucose production, likely through vagal efferent signals. Recent human studies are consistent with this hypothesis. The contributions of direct and central inputs to metabolic regulation are likely of comparable magnitude, with somewhat delayed central effects and more rapid peripheral effects. Understanding central regulation of glucose metabolism could promote the development of novel therapeutic approaches for such metabolic conditions as diabetes mellitus.

The estimated global prevalence of Type 2 diabetes (T2DM)\textsuperscript{2} is 347 million (1). Because glycemic control is achieved in only \textasciitilde{}40% of patients, additional therapeutic strategies are needed (2). Increased endogenous glucose production (EGP) is the main source of fasting hyperglycemia (3, 4), contributing \textasciitilde{}80% of diurnal hyperglycemia in T2DM (5). Apart from insulin, there is no treatment targeting basal EGP. Better understanding its regulation would have important therapeutic implications.

We will examine the evidence for central sensing of nutritional and hormonal signals in animal models and humans, focusing on CNS regulation of glucose metabolism.

Evidence for CNS Nutrient and Hormone Sensing in Animals

Unlike other organs, the brain is an obligate consumer of glucose (6). Central regulation of EGP would therefore be teleologically advantageous. Since the first demonstration by Claude Bernard (7) that lesions in the floor of the fourth ventricle altered blood glucose levels, the ability of central glucose sensing to regulate peripheral glucose homeostasis has been extensively examined in animal models. There are glucose-sensing neurons in many areas of the brain (8), particularly the hypothalamus (9). Specifically, the ventromedial hypothalamus (VMH) and arcuate nucleus (10) integrate hormonal and nutrient signals impacting peripheral metabolism (Fig. 1). Central signals appear to activate hypothalamic ATP-sensitive potassium (K\textsubscript{ATP}) channels (9, 11, 12) composed of an inward rectifier potassium ion channel Kir6.2 subunit and a sulfonylurea receptor (SUR) subunit. Pharmacologic compounds including diazoxide activate and thereby close hypothalamic K\textsubscript{ATP} channels, whereas sulfonylureas inhibit and thereby open them, ultimately modulating EGP (12).

Glucose—Elegant studies in rats showed that direct infusion of D-glucose into the VMH inhibited counterregulatory hormonal responses to systemic hypoglycemia during a hypoglycemic clamp, indicating that VMH glucose sensing is needed for the systemic response to peripheral hypoglycemia (13). VMH infusion of L-lactate, a byproduct of glucose metabolism and an alternate fuel source for neurons in conditions of glucose deficiency, produced similar suppression of the counterregulatory hormonal response to systemic hypoglycemia (14). In mice, intracerebroventricular (ICV) injection of glucose suppressed hypothalamic AMP-activated protein kinase (AMPK), an evolutionarily conserved serine/threonine kinase that regulates energy consumption and food intake (15).

Other key studies have examined the role of central glucose sensing in regulating EGP. In conscious rats, ICV glucose infusion decreased peripheral glucose and insulin levels (16). Furthermore, under clamp conditions with replacement of basal insulin, ICV glucose suppressed EGP via inhibition of hepatic glucose-6-phosphatase expression, causing decreases in plasma glucose. Similar findings were reported with ICV infusion of lactate. Because lactate is converted to pyruvate by glial cells, this supported the hypothesis that glial cells provide essential nutritional support to neurons, which in turn generate signals that modulate peripheral glucose handling (17). Importantly, ICV infusion of the K\textsubscript{ATP} channel blocker glibenclamide abolished the effects of ICV glucose and lactate, showing that EGP is ultimately impacted by central conversion of glucose to lactate to pyruvate, via hypothalamic K\textsubscript{ATP} channel activation (16). Hypothalamic infusion of glucose similarly suppressed EGP, an effect negated by hypothalamic coinfusion of glibenclamide, further supporting the ability of glucose to regulate EGP via central K\textsubscript{ATP} channel activation. In addition, peripheral hyperglycemia in rats increased hypothalamic glucose levels and suppressed EGP, whereas inhibiting central metabolism of lactate partially abolished suppression of EGP by hyperglycemia (16).

Further studies showed that transgenic mice with impaired glucose sensing by pro-opiomelanocortin (POMC) neurons due to expression of a mutant Kir6.2 subunit developed impaired glucose tolerance (18). Additionally, obese mice on a high fat diet developed similarly impaired firing of POMC neurons in response to glucose (19). Together, this suggests that the normal physiology of central glucose sensing can be disrupted under certain nutritional and metabolic conditions.

Insulin—Since the first study reporting that impairment of central insulin sensing causes peripheral glucose intolerance...
there has been extensive research into the role of central insulin in the regulation of glucose metabolism. Mice with neuron-specific disruption of the insulin receptor gene developed diet-induced obesity, mild insulin resistance, elevated fasting plasma insulin levels, and hypertriglyceridemia (20). The role of hypothalamic KATP channels in modulating the effects of central insulin has been well documented in rodents. In hypothalamic glucose-sensing neurons obtained from lean rats, insulin stimulated firing of KATP channels, but this effect was impaired in neurons from obese rats, with coadministration of the KATP channel inhibitor tolbutamide or coadministration of phosphatidylinositol 3-kinase (PI3K), the downstream signaling molecule of insulin (19).

Infusion of an insulin receptor antagonist into the third cerebral ventricle decreased insulin receptor content in the medial arcuate nucleus of the rat hypothalamus, with subsequent development of hyperphagia, increased fat mass, and failure to suppress EGP during hyperinsulinemic clamps (21). Moreover, ICV infusion of insulin or a small-molecule insulin mimetic enhanced peripheral insulin action within 6 h when insulin was maintained at basal levels and the pancreas was “clamped” with somatostatin (i.e. “pancreatic-euglycemic clamp” conditions) (22). Of note, these clamp studies were of relatively short (2-h) duration, but central insulin infusions were initiated 4 h prior to the start of the clamp. Because pancreatic insulin secretion was blocked by somatostatin infusion, the improvement in peripheral insulin action demonstrated in these studies was attributed to suppression of EGP by central insulin or its mimetic. Furthermore, inhibition of central insulin action (by ICV coinfusion of insulin receptor antibodies or inhibitors of PI3K) impaired the ability of central insulin to suppress EGP by ~50%, suggesting comparable degrees of regulation by central versus peripheral inputs (22). No such impairment was observed when an alternate insulin signaling pathway, mediated by mitogen-activated protein kinase (MAPK), was blocked, suggesting that the PI3K branch of the insulin signaling pathway is the key player in central suppression of EGP. Decreased PI3K signaling in murine hypothalamic POMC neurons was also shown to impair whole body glucose regulation, whereas increased PI3K activity improved insulin sensitivity (23). ICV coinfusion of KATP channel blockers tolbutamide or glibenclamide blunted the acute effect of central insulin on EGP, showing that central insulin mediates its metabolic effects via hypothalamic KATP channel activation in vivo (22). The ability of central insulin to activate PI3K was subsequently confirmed in rats. Hypothalamic insulin infusion activated insulin receptor substrate (IRS)-1 and IRS-2, PI3K, and its downstream target Akt with consequent decreased food intake (24). These effects were blocked by coinfusion of PI3K inhibitors into the ICV. Further studies also showed that intrahypothalamic insulin administration suppressed pancreatic glucagon release under hypoglycemic clamp conditions in rats (25).

As discussed, central KATP channel activation impacts EGP and whole body glucose metabolism. ICV or intrahypothalamic infusion of the KATP channel activator diazoxide reduced peripheral glucose levels and suppressed EGP within 4 h (12). Specifically, gluconeogenesis was inhibited, with decreased hepatic expression of gluconeogenic enzymes, whereas glycogenolysis was not affected (12). Further, ICV coinfusion of the KATP channel blocker glibenclamide abolished the effect of central insulin on EGP, as did hepatic efferent branch vagotomy. In addition, clamp studies in SUR1 null mice showed that these mice had hepatic insulin resistance with dramatically increased EGP. Thus, the above work defined the role of hypothalamic SUR1-containing KATP channels in modulating hepatic gluconeogenesis and suggested that central insulin mediates its effect on EGP via vagal nerve efferent signaling to the liver (12). Recent work has also implicated extra-hypo-
The mechanism whereby central insulin suppresses EGP appears to be via phosphorylation of hepatic signal transducer and activator of transcription 3 (STAT3) (28–30). Mice with liver-specific STAT3 deficiency are insulin-resistant with increased gluconeogenic enzyme expression, whereas constitutive hepatic STAT3 activation improves glucose tolerance in diabetic mice (29). Clamp studies in mice showed that rises in peripheral insulin promote hepatic STAT3 phosphorylation in a time-dependent fashion (28). Mice deficient in hepatic STAT3 also displayed blunted effects of ICV insulin infusion on EGP and gluconeogenic enzyme expression. Intriguingly, insulin failed to induce STAT3 phosphorylation in cultured hepatocytes (29), suggesting that insulin mediates this effect independent of its hepatic signaling. In addition, interleukin-6 (IL-6) appears to activate STAT3 and inhibit gluconeogenic enzyme expression (29). ICV insulin infusion also failed to increase hepatic STAT3 phosphorylation in mice lacking IL-6 (28), suggesting that central insulin may function via IL-6-mediated hepatic STAT3 activation to suppress EGP. The importance of hepatic STAT3 was further shown in mice with inducible insulin receptor inactivation, either in the whole body or in peripheral tissues only (30). Mice with brain insulin receptor inactivation had worse hyperglycemia and failed to increase hepatic STAT3 phosphorylation or up-regulate IL-6 expression. Furthermore, control mice given chronic ICV insulin had increased fat mass and adipose tissue lipoprotein lipase expression (30). This work highlights the importance of central insulin in regulating peripheral glucose and lipid metabolism via hepatic STAT3 activation.

Other important work has established specific features of the signaling pathways whereby central insulin suppresses EGP in rodents. ICV insulin infusion failed to suppress EGP in mice lacking hepatic Irs1 and Irs2 (double knock-out mice) during hyperinsulinemic-euglycemic pancreatic clamps (31). In addition, agouti-related peptide (AgRP)-expressing neurons of the arcuate nucleus of the hypothalamus were identified as the specific neurons responsive to central insulin and driving suppression of EGP in mice (32). This was confirmed by additional studies in mice establishing the key role of insulin action in AgRP neurons in suppressing EGP (33), as opposed to POMC neurons in which constitutive PI3K activation led to hyperphagia and diet-induced obesity in female mice (33, 34). The role of melanocortin receptor activation was also elucidated in rats, in studies showing that ICV α-melanocyte-stimulating hormone infusion accentuated the peripheral action of insulin (35). Conversely, hypothalamic S6 kinase seems to have an inhibitory effect on hypothalamic insulin action. After only 1 day of high fat diet, the ability of hypothalamic insulin to suppress EGP was blocked, an effect likely mediated by hypothalamic S6 kinase activation (36).

The relevance of central insulin action to the treatment of diabetes has been a subject of extensive study, with some animal models suggesting that impaired central insulin action contributes to the metabolic defects of diabetes. Hypothalamic signaling via the IRS-PI3K pathway was reduced in rats with uncontrolled streptozocin-induced diabetes. Enhancement of central insulin action via hypothalamic overexpression of IRS-2 or a downstream mediator of PI3K action improved the glucose-lowering effect of peripheral insulin by 2-fold (37). The benefit of central insulin action in improving peripheral glucose metabolism was shown both in the acute setting and over several days of insulin therapy, suggesting both acute and chronic roles for hypothalamic insulin signaling in diabetes treatment (37).

First, diabetic rats receiving ICV insulin infusions or insulin plus glucose for 4 weeks had decreased food intake and body weight and reduced EGP during hyperinsulinemic clamps (38). This work highlighted the crucial role of central insulin on whole body glucose and nutrient handling in rats, opening the possibility of future diabetes treatments directed at central targets.

A key area of controversy has been translating evidence for central regulation of EGP from rodents to the physiology of larger mammals. Short duration pancreatic clamp studies in conscious dogs failed to show an acute impact on EGP when insulin delivery to the head was increased 4-fold (39). Further work in dogs confirmed the ability of ICV insulin infusion to increase hepatic STAT3 phosphorylation and suppress hepatic gluconeogenic enzyme expression (40). Although glucose production was not affected in this acute setting, net hepatic glucose output did slowly decrease over the course of these clamps. Given the reduction in gluconeogenic enzyme gene expression, longer duration studies might have revealed an effect on EGP. This possibility was raised by follow-up clamps in dogs showing a trend toward decreased EGP in the setting of ICV insulin infusion, which was not significant in the acute (<4 h) setting, but may have required a longer duration clamp to detect (41).

Of note, the rodent studies discussed above were of longer duration and in some cases involved chronic models. Indeed, although the maximal effects of insulin on tissue signaling are seen shortly after administration (42), an extended duration of about 5 h of hyperinsulinemia is needed to demonstrate its maximal whole body effects on glucose handling (43), highlighting the potential importance of more prolonged central signaling on the regulation of glucose production. Importantly, no studies to date have evaluated the time-dependent effect of CNS insulin on glucose production in rodents, and such studies would add important insights to the field. Furthermore, it is possible that some metabolic endpoints may be rapidly impacted by central pathways (44), whereas others may require more prolonged central pathway activation to manifest their full effects.

**Fatty Acids**—Fatty acids are another key modulator of EGP, and accumulating evidence shows that the hypothalamus senses circulating nutrients, including fatty acids, with consequent effects on food intake and whole body glucose handling (45). ICV infusion of the long-chain fatty acid (LCFA) oleic acid in rats led to rapid reductions in food intake, gluconeogenic enzyme expression, and EGP, whereas ICV infusion of a short chain fatty acid had no effect on these parameters (46). Central effects of LCFA infusion were completely abolished after only a few days of high fat feeding, highlighting the potential for dysregulation of central monitoring of nutrient intake in the pathogenesis of obesity and insulin resistance (47). Furthermore,
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inhibition of LCFA breakdown via selective inhibition of hypothalamic carnitine palmitoyltransferase (CPT1) also led to decreased food intake and EGP in rats, highlighting the role of the hypothalamus as a nutrient sensor and the role of LCFAss as a signal of nutrient abundance (48). Of note, hypothalamic CPT1 inhibition in overfed rats restored hypothalamic lipid sensing and suppression of EGP, suggesting potential therapeutic avenues in obese and overfed models (49).

Furthermore, in rats, hypothalamic K\(_{\text{ATP}}\) channels are activated by central lipid fluxes, and efferent vagal input from the brainstem to the liver is required for hypothalamic lipids to impact expression of gluconeogenic enzymes and EGP (50). A key study integrating the above findings confirmed in rats that physiologic increases in circulating LCFAss lead to suppression of EGP, and blocking hypothalamic K\(_{\text{ATP}}\) channels with ICV glibenclamide abolishes this effect, as does inhibition of fatty acid esterification by ICV infusion of an acyl-CoA synthetase inhibitor, genetic deletion of hypothalamic K\(_{\text{ATP}}\) channels, or hepatic vagotomy (51). Thus, hypothalamic K\(_{\text{ATP}}\) channels were established as a common pathway for central insulin, glucose, and fatty acid sensing in rat models. Some of the molecular mechanisms of hypothalamic K\(_{\text{ATP}}\) channel lipid sensing were later clarified; hypothalamic protein kinase C (PKC) activation was necessary for central lipid administration to modulate EGP in rats (52). Conversely, central insulin also seems to modulate peripheral lipid metabolism because central insulin administration restrains lipolysis in white adipose tissue, whereas mice lacking central insulin receptors have unrestrained white adipose tissue lipolysis (53). Thus, a complex interplay between central and peripheral lipid metabolism has been established in rodent models.

Central Sensing of Nutritional Status—Extensive studies suggest that the CNS, specifically the hypothalamus, is a sensor of overall nutrient status, modulating food intake and glucose metabolism (45). Malonyl-CoA, the intermediate molecule in fatty acid biosynthesis, is a hypothalamic indicator of whole body nutritional status in mice (54) and rats (55). The mammalian target of rapamycin (mTOR) is also an important hypothalamic fuel sensor in rats, colocalizing with anorexigenic POMC neurons and increasing in response to both central leucine and leptin administration to decrease food intake and body weight (56). Additionally, constitutive hypothalamic expression of AMPK leads to increased food intake and body weight, whereas its suppression has an anorexigenic effect (15). Indeed, hypothalamic AMPK is suppressed in response to central insulin, glucose, and leptin in mice, and stimulated in response to ICV infusion of the orexigenic agouti-related protein (15). mTOR and AMPK may in fact change in tandem to control energy status because ICV leucine administration causes decreased hypothalamic AMPK activity and increased mTOR activity in rodents (10), suggesting a complex balance between neural molecular signals. Another hypothalamic signal of nutrient status is \(\alpha\)-KB kinase \(\beta\) (IKK\(\beta\)/NF\(\kappa\)B), a mediator of inflammation normally quiescent in the hypothalamus, but activated in the setting of overnutrition (57). Finally, \(\alpha\)-melanocyte stimulating hormone is a product of POMC production and cleavage that binds to CNS melanocortin receptor 4 (MCR4) and inhibits feeding (58). This evidence supports the ability of central nutrient sensing to affect whole body glucose handling and energy balance.

Leptin—Since the identification of the murine obese (ob) gene and its product, leptin (59–61), extensive work has demonstrated the central effects of leptin on whole body glucose and nutrient metabolism. Initial studies suggested that leptin mediates its effects on food intake and body weight at least partly via its ability to suppress expression of hypothalamic neuropeptide Y, an orexigenic molecule (62, 63). Like glucose and insulin, leptin hyperpolarized hypothalamic K\(_{\text{ATP}}\) channels in neurons from lean, but not obese, rats (64). In vivo, the central effects of leptin in rats were dependent on hypothalamic STAT3 signaling (65, 66). Indeed, the ability of systemic leptin to activate hypothalamic STAT3 was abolished in mice fed a high fat diet for 15 weeks, suggesting a mechanism for leptin resistance (67). Although leptin stimulates hypothalamic POMC neurons, causing decreased food intake and weight loss, leptin deficiency inhibits anorexigenic POMC neurons and stimulates orexigenic neuropeptide Y/Agrp neurons, resulting in hyperphagia and insulin resistance (15, 68). Like nutrients, ICV leptin inhibits AMPK, stimulates acetyl-CoA carboxylase, and up-regulates malonyl-CoA in the rat hypothalamus (69). The central effects of leptin also appear to be mediated at least in part via PI3K-dependent pathways, again demonstrating similarities with the hypothalamic insulin signaling pathway (70, 71). Of note, at least some of the hypothalamic actions of leptin depend on melanocortin receptor activation, particularly its central effects on EGP (15, 72), and loss of hypothalamic leptin signaling is sufficient to promote obesity or T2DM (65, 73). Furthermore, low doses of ICV leptin improved insulin resistance in lipodystrophic mice, whereas similar doses given peripherally were ineffective (74). Additionally, mice lacking hypothalamic POMC neuron receptors for insulin and leptin are insulin-resistant (75). The therapeutic potential of central leptin to regulate glucose fluxes in models of obesity and insulin resistance was highlighted by the observation that central leptin inhibited glucose production in rats with hepatic insulin resistance following short term high fat feeding (76).

Evidence from Human Studies Supporting CNS Regulation of Metabolism

The presence of glucose-sensing neurons and insulin receptors in the human brain is well documented (9, 77), and recent evidence has demonstrated a potential role for central regulation of EGP. Consistent with findings in rodents that ICV infusion of the K\(_{\text{ATP}}\) channel activator diazoxide decreased EGP (12), our group recently reported the first studies in humans suggesting central regulation of EGP (78). We performed euglycemic “pancreatic clamp” studies, using somatostatin to inhibit endogenous insulin secretion along with replacement of basal insulin and glucoregulatory hormones following administration of diazoxide in healthy subjects. Because diazoxide markedly inhibits pancreatic insulin secretion (79), the pancreatic clamp technique allowed us to examine the extrapancreatic effects of diazoxide. Our studies demonstrated an \(\sim 30\%\) decrease in EGP during the final hours of the clamp, \(6–7\) h after oral administration of diazoxide. Of note, complementary studies in rats (78) showed that diazoxide crosses the blood-
brain barrier and confirmed the suppression of EGP during euglycemic pancreatic clamp studies following oral diazoxide, along with decreases in glucose 6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) expression and increased hepatic STAT3 phosphorylation. When the KATP channel blocker glibenclamide was administered ICV in rats, the effects of oral diazoxide on EGP, gluconeogenic enzyme expression, and hepatic STAT3 phosphorylation were completely abolished (78). Together, these studies strongly suggest that hypothalamic KATP channels regulate EGP, at least in part, in humans as well as in rodents.

Consistent with the above work, a number of other studies suggest that the brain plays a regulatory role in glucose homeostasis in humans. Human subjects with an activating variant of the Kir6.2 subunit of the KATP channel (E23K variant) are at increased risk of developing T2DM over their lifetimes, although studies of E23K homozygotes with normal glucose tolerance raised an intriguing conundrum as these subjects appeared more insulin-sensitive than control subjects. E23K homozygotes underwent oral glucose tolerance tests and hyperinsulinemic-euglycemic clamp studies, showing reduced insulin secretion but enhanced insulin sensitivity (80). Indeed, E23K subjects were ~40% more insulin-sensitive than controls, and therefore had normal glucose tolerance despite reduced insulin secretion. The authors hypothesized that as insulin resistance develops later in life, the effects of reduced insulin secretion are manifested by development of T2DM. Another study of subjects with Type 1 diabetes (T1DM) also supports a potential clinically important role for central KATP channels: metabolic control improved in T1DM subjects after a 6-month course of low dose diazoxide, with initial improvement after just 3 months of therapy, despite no measurable effect on insulin secretion (81). The improved homeostasis model assessment of insulin sensitivity (HOMA-S%) scores of the subjects suggested that this effect was due to improved insulin sensitivity. Although the study was not designed to clarify the precise time course of the central effects of diazoxide on whole body glucose handling, the results suggest that diazoxide exerted its beneficial metabolic effects via activation of central pathways.

Studies of extrapancreatic effects of glucagon-like peptide (GLP-1) also support a role for the brain in regulating peripheral glucose metabolism. Sandoval et al. (82) demonstrated decreased EGP in rats when GLP-1 was infused into the arcuate nucleus. In healthy humans, Prigeon et al. (83) reported decreased EGP with intravenous GLP-1 infusion for 60 min under pancreatic clamp conditions, which prevented any GLP-1 effects on islet hormones. There was no effect on peripheral glucose uptake. Because GLP-1 receptors have been shown in various human brain regions (84, 85), these studies suggest that central GLP-1 signaling may regulate EGP in humans.

Several brain imaging studies have implied that the brain serves as a metabolic sensor impacting whole body energy homeostasis in humans. Functional MRI scans detecting blood oxygen level-dependent signals showed hypothalamic signaling changes in response to glucose infusions (86–88). These changes were diminished or absent in obese (89) and T2DM subjects (88). In addition, a link between CNS insulin and peripheral glucose metabolism was suggested by studies of intranasal insulin. Insulin effectively crosses the blood-brain barrier and appears in the CNS in significant concentrations within 30 min of intranasal administration, without significant elevations in circulating insulin levels (90). Therefore, intranasal insulin enables examination of central insulin effects on peripheral metabolism in humans. Benedict et al. (91) showed reduced postprandial serum insulin levels in healthy men following intranasal insulin administration, suggesting enhanced postprandial peripheral insulin sensitivity, and also reported decreased food intake in men after a single dose of intranasal insulin (92). The same group subsequently reported reduced body weight, body fat, and leptin levels in healthy male subjects following 8 weeks of intranasal insulin administration as compared with placebo (93). Interestingly, the above effects were not observed in human female subjects, consistent with noted gender differences in peripheral responses to central insulin administration in some rodent studies (94, 95).

Thus, supporting previous work in animal models, a growing body of evidence strongly suggests that central pathways play a key regulatory role in glucose and lipid homeostasis in humans. Given the growing global diabetes epidemic, identifying new therapeutic targets is imperative. The paucity of human data concerning regulation of glucose homeostasis highlights this as an important area of future research with the potential to substantially impact the clinical outcomes of people with diabetes.

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