Galanin-Like Peptide as a Link Between Metabolism and Reproduction

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Abstract
Galanin-like peptide (GALP) is a hypothalamic neuropeptide that binds and activates galanin receptors in vitro. Following the discovery of GALP, researchers have attempted to properly place it in the context of galanin receptor physiology. Central injections of GALP have revealed some common actions with galanin, such as acutely increased food intake and suppression of the thyroid axis. Other actions are unique to GALP, such as long-term inhibition of food intake and stimulation of luteinizing hormone (LH) secretion in male rats. GALP and galanin also produce differential effects on expression of the immediate early gene product Fos in the brain. Determining which of these actions are dependent on galanin receptors (versus a putative GALP-specific receptor), as well as which actions represent the authentic physiology of endogenous GALP will require continued experimentation. GALP gene expression is positively regulated by several hormones involved in the control of energy balance and metabolism, namely leptin, insulin and thyroid hormone. Based on current evidence, GALP neurones may serve as a hypothalamic relay, transmitting information from the periphery to circuits within the brain involved in the physiological control of metabolism and reproduction.

Although the pharmacology of the known members of the galanin receptor family (GALR1, GALR2, GALR3) is well-studied (1), the physiological significance of these receptors is not yet manifest. The want of appropriate tools has hindered progress towards defining the discrete functions of these receptors. Chimeric galanin analogs with high affinity for galanin receptors have been synthesized, but most of these compounds lack subtype specificity (2). In addition, they sometimes have dichotomous actions, functioning as agonists in vitro, while antagonizing the effects of galanin in vivo. In the central nervous system (CNS), the mRNAs for the galanin receptors are largely overlapping in their distribution (3–5), making an anatomical dissection of their individual behaviours problematic. Galanin receptor-specific antisera have also not been widely available for experiments. As a result of these complications, few of the many roles proposed for galanin in the brain have been ascribed to a specific galanin receptor subtype. The discovery of galanin-like peptide (GALP) in 1999 as a putative endogenous ligand for the galanin receptors has only added complexity to our understanding of galaninergic systems.

Discovery
GALP was discovered when Ohtaki and colleagues used GTP\(_{\gamma}\)S binding assays to mine porcine hypothalamic extracts for compounds demonstrating activity at GALR1 and GALR2 (6). They isolated a 60 amino acid peptide that contained, at amino acids 9–21, the first 13 amino acids of galanin; this is the minimum fragment of galanin required to convey agonist activity at galanin receptors (7). GALP binds GALR1 with 18-fold lower affinity than it binds to GALR2 (6), but how GALP interacts with GALR3 is unknown. Although GALP and galanin bind and activate GALR2 with an approximate equal affinity, GALP binds and activates GALR1 with substantially lower affinity than galanin. GALP was initially cloned from the pig, human and rat, with cDNAs from macaque and mouse characterized shortly thereafter (6, 8–10). GALP and galanin are encoded by distinct genes, which are located on separate chromosomes in humans (chromosome 19 and 11, respectively) and mice (chromosome 7 and 19, respectively), but on the same chromosome in rats (chromosome 1). In humans, the GALP and galanin genes both comprise six exons, and share other
Pig
Mouse
Rat
Human
serotonin 2C receptor; CNS, central nervous system; GnRH, gonadotropin-neuropeptide Y; Ob-R, leptin receptor; OX 1R, orexin receptor 1; SNS, releasing hormone; IR, insulin receptor; LH, luteinizing hormone; NPY, protein 1; Y1, NPY Y1 receptor.
sympathetic nervous system; TR, thyroid receptor; UCP-1, uncoupling
the GALP neurone indicate efferent signals. 5-HT, Serotonin; 5-HT2C, leading to the GALP neurone indicate afferent signals; arrows leading from injections or receptors that have not been observed experimentally. Arrows
erning reproductive function. Question marks indicate the presence of pro-
may also convey information regarding energy reserves to pathways gov-
mulating feeding behaviour and increasing thermogenesis. GALP neurones
hormones involved in control of energy balance, and may receive inputs
in the central nervous system. GALP neurones are regulated by circulating
all species; amino acids highlighted in grey are conserved in at least three orthologs. Amino acids that are identical to galanin 1–13 are marked with a sterisks.
rostral arcuate nucleus, there are relatively few GALP
dibular stalk and posterior pituitary (11–13). Within the
exclusively in the arcuate nucleus, median eminence, infun-
dile (14, 17). In addition, although it was not explicitly
test, Larm and Gundlach (13) noted a lack of
overlap between the distributions of GALP mRNA with any of the above-mentioned neuropeptides in the arcuate nucleus (14, 17). In addition, although it was not explicitly
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unique population of neuropeptide-expressing cells in the arcuate nucleus.

Attempts to colocalize receptors with GALP neurones have been more fruitful. Because the arcuate nucleus has been long

structural similarities as well (8). GALP 1–60 appears to be
cleaved from a prohormone of 115–120 amino acids, depending
on species. Sequence alignment of GALP 1–60 orthologs reveals
two highly conserved regions, including amino acids 1–
24, and 38–54 (Fig. 1). The first conserved region contains the
portion that is identical to galanin 1–13; the second region is
dissimilar to any other known proteins, and thus may represent
a moiety capable of binding a putative GALP-specific receptor.

Neuroanatomy
Shortly after the discovery of GALP, several groups published detailed descriptions of the hypothalamic localization of the GALP gene. In the rat, GALP mRNA is expressed exclusively in the arcuate nucleus, median eminence, infundibular stalk and posterior pituitary (11–13). Within the rostral arcuate nucleus, there are relatively few GALP mRNA-expressing cells; these cells lie in close proximity to the third ventricle. In the caudal arcuate nucleus, increased numbers of GALP mRNA-expressing cells are found that are more uniformly distributed across the medial and lateral aspects of the nucleus. The distribution of cells expressing GALP mRNA is well conserved across mammalian species, as both macaque and mouse brains demonstrate similar patterns of expression (8, 10).

An immunocytochemical study by Takatsu et al. (14) substantiated the limited pattern of GALP-expressing perikarya that was shown previously by in situ hybridization. Fibres expressing GALP immunoreactivity are found in several forebrain nuclei, including the paraventricular nucleus (PVN), medial preoptic area (MPOA), bed nucleus of the stria terminalis and ventral part of the lateral septum, periventricular nucleus, as well as within the arcuate nucleus itself (14). Although the arcuate nucleus sends numerous efferents to both the external layer of the median eminence and the hindbrain (15), GALP-immunoreactive fibre projections have not been found in either location (14). Neurones in the arcuate nucleus that project outside of the blood–brain barrier (as shown by retrograde labelling after peripheral injection of Fluoro-Gold) rarely express GALP mRNA (unpublished observations), which is consistent with the conclusion that GALP neurones do not project to the external median eminence. Taken together, these results suggest that GALP does not have a direct effect on the secretion of hormones from the anterior pituitary.

With anatomical tools in hand to discern both GALP mRNA and protein, several groups performed colocalization studies to unravel the tapestry of GALP connectivity within the brain. The topography of GALP mRNA-expressing cells within the arcuate nucleus gave promise that its presence might coincide with any of several well-known neuropeptides: α-melanocyte stimulating hormone (α-MSH), neuropeptide Y (NPY), somatostatin, agouti-related protein (AgRP), or galanin. With the exception of one study showing a modest amount of coexpression between GALP and α-MSH (16), no evidence has been adduced for the coexpression of GALP with any of the above-mentioned neuropeptides in the arcuate nucleus (14, 17). In addition, although it was not explicitly tested, Larm and Gundlach (13) noted a lack of ‘conspicuous overlap’ between the distributions of GALP mRNA expression and either GHRH or tyrosine hydroxylase mRNAs. Therefore, it would appear that GALP neurones represent a unique population of neuropeptide-expressing cells in the arcuate nucleus.

established as an important locus in the neural control of energy homeostasis (18), it is no surprise that these efforts have focused on receptors that are believed to be integral to metabolic regulation. Using double-label immunocytochemistry and in situ hybridization, two groups have shown independently that nearly all GALP neurones express the long form of the leptin receptor (8, 14). GALP neurones may also be sensitive to factors intrinsic to the brain that are implicated in the control of food intake. For example, in the macaque, approximately 40% of GALP neurones coexpress mRNA for the NPY Y1 receptor, and 25% of GALP neurones coexpress mRNA for the serotonin 5-HT2c receptor (17); these receptors are thought to be responsible in part for the orexigenic and anorexigenic actions of NPY and serotonin, respectively (19, 20). A small percentage (approximately 10%) of GALP neurones appear to express the orexin-1 receptor (OX1R) (21), which is believed to be the receptor subtype responsible for the stimulation of food intake by orexin-A (22). With the exception of leptin, functional relationships between the ligands for these receptors and GALP neurones have not yet been established.

To identify cellular targets for the action of GALP in the brain, two groups have mapped the regions of the brain where the immediate early gene product Fos is produced in response to intracerebroventricular (i.c.v.) injections of both GALP and galanin (Table 1). GALP elicits Fos immunoreactivity in the horizontal limb of the diagonal band, preoptic area, arcuate nucleus, dorsomedial nucleus (DMH), and the lateral hypothalamus (23, 24). Additionally, Lawrence and colleagues report that in areas adjacent to the third ventricle, GALP produces a significant increase in Fos expression that occurs predominantly within astrocytes (23). Although Lawrence et al. (23) did not corroborate the induction of Fos in the preoptic area following GALP injection observed by Fraley et al. (24), this may be due to the lower dose of GALP used by Lawrence et al. (23). However, these two studies do concur that GALP is more potent than galanin at inducing Fos in the arcuate nucleus, while galanin is more potent than GALP at inducing Fos in the PVN. This may prove to be part of the anatomical basis for the disparate actions of these two neuropeptides following central injection. Because both of these hypothalamic nuclei are reported to have mRNA for all three cloned galanin receptors (Table 1), it appears unlikely that this divergent pattern of Fos expression is attributable to a differential activation of galanin receptor subtypes, and instead may reflect a difference in activation of a GALP-specific receptor.

### Physiology

#### Gene regulation

Homeostasis of food intake and body weight is achieved through the actions of hormonal signals such as leptin, which provide feedback on levels of energy reserves to the CNS (25). Leptin exerts its influence on food intake and body weight primarily through the regulation of neuropeptide genes [e.g. NPY, pro-opiomelanocortin (POMC)] in hypothalamic nuclei that express the leptin receptor (26). Leptin given to rats during a 48 h fast caused a nearly four-fold increase in the expression of GALP mRNA compared to saline-injected, fasted rats (11). Conversely, in genetic models of deficient leptin signalling [obese (ob/ob) and diabetic (db/db) mice; Zucker obese rats (fa/fa)], GALP mRNA expression is reduced compared to their wild-type counterparts (9, 10). Either central or peripheral injections of leptin to ob/ob mice increase GALP mRNA expression to levels comparable with wild-type expression (9, 10). Presumably, leptin acts directly (through its receptor) on GALP neurones to affect transcription, although this has not been shown explicitly.

The pancreatic hormone insulin also regulates GALP gene expression. Similar to leptin, insulin signals adiposity levels to the hypothalamus and circulates at reduced levels during fasting (26). In the rat, i.c.v. injections of insulin prevented the down-regulation of GALP mRNA expression observed during a 48 h fast, indicating that insulin likely acts directly on the brain to regulate GALP mRNA (27). Moreover, rats with streptozotocin (STZ)-induced diabetes have reduced GALP mRNA expression compared to vehicle-treated rats; 5 days of peripheral insulin injections, which brought serum insulin concentration to approximately control levels, were able to restore GALP mRNA expression to normal levels (27). Interestingly, returning serum leptin concentrations to control levels was also able to reverse the effects of STZ-induced diabetes on GALP mRNA expression. The effects of combined leptin and insulin treatment on GALP mRNA in diabetic rats were not additive, which may be indicative of a shared signalling pathway downstream of their respective receptors in GALP neurones (28).

Whether GALP mRNA expression is reduced as a function of the declining levels of circulating leptin and insulin that accompany fasting is unclear. In the Japanese macaque (Macaca fuscata), a 48 h fast produces a small, but significant reduction in GALP mRNA expression compared to fed

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**Table 1. Summary of Galanin-Like Peptide (GALP)-Related Neurochemistry.**

<table>
<thead>
<tr>
<th>Area</th>
<th>GALP-ir fibres</th>
<th>Fos induction</th>
<th>Galanin receptor mRNA</th>
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Symbols represent the presence of either GALP immunoreactive (GALP-ir) fibres, Fos induction following central injection of GALP or galanin, or mRNA for galanin receptors in the areas of the forebrain listed in the left-most column. Table data were compiled from the following references: GALP fibre distribution (14); Fos induction (23,24); galanin receptor mRNA expression (3–5,52,53). Arc, Arcuate nucleus; BNST, bed nucleus of the stria terminalis; DMH, dorsomedial hypothalamic nucleus; HDB, horizontal limb of the diagonal band; LH, lateral hypothalamus; LSV, ventral portion of the lateral septum; PeN, periventricular hypothalamic nucleus; POA, preoptic area; PVNp, parvicellular division of the paraventricular hypothalamic nucleus; P3V, perihypothalamic region.
macaques (17). Jureus et al. (10) and Fraley et al. (27) showed by in situ hybridization that the number of detectable GALP mRNA-expressing cells is reduced by 40–50% during a 48 h fast in Sprague-Dawley rats; however, only the latter study achieved statistical significance (likely due to an increased sample size). Using real-time RT-PCR, Kumano et al. (9) did not detect a change in GALP mRNA expression after fasting in Wistar rats, although this may reflect variation in the physiology of these two rat strains or differences in measurement technique. Large changes in leptin and insulin may alter GALP gene expression, but there is currently no evidence that GALP expression is influenced by meal-to-meal fluctuations of these hormones.

**Food intake**

Armed with the knowledge of the profound effects of leptin on GALP gene expression, scientists began to investigate the possibility that GALP acts as a downstream effector of leptin within the brain. However, these experiments produced unexpected results; unlike leptin, which is a potent inhibitor of food intake (25), GALP injected into either the cerebral ventricles (29–31) or directly into the PVN (32) of rats causes an increase in food intake for the first hour after injection. Coincidently, these studies also reported orexigenic effects of galanin, which acts both with similar potency and in a similar time frame to GALP (30–32). GALP and galanin both induce Fos immunoreactivity in the DMH and the lateral hypothalamus (23), two areas implicated in the control of food intake (18). Collectively, these shared effects of centrally administered GALP and galanin may indicate the common activation of a galanin receptor.

This orexigenic action of GALP appears to be short-lived, as several groups report that by 24 h after GALP injection, cumulative food intake and body weight in rats are either significantly reduced or unchanged from vehicle-injected rats (29, 31, 32). In the mouse, GALP administration decreases food intake within 2 h, and suppresses both food intake and body weight for approximately 24 h. In ob/ob mice, a single injection of GALP causes a prolonged decrease in food intake and body weight that lasts for several days post-injection (33). The reason for the apparent difference between rats and mice in the effects of GALP on feeding behaviour is unclear, but may be related to the fact that mice display additional responses to GALP injections. Mice given GALP injections exhibit depressed locomotor activity for several hours post-injection (29). Similar behaviour has not been reported in rats, with the exception of Matsumoto et al. (30) who reported that GALP injections caused immobility in rats for 15 min post-injection. Mice also develop a conditioned taste aversion following exposure to GALP, although this result is somewhat equivocal (29). These differences aside, it still remains to be established that GALP is involved in the physiological regulation of feeding behaviour in any species.

**Thermogenesis**

**Metabolism**

Leptin is also known to contribute to diet-induced thermogenesis, whereby excessive caloric intake leads to increased energy expenditure, which is reflected as an increase in body temperature. Leptin injections cause a transient increase in body temperature (34) that is attributable in part to the activation of sympathetic outflow, which leads to the induction of uncoupling protein 1 (UCP-1) in brown adipose tissue (BAT) (35). Luheishi et al. (34) have shown that the thermogenic effect of leptin can be blocked by co-administration of the cyclooxygenase inhibitor, flurbiprofen, and is thus dependent on prostaglandin synthesis. Central injections of GALP produce effects that are reminiscent of those produced by leptin. Rats given a single i.c.v. GALP injection show a transient rise in body temperature that is blocked by concomitant injection of flurbiprofen (31). Temperature increases are also observed in ob/ob mice given chronic i.c.v. injections of GALP; this increase in body temperature is accompanied by an increase in UCP-1 expression (mRNA and protein) in BAT (33). Might the ability of GALP to elicit prostaglandin-dependent fever and UCP-1 stimulation represent a single mechanistic pathway? GALP stimulates Fos expression in hypothalamic astrocytes (23), which express cyclooxygenase (36). Prostaglandin injection into the lateral ventricle has been shown to increase BAT thermogenesis through a β-adrenergic-dependent mechanism (37). Thus, the possibility of a GALP > prostaglandin > β-adrenergic > BAT pathway exists, although this hypothesis requires confirmation. Alternatively, GALP may signal sympathetic efferents directly, as there is a strong GALP innervation of the anterior parcellar region of the PVN, which is part of the sympathetic pathway leading to BAT (38). The stimulation of BAT by GALP may occur independently of galanin receptors, as central injections of galanin actually suppress the firing rate of sympathetic nerves innervating BAT (39). The thermogenic response of GALP awaits proper physiological context because it is not clear whether GALP acts as an effector of leptin in diet-induced thermogenesis, or if GALP-induced fever is part of the acute response to inflammation.

**Thyroid function**

The thyroid axis becomes suppressed when animals are in a fasted state, and this suppression is believed to be due to a reduction in leptin drive to thyrotropin-releasing hormone (TRH) neurones in the PVN (40,41). There is evidence that the influence of leptin on TRH neurones is indirect and may be routed through neurones in the arcuate nucleus, including those expressing NPY and POMC (40,41). Although GALP neurones are anatomically situated to be effectors of leptin on the thyroid axis, the evidence to date suggests that GALP may be inhibitory to thyroid function. GALP injected directly into the PVN causes a reduction in thyroid-stimulating hormone (TSH) secretion, and GALP suppressed TRH release from hypothalamic explants (32). This leads to a conundrum wherein leptin could potentially both stimulate (through NPY/POMC) and inhibit (through GALP) thyroid function. Seth et al. (32) have reported that galanin elicits inhibitory effects on TRH and TSH secretion that are of similar magnitude to those observed in response to GALP; therefore, it seems plausible that endogenous GALP may be usurping the function of endogenous galanin in this context. Several observations are consistent with this interpretation. First, other groups who have administered GALP into the
cerebral ventricles rather than the PVN have reported no changes in thyroid-related parameters in response to GALP exposure (33,42). Second, the number of projections made by galanin fibres onto TRH neurones in the PVN vastly outnumbers the number of projections made by GALP fibres (43). In a more physiological context, thyroidectomized rats have decreased GALP mRNA expression in the arcuate nucleus compared to intact rats, and thyroxine treatment to thyroidectomized rats reverses this effect (44). However, the regulation of GALP mRNA by thyroid hormone does not by itself establish a role for GALP in feedback regulation of TRH secretion. Should GALP be found to have an unequivocal influence on the thyroid axis, this will need to be considered in the discussion of the effects of GALP on thermogenesis.

Reproduction

Leptin and insulin play important roles in the regulation of the hypothalamic–pituitary–gonadal axis. Evidence from mutant models suggests that disrupted leptin or insulin signalling produces hypogonadism that is of hypothalamic origin (45–47). Although the mechanisms by which these metabolic hormones influence gonadotropin-releasing hormone (GnRH) secretion are not entirely understood, the effects of leptin on GnRH secretion are believed to be mostly indirect (47). Therefore, leptin receptor-expressing GALP neurones may represent a novel conduit for information between energy stores and the reproductive axis. GALP injections into the cerebral ventricles stimulate luteinizing hormone (LH) secretion in rats, mice and macaques (17, 29, 42). In rats and macaques, previous administration of a GnRH antagonist eliminates GALP-induced LH secretion (17, 42), suggesting a hypothalamic (rather than pituitary) effect of GALP. In addition, GALP evokes GnRH release from hypothalamic explants (48). It is possible that GALP neurones directly activate GnRH neurones because a modest number (approximately 5%) of GnRH neurones in the medial preoptic area receive contacts from GALP fibres, and i.c.v. administration of GALP has been reported to induce Fos immunoreactivity in GnRH neurones (14, 42). There is some evidence that GALP mediates the effects of leptin on GnRH secretion because GALP antisera blocks the ability of leptin to stimulate GnRH release from hypothalamic explants (48).

It is not yet known what role GALP might play in the physiological control of LH release. Several experiments have investigated the potential involvement of GALP in negative/positive feedback of LH release by looking for regulation of GALP mRNA by gonadal steroids. GALP mRNA expression is not detectably different between gonadally intact male rats and castrated rats (44). Treatment of ovariectomized female rats or monkeys with oestradiol does not alter GALP mRNA expression compared to ovariectomized, non-treated animals (17, 44). Furthermore, GALP gene expression does not fluctuate from controls in ovariectomized rats given oestradiol and progesterone injections to induce a LH surge (44). Although these results cannot rule out a role for GALP in the regulation of the preovulatory LH surge, it appears that any involvement of GALP is not dependent on changes in GALP gene transcription.

GALP as a link between metabolism and reproduction

The nature of the receptor that mediates the effect of GALP on GnRH neurones is not fully understood. GALR1 is expressed by a subset of GnRH neurones in the rostral POA/vascular organ of the lamina terminalis in female rats (49); whether GnRH neurones express GALR2 or GALR3 is currently unknown. Seth et al. (48) have reported that the galanin receptor antagonist galantide partially inhibits the ability of GALP to stimulate GnRH release from hypothalamic explants. Therefore, it would appear that at least part of the GnRH response to GALP is galanin receptor mediated; the balance may be attributable to an as-yet-unfound GALP receptor. The immortalized GnRH-secreting neuronal GT1–7 cell line releases GnRH when exposed to GALP (but not galanin), an effect that is not blocked by galantide (48). As GT1–7 cells do not express galanin receptor mRNA (48), these cells could prove to be a source of a putative GALP receptor.

GALP receptor

Although GALP binds and activates GALR1 and GALR2 in vitro, it has not yet been shown that galanin receptors mediate any of the known effects of GALP in vivo. Circumstantial evidence exists for a GALP-specific receptor, in the form of a growing array of experimental differences between the actions of exogenously administered GALP and galanin. The difference in the pattern of Fos induction between GALP and galanin is detailed in Table 1 and has been described above. In the rat, GALP injections reduce food intake and body weight after 24 h, an effect that is not observed with equimolar doses of galanin (31). Matsumoto et al. (42) showed that GALP stimulates LH release following i.c.v. injection in male rats, whereas galanin does not, and recent experiments have demonstrated that central GALP injections stimulate sex behaviour in the male rat, whereas galanin inhibits these same behaviours (50). Studies by Krasnow et al. (51) have attempted to address the question of which galanin receptors, if any, are responsible for the observed effects of GALP. The ability of GALP to inhibit food intake, reduce body weight, or stimulate LH release is not impaired in mice that lack either GALR1 or GALR2, implying that neither of these receptors is solely responsible for the observed effects of GALP. In addition, an N-terminal fragment of GALP (GALP 1–21), which contains what is presumably the galanin receptor agonist activity of GALP, is not sufficient to recapitulate the effects of the full-length molecule (51). Although the influence of GALR3 or other unknown galanin receptors cannot be excluded at this point, these studies add further weight to the hypothesis that there is a separate GALP receptor.

Future studies

Studies of GALP to date have expanded our understanding of hypothalamic circuitry and provided an additional pathway through which hypophysiotropic GnRH neurones might sense fluctuations in energy balance (Fig. 2). There are several other frontiers in the study of GALP that have yet to be fully explored besides the aforementioned putative GALP receptor. Injecting GALP into the cerebral ventricles leads to
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a host of effects, all of which may not be pertinent to the prescribed duties of endogenous GALP; it is important to sort out which of these effects are physiological versus pharmacological. Although it appears clear that GALP should be an effector of leptin, the degree to which leptin depends on GALP to carry out any of its myriad functions in the CNS is not clear at all. Further knowledge regarding the cellular targets of GALP neurones is also essential to establishing their proper physiological context. With any luck, the development of a GALP knockout mouse, in concert with increasingly refined experimental designs, will hasten our understanding of galanin’s only known sibling.

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