Central Regulation of Energy Homeostasis

The Key Role of Insulin

Daniel Porte, Jr.

Insulin has two important functions that relate to overall metabolic homeostasis. The phylogenetically oldest is the maintenance of sufficient energy stores to allow for development, growth, and reproduction. The newer is as a feedback regulator of plasma glucose. The key role of the central nervous system in both functions is reviewed from a personal perspective, and the development of the concept that both body weight (adiposity) and plasma glucose are critically regulated by the same hormone is described. The recent suggestion that diabetes and obesity are linked by their common reliance on this central nervous system insulin signaling system is reviewed. Recent efforts to understand the hypothalamic mechanisms involved are described, and the common use of insulin receptor substrate 2 and the phosphatidylinositol 3-kinase signaling mechanism is emphasized. Potential consequences of defects in the secretion of insulin or the action of insulin in the central nervous system are given, and linkage between obesity and diabetes is illustrated with a potential clinical representative. *Diabetes* 55 (Suppl. 2):S155–S160, 2006

HISTORY

Insulin and insulin-like molecules have played a key role in energy homeostasis throughout evolution. Elegant studies in the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster* have demonstrated insulin-like molecules along with insulin and insulin-like signaling systems that, in *C. elegans*, are crucial to the regulation of body adiposity and nutrient storage, and in *Drosophila* play a similar role, plus regulate glucose metabolism. These peptides secreted from neurons are also critical for the regulation of reproduction in these organisms and, in relation to nutrient availability, determine lifespan (1,2).

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AgRP, agouti-related peptide; CART, cocaine- and amphetamine-related transcript; CCK, cholecystokinin; CNS, central nervous system; GABA, γ-amino butyric acid; K_{ATP} channel, ATP-sensitive K^+ channel; NPY, neuropeptide Y; PI, phosphatidylinositol; POMC, proopiomelanocortin.

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Whereas the role of the brain in mammalian glucose homeostasis was suggested more than a century ago by Claude Bernard (3), the discovery of pancreatic insulin in 1923 led to neglect of the brain as a major participant in carbohydrate homeostasis. Because of our interest in the relationship between body weight regulation and plasma insulin levels, Stephen Woods and I again focused on this mechanism, beginning in 1975. We observed that overfed or underfed animals who gained or lost substantial amounts of weight during controlled regulation of food intake rapidly returned to the body weights of control animals when allowed to free-feed. At their stable elevated and depressed body weights, which produced obese and lean animals, we found simultaneously elevated and depressed plasma insulin levels (4). Based on this observation, we hypothesized that insulin might have accessed the brain by its uptake from plasma to cerebrospinal fluid and acted as a signal indicating the degree of fat accumulation. While the amounts of cerebrospinal fluid insulin were considerably lower than plasma when we measured them, we found that the infusion of insulin into plasma promptly raised them (5). This was consistent with our suggestion that insulin could be a signal to the central nervous system (CNS) that body fat had been stored so that energy intake would be reduced and body weight stabilized, consistent with what we had observed in the experimental manipulation of body fat stores by forced under- or overfeeding.

Subsequent studies demonstrated that insulin given intracerebroventricularly alone or intravenously with glucose to maintain euglycemia reduced food intake (6,7). Others demonstrated that insulin receptors were present throughout the CNS, but, of interest, were particularly concentrated in the arcuate nucleus of the hypothalamus, thus supporting the hypothesis that insulin was a negative feedback regulator of food intake and body weight (8). During the time of these studies, the first gut peptide, cholecystokinin (CCK), was shown to reduce the size of a single meal by Smith and Gibbs (9), who suggested that this was an important feedback signal for the regulation of food intake and potentially body adiposity. In pursuing this hypothesis, Woods et al. showed that when CCK was injected with every single meal in a computer-controlled rat study, body weight only fell for a day or two and then stabilized parallel to controls, even though each meal was suppressed by 50%, indicating that some form of compensation had taken place (10). The explanation became apparent when assessing the number of meals ingested during the study period, as it became clear that they had doubled to compensate for the fact that individual meal size had halved. Therefore, compensation had promoted weight stabilization even in the presence of effective CCK at every meal. Because of our studies with insulin, we postulated that the long-term adiposity signal insulin was the mechanism for compensation to the restriction of

calories from the single-meal signal CCK. This was subsequently demonstrated by showing that insulin infused intracerebroventricularly potentiates the reduction of a single meal by CCK given intravenously or intraperitoneally (11,12) and was consistent with a model first presented in 1981 for energy balance in which the feedback control of single meals was integrated with the long-term adiposity signal insulin (13). Single meal size was known to be regulated by a number of other inputs besides CCK, such as the physicochemical quality and amount of the food in the gut, from chemoreceptor feedback, which was added to the gastro-entero-pancreatic signals such as CCK feeding back to the hypothalamus. We later suggested that all short-term signals interacted with insulin so that single meal size was simultaneously modulated by total adipose mass to control total food intake during the long term. The hedonic qualities of food were believed to combine with learned experience stored in the cortex to be another modifier of single meal intake and explain how food intake varied from meal to meal, yet body weight remained so constant over long periods of time.

BRAIN MECHANISM

The problem was that the mechanism and site for insulin action in the brain was totally unknown at that time, although the hypothalamus was clearly considered most likely, since it was known that insulin secretion could be regulated by electrical stimulation of the hypothalamus, and the hypothalamus was a known site of lesion-induced change in body weight. Therefore, it seemed logical that a signal related to insulin would give feedback to this site. The resolution of this problem was provided by an article from Williams et al. (14), who systematically evaluated peptides in the hypothalamus from normal and diabetic animals and found that only neuropeptide Y (NPY) showed a major change in diabetic animals, suggesting that NPY in the hypothalamus was regulated by insulin. Following up on this observation, White et al. (15) showed an increase in hypothalamic NPY mRNA in diabetic animals consistent with the hypothesis that insulin deficiency led to activation of the synthesis and release of NPY. NPY was known at the time to be the most orexigenic peptide that had been studied to date, and therefore it was concluded that lack of hypothalamic insulin feedback to NPY was a major contributor to, if not the cause of, diabetic hyperphagia. Our studies, which had shown reduced food intake and body weight when insulin was given intracerebroventricularly in both rats and baboons or when given intravenously along with glucose in baboons, that insulin given intracerebroventricularly potentiated CCK reduction of a single meal when given intraperitoneally in rodents and intravenously in baboons, along with the demonstration of insulin receptors and receptor mRNA in the hypothalamus, strongly supported this possibility. Therefore, we investigated the ability of intracerebroventricular insulin to regulate NPY message in the arcuate nucleus of normal rodents. We confirmed that NPY message was increased in fasted animals and then showed that administration of a small dose of insulin intracerebroventricularly suppressed the increase back to control-fed levels, directly supporting the hypothesis of an insulin feedback loop for food intake and body weight regulation using NPY (16). Insulin uptake from plasma into cerebrospinal fluid was subsequently shown to be provided by a saturable transport system into brain interstitial fluid before its entry into cerebrospinal fluid, and glucocorticoids were shown to interfere with this transport mechanism (17,18).

TABLE 1
Key facts about body adiposity regulation

1. A negative feedback system involving the CNS
2. A balanced regulation, with no hard-wired set point
3. All known adiposity afferents circulate:
   a. Insulin
   b. Leptin
   c. Glucocorticoids
   d. Others? ghrelin, PYY 3-36, glucagon-like peptide 1, amylin
4. All adiposity afferents are also regulated by non-adiposity factors.
5. Single meals are regulated by vagal neural inputs and circulating hormones (CCK, glucagon, bombesin [GRP], ***amylin, glucagon-like peptide 1, PYY, ApoAIV, enterostatin, ghrelin, obestatin,*** etc.) from the gastrointestinal tract ***as well as hedonic factors affecting the cerebral cortex***.
6. CNS integration occurs in the hypothalamus using:
   a. AMINES-norepinephrine, serotonin, dopamine
   b. NEUROPEPTIDES-NPY, AgRP, MSH, CART, etc.
   c. ENDOCANNIBINOIDS-2-AG, AEA (anandamide)
7. EFFERENTS are FOOD INTAKE and ENERGY EXPENDITURE
8. OBESITY and CACHEXIA (wasting syndromes) are disorders of this regulatory system.

From Porte et al. (22). Items modified in 2006 are in bold italics. Apo, apolipoprotein; GRP, gastrin-releasing peptide; PYY, peptide YY.

In 1994, the *OB* gene was cloned, and shortly thereafter leptin was described, isolated, its effects on food intake characterized, and its presence in human plasma identified. Both leptin and insulin were found to be present in cerebrospinal fluid and eventually a model very similar to insulin was proposed for the uptake, transport, and action of leptin in the hypothalamus (19,20). Because both insulin and leptin were known to be associated with body adiposity, the potential redundancy of the system was questioned, and at times it was suggested that perhaps insulin was primarily related to carbohydrate metabolism and leptin to adipose tissue energy storage. However, subsequent research has suggested that plasma leptin and plasma insulin provide different information to the CNS about the state of adiposity and its site of storage (21). Leptin appears to be primarily regulated by total adipose mass, whereas insulin appears to be primarily regulated by insulin sensitivity, which particularly represents storage of triglyceride in visceral or abdominal adipose tissue. Thus, individuals who have a relatively small total adipose mass and relatively low leptin level can be quite insulin resistant and have high insulin levels because of triglyceride storage in visceral fat, whereas other individuals can have considerable triglyceride storage in legs, thighs, and buttocks and will have increased leptin, but a minimal increase in plasma insulin because they remain relatively insulin sensitive. We suggested that the two hormones provide complementary information to the CNS as to the nature and sites of triglyceride storage in adipose tissue.

Early summary of the system. This complex system for the regulation of food intake and body weight was summarized by us in 1998 as eight key "facts" given in Table 1 with updated modifications added in 2006 (22) and modeled (Fig. 1). First, there is a negative feedback system for body adiposity that involves the CNS. Second, regulation is

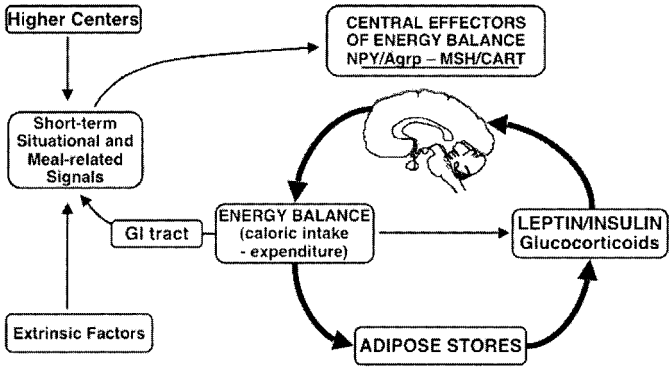

FIG. 1. Body weight regulation system (as of 2000). From Porte et al. (22). GI, gastrointestinal.

balanced, but there is no particular set point. Rather, the balance point is provided by the interaction among all of the factors involved. Third, all known adiposity signals circulate. In 1998, three circulating adiposity signals had been identified; by 2006, four other potential regulators were pointed out. Fourth, each of these adiposity inputs is also regulated by nonadiposity factors. Therefore, there is nothing adiposity specific for any of these signaling molecules. Fifth, single meals are regulated by a variety of vagal neuronal inputs from the gastrointestinal tract that are transduced from mechanical, chemical, and peptidergic signals that are integrated with hedonic factors. The number of gut peptides were few that could be definitively identified in 1998, but many have been added since, including obestatin as recently as 2006. Sixth, amines and neuropeptides were listed as CNS-integrating transmitters in 1998, with the endocannabinoids added just within the past few years. Seventh, both food intake and energy expenditure are known to be regulated in animals. In humans, food intake was thought to be the major output, but it is becoming clear that energy expenditure is probably also controlled centrally by this feedback system. Eighth, disorders of this system are extraordinarily common and include obesity and many wasting syndromes.

While many factors are involved in energy balance, insulin seems to be the only one that it is both a feedback regulator of body weight and a feedback regulator of plasma glucose. Because of this, we have suggested that dysfunction of this one hormone is an important explanation for the common association of obesity and diabetes, two major clinical disorders.

THE MODERN ERA

Strong support for this model and the physiological studies that argued for a key role for insulin was provided when the insulin receptor was knocked out selectively in the brain in 2000 and shown to produce an increase in adipose mass, particularly in females, and a major defect in reproduction (23). Subsequently, the same abnormalities were observed when hypothalamic insulin receptors were selectively reduced using insulin receptor antisense technology (24). At almost the same time, a major insulin action intermediate, insulin receptor substrate 2, was knocked out and shown to confer a similar phenotype with an increase in food intake and percent body fat along with a reduction in reproductive capacity with low luteinizing hormone and testosterone, suggesting that the signal generated by the hypothalamic insulin receptor was coupled with insulin receptor substrate 2 in the CNS (25). Insulin's downstream signaling phosphatidylinositol (PI) 3-kinase, which was known to be a critical biochemical intermediate in the periphery for insulin, was assessed in the hypothalamus and shown to increase when insulin was infused intracerebroventricularly into the rat third ventricle, and a PI 3-kinase inhibitor blocked insulin's suppression of food intake (26). Previous data showed that the same system contributed to leptin's action to acutely suppress food intake (27).

Recent follow-up data has indicated that both agouti-related peptide (AgRP)/NPY neurons and proopiomelanocortin (POMC)/cocaine- and amphetamine-related transcript (CART) neurons contain PI 3-kinase and that activation by insulin will increase PI 3-kinase in both (28). Insulin had been shown to hyperpolarize glucose-responsive neurons in the hypothalamus using a PI 3-kinase and ATP-sensitive K^+ (K_{ATP}) channel mechanism, consistent with suppression of firing in what were potentially NPY/AgRP neurons (29); however, activation of PI 3-kinase by leptin in POMC/CART neurons has been found to depolarize these neurons and lead to a presumed increase in melanocyte stimulating hormone release in association with an increase in PI 3-kinase (30). With this scenario, both phenomena would be consistent with the reported suppression of food intake by both peptides through a PI 3-kinase mechanism. The conundrum is how the same mechanism in two different neurons could lead to hyperpolarization in one and depolarization in the other. One possible explanation is related to the known presence of γ-amino butyric acid (GABA) and GABA receptors in hypothalamic neurons, including both NPY/AgRP and POMC/CART neurons (30,31). Because GABA is the major inhibitory transmitter of the brain that hyperpolarizes neurons, release of GABA might be involved. This potential is raised because of evidence that translocation of GABA receptors from a cytoplasmic compartment to the plasma membrane has been demonstrated to be regulated by insulin in neuronal cell systems (32) and recently characterized in the α-cell of the endocrine pancreas to hyperpolarize the membrane and inhibit peptide release, thus supporting the concept of sensitizing the tissue to the inhibitory effects of GABA (28). The mechanism involves the phosphorylation of the GABA receptor by activated AKT from insulin-stimulated PI 3-kinase, so the GABA receptor is translocated to the cell membrane. If insulin and/or leptin release GABA from POMC/CART neuronal endings near the AgRP neurons while insulin increases the number of membrane active GABA receptors in NPY/AgRP neurons, then one could have the simultaneous release of melanocyte stimulating hormone and the inhibition of NYP/AgRP that is predicted physiologically with insulin or leptin. The glucose-responsive neurons that were reported to be hyperpolarized by insulin may not in fact have been NPY/AgRP neurons, or rather it may be that the GABA receptor translocation effect of insulin is responsible after PI 3-kinase activation for hyperpolarization of NPY/AgRP neurons. The complexity of the wiring in the arcuate nucleus that has been described so far suggests that we are far from understanding the regulatory system with which we have become involved and that it will require many years of additional research by investigators in a variety of fields if there is to be progress in the future. The development of collaborative networks between physiologists, neuroscientists, pharmacologists, biochemists, and molecular biologists is certainly to be encouraged and is probably going to be essential.

CARBOHYDRATE METABOLISM

While regulation of body weight is a natural entry into the regulation of carbohydrate metabolism through the known impact of obesity on insulin action, recent data regarding the effects of CNS insulin on the production of glucose by the liver, a major contributor to fasting plasma glucose levels, provides another view and has been extensive. It was first demonstrated that insulin infused intracerebroventricularly produces a marked and rapid suppression of hepatic glucose production in rodents, and the effect is blocked by insulin antibodies infused simultaneously (33). Recently, this effect was shown to depend on hypothalamic K_{ATP} channels, since it was blocked by the simultaneous local administration of glibenclamide, a sulfonylurea K_{ATP} blocker (34). An activator of K_{ATP} channels, diazoxide, given through the same cannula into the arcuate nucleus, produces the opposite effect on hepatic glucose production, thereby solidifying the role of K_{ATP} channels for the glucoregulatory effect of insulin in the arcuate nucleus. Insulin action in the arcuate nucleus to reduce hepatic glucose production is blocked by selective hepatic branch vagotomy and is associated with activation of cells in the nucleus of the solitary tract and the dorsal medial nucleus of the vagus. Similarly, carnitine palmitoyltransferase 1 inhibition of fatty acid CoA metabolism in the hypothalamus reduces hepatic glucose production by a K_{ATP} channel–dependent mechanism. This hypothalamic effect also leads to activation of cells in the nucleus of the solitary tract and dorsal motor nucleus of the vagus and is also blocked by hepatic vagotomy (35). Thus, fatty acids and insulin play important regulatory roles in glucose metabolism by acting in the brain as well as the periphery, while at the same time, insulin plays a key role in food intake and body weight regulation.

Much of the material that has been discussed has been based on the use of molecular and cell biological tools as well as physiological evaluation. At times, particular emphasis has been placed on the phenotype of molecular knockout models to determine the specific importance of particular cells or molecules. These knockouts have also been used to alter the cellular characteristics of specific neuronal populations, so that the critical importance of a cell type or neuropeptide can be evaluated in specific brain areas. One model that appeared to play a critical early confusing role was the NPY knockout model because it disappointedly showed no body weight–altering phenotype, despite the extensive physiological and cellular studies, indicating the robustness of NPY's effects on food intake and body weight regulation by insulin, fasting, and diabetes (36). However, a recent study indicates the caution that must be used when interpreting such knockout data. The new study used diphtheria toxin to treat mice in whom NPY/AgRP neurons were modified to express diphtheria toxin receptors. The mice were exposed to diphtheria toxin as either neonates or adults. Exposure of the neonates to diphtheria toxin at 9 weeks of age was not associated with any change in 24-h food intake or in the pattern of food intake throughout the 24 h or in the hyperphagic response to a short-term fast, and weight was maintained normally. However, when adult NPY/AgRP diphtheria toxin receptor mice were treated similarly, there was rapid onset of a marked reduction in 24-h food intake followed by loss of weight (37). The investigators concluded that there must be some type of neuronal mechanism in neonates that compensates for the loss of NPY, but that does not occur when these neurons are fully developed in adults. Therefore, NPY/AgRP neurons become essential for the regulation of normal food intake and body weight in adults and the compensatory mechanism in neonates is lost. This experience indicates that "knockout" before full development may lead to results that can be misleading if extrapolated to physiological studies performed in adult animals. Further, it indicates the extreme plasticity of the nervous system during development and the caution with which investigators must make conclusions from findings in conventional "knockouts" whose outcomes are contrary to physiological experience.

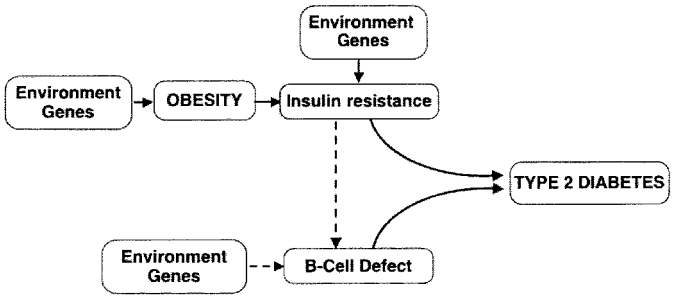

FIG. 2. Traditional model linking obesity and type 2 diabetes.

DIABETES AND OBESITY

Finally, the question arises as to how these data on the role of CNS insulin affect our potential understanding and thinking about diabetes and obesity. The model that was first developed and has now become "traditional" is to link obesity and diabetes based on the concept that insulin resistance develops first and leads to the β-cell defect that develops afterward (Fig. 2) (38). In this model, obesity is one prominent cause of insulin resistance, which itself may depend on environmental and genetic influences, but that environment and genes are independently responsible for much of the insulin resistance that is seen. The etiology of the β-cell defects are represented as either a direct result of insulin resistance to impair β-cell function by increasing demands on perfectly normal β-cells or, in some cases, secondary to genetic abnormalities that are only expressed in the presence of insulin resistance. This view places insulin resistance as the primary defect and β-cell defects as secondary. Plasma glucose was considered to be primarily regulated through a loop that involved the endocrine pancreas, the liver, and the periphery. The CNS was not believed to be involved nor was it considered. The alternate model that we have proposed is based on the addition of CNS insulin to regulate both carbohydrate metabolism and energy balance (39,40). Under this scenario, insulin becomes the key explanation for the coupling of type 2 diabetes and obesity. Environment and genes interact independently with each system, at the β-cell defect level, the insulin resistance level, and the obesity level to create the complex interactions that will need to be unraveled (Fig. 3). Whereas the traditional view had been that peripheral insulin resistance is always first, we would suggest that β-cell dysfunction or impairment of insulin action in the central nervous system could be the initiating event and point out that evidence does exist from clinical studies to support the primacy of β-cell dysfunction.

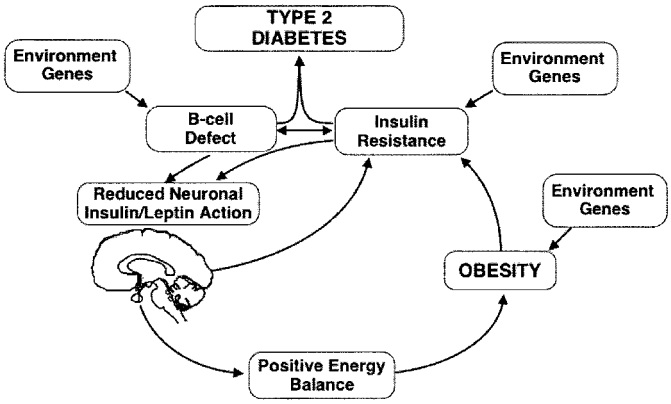

FIG. 3. 2005 model linking obesity and type 2 diabetes.

Clinical implications. In an epidemiological evaluation of the predictors of type 2 diabetes, β-cell function and intra-abdominal obesity were assessed in a group of 137 middle-aged male Japanese Americans in Seattle with nondiabetic glucose tolerance tests at baseline and again at 2.5 and 5 years (41). It was found that those who developed type 2 diabetes at 2.5 and 5 years had reduced β-cell function at baseline by ~40–50%. On the other hand, intra-abdominal fat was only increased in the group that developed type 2 diabetes after 2.5 years, whereas those who were to develop type 2 diabetes at 5 years were not found to have an intra-abdominal fat increase until the last examination at 5 years. Thus, overall, both abnormalities were present 2.5 years before the onset of diabetes, but only impaired β-cell function was present 5 years before the onset of type 2 diabetes. Because intra-abdominal fat has been shown to be the best fat compartment to correlate obesity with insulin sensitivity (42), it would appear that, in this group of subjects, the β-cell dysfunction was present first and predisposed to CNS-related obesity with insulin resistance later, as consistent with our new model. In a separate study of β-cell function in this population, it was also found that there was an increased prevalence of a genetic polymorphism in the promoter for the glucokinase gene in the group that was to develop impaired glucose tolerance (43). This common −30 G→A glucokinase promoter polymorphism has not always been associated with type 2 diabetes; however, recently, it was shown by another group to be clearly a risk factor for a small but statistically significant increase in fasting plasma glucose in normoglycemic adult Caucasian subjects during pregnancy and a small but statistically significant increase in birth weight in the children born to such mothers (44). Thus, it appears that minor defects in insulin delivery to the CNS or insulin action in the CNS, such as that produced by the −30 G→A glucokinase promoter defect, may interact to increase the drive for food intake and the risk of development of obesity leading to insulin resistance with increased demand on the pancreas. We would suggest that this concordant impairment of function would lead to an increased risk of hyperglycemia over time, particularly when associated with the modern "obesigenic" environment. Regardless of the validity of this hypothesis, the overwhelming evidence that insulin plays a key dual role in the regulation of carbohydrate metabolism and body weight suggests that further analysis of its CNS effects will continue to be a fruitful area for study and potentially therapeutic intervention.

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