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Neuroendocrine Mechanisms in Insulin Resistance

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Abstract

Dysregulated hormonal, metabolic and neural signalling within and between organs can contribute to development of metabolic diseases including type 2 diabetes. Insulin-antagonistic effects of hormones, cytokines and excess metabolic substrates such as glucose and fatty acids may be exerted via common mechanisms involving for example reactive oxygen species (ROS) accumulation and associated inflammatory responses. Visceral adiposity is a central component of the metabolic syndrome and it is also strongly associated with insulin resistance. Both visceral obesity and insulin resistance are important risk factors for the development of type 2 diabetes. In the development of insulin resistance, it is likely that intra-abdominal adipose tissue plays a critical role in a complex endocrine and neural network involving several tissues. This review paper focuses on neuroendocrine 'stress' factors that target insulin-responsive tissues, in particular adipose tissue. We propose that there are common pathways by which dysregulation in different endocrine systems may contribute to the development of type 2 diabetes.

Introduction

Dysregulation in several neuroendocrine pathways can lead to insulin resistance and altered glucose and lipid metabolism in various tissues. Specific disorders, e.g. pituitary tumors, can obviously lead to altered activity in neuroendocrine systems. The resulting dysregulation of neural and/or hormonal outflow can lead to derangements in substrate metabolism in other organs. But it is also known that altered activity in these systems that is not due to specific neuroendocrine pathology will influence metabolic regulation in most organs of the body. The activity in neuroendocrine systems is influenced by physiological feed-back systems but also by genetic background and external factors. The latter include psychosocial stress, intake of food, alcohol and other drugs as well as other life style factors. Thus, there is a multitude of internal and external stimuli that interact and can influence neuroendocrine function. Defective regulation of these complex networks can be an important component in the development of common metabolic disorders of today's affluent society.

Stress and insulin resistance

Neuroendocrine responses to various environmental stress factors can be seen as physiological compensatory mechanisms that aim at maintaining homeostasis. However, when these responses are insufficient or become unbalanced the result will be either a new stable steady-state condition diverging from the normal situation, allostasis, or alternatively a progressing perturbation of biological processes. Stress can be seen as a broad concept comprising various threats to the maintenance of the organism's homeostasis. Physiological systems maintain stability via sensitive feedback and control mechanisms, i.e. homeostasis (1). The allostasis concept proposes that altered stable states are produced in response to repeated activation of neuroendocrine mechanisms, such as the hypothalamic pituitary adrenal axis and the autonomic nervous system (2). Visceral adiposity, the metabolic syndrome and type 2 diabetes are common 'alternative states' in modern industrialized societies. However, in current as well as historic pre-industrial societies, the recognized prevalence of such conditions is low.

There is currently much evidence that, besides the external environment, also internal stress factors are of importance in the development of the metabolic syndrome and type 2 diabetes (3). Thus, socio-economic and other psychosocial factors will interact with biological mechanisms at several levels in the organism. Those mechanisms include cognitive, neuroendocrine, metabolic and molecular responses. At the molecular level, oxidative stress is an important example. It is exerted by the intracellular accumulation of reactive oxygen species (ROS) and it has been implicated in atherosclerosis, microvascular complications of diabetes as well as in beta cell failure in type 2 diabetes (4-6). There is now also growing evidence for an important role of ROS in various forms of insulin resistance (7-9).

Brunner and coworkers proposes that the link between psychosocial factors and disease development can be accounted for by direct and indirect pathways, respectively (10). Hence, adverse psychosocial circumstances can directly lead to behavior-related perturbations such as overeating and obesity. Also, acute psychosocial stress has been reported to decrease insulin sensitivity as well as β -cell function (11). Stress-related neuroendocrine responses can produce metabolic alterations in various tissues, i.e. via an indirect pathway. In the Whitehall studies, for example, subjects with metabolic syndrome display elevated urinary cortisol and norepinephrine metabolites and heart rate and altered autonomic nerve activity (12). Low social position in men was associated with higher heart rate and signs of low vagal and high sympathetic tone. There were also evidence for a relationship between lower social position and higher risk of metabolic syndrome, and this could be accounted for by autonomic imbalance, behavioral factors and low job control (12). Thus, there is population-based evidence that alterations in neuroendocrine function can be involved in mediating the effect of psychosocial factors to promote development of metabolic syndrome and cardiovascular disease.

Neuroendocrine stress

Neuroendocrine pathways are considered as important mediators of the brain's reactions upon stress. In general, stress can be seen as a threat of the organism's homeostasis. Various biological responses are triggered in the central nervous and

neurohormonal systems as well as at the cellular and molecular levels, and they aim to dismantle the stressor and maintain equilibrium (3). However, when inappropriate magnitude or duration of these defence mechanisms occurs, they can exert detrimental effects on brain function, on the cardiovascular system as well as on nutrient metabolism. For rapid signalling to peripheral tissues, the brain uses the autonomic nervous system. Most tissues that are important for whole-body metabolism, e.g. skeletal muscle, heart, adipose and liver, have autonomic innervation with both sympathetic and parasympathetic nerves (3). In addition, release of adrenaline from the adrenal medulla is regulated largely by autonomic nerve activity. Sympathoadrenal activation will have profound metabolic effects including insulin resistance (3, 13). For more long-term communication the brain can use the hypothalamo-pituitary hormonal systems and other neurohormonal pathways. In this context, prolonged elevation of insulin-antagonistic hormones like cortisol (14) and growth hormone can contribute to insulin resistance in several tissues.

On the other hand, these hormones are obviously critical in emergency situations of urgent need for extra delivery of fuel to tissues, in prolonged fasting and also as a response against hypoglycemia (15). Nonetheless, the ability of counter-regulatory hormones, including glucagon, adrenaline, cortisol and growth hormone, to increase blood glucose can contribute to insulin resistance and development of type 2 diabetes if there is an inappropriately large response (13)

Insulin resistance in the pathobiology of type 2 diabetes

Insulin resistance is an important component of the pathophysiological processes that underlies the development of type 2 diabetes, and it is likely to play a role in development of other conditions such as dyslipidemia, hypertension and atherosclerosis. Insulin resistance can be defined as an attenuated effect of defined amounts of insulin in target tissues (16). In patients with type 2 diabetes, insulin secretion from the pancreatic beta cells is by definition insufficient to compensate for the prevailing insulin resistance. In muscle, insulin-stimulated transmembrane glucose uptake appears to be the major rate-limiting defect. In adipose tissue, insulin resistance is manifested as impaired

suppression of lipolysis and increase release of free fatty acids (FFA) but there is also impaired glucose uptake and utilisation. In addition, it can also lead to dysregulated production and secretion of adipokines and other adipose-derived biomolecules. In the liver, the impaired insulin action leads to reduced glucose uptake and storage and to uninhibited release of glucose and very low density-lipoprotein (VLDL) particles. Stress mechanisms convey risk of type 2 diabetes and metabolic syndrome partly via the insulin resistance pathway, but obviously there can also be other routes that directly affect the function of, for example, pancreatic beta cells and vascular endothelial cells (3). The interplay between stress and biological systems in the pathobiology of type 2 diabetes and the metabolic syndrome is schematically depicted in Fig 1.

Insulin resistance is manifested by alterations at the level of insulin's target cells, and those cells display alterations in their insulin-responsive signalling or effector systems. The mechanisms for cellular insulin resistance are not clarified in detail. However, there is accumulating evidence suggesting that such cellular mechanisms are not primary phenomena in the development of whole-body insulin resistance. Accordingly, prediabetic subjects can display essentially normal cellular insulin sensitivity, and in insulin-responsive cells in type 2 diabetic patients, it seems that insulin resistance is largely reversible (15, 17). Thus, perturbations in the extracellular environment may appear first and they may, in turn, lead to cellular insulin resistance. Such factors of the 'internal tissue environment' may include metabolic, neural, inflammatory and hormonal signals. For example, high levels of glucose and free fatty acids will have detrimental effects in some tissues, e.g. muscle and liver (13). As obesity is a very important component in the metabolic syndrome and also is a major risk factor for the development of type 2 diabetes, adipose-related mechanisms are of interest. In adipose dysfunction, inflammatory mediators such as cytokines and chemokines as well as inflammatory cells are implicated as important players contributing to metabolic dysregulation and insulin resistance.

The sympathetic nervous system and insulin resistance

There are autonomic innervations (with both sympathetic and parasympathetic nerves) in metabolically active tissues such as adipose, muscle, liver and pancreas.

Sympathetic activation releases catecholamines that are known to have an insulin-antagonistic effect. Sympathetic nervous activation induces insulin resistance measured by hyperinsulinemic euglycemic clamp and inhibits the antilipolytic action of insulin (18). Increased circulating noradrenaline levels induces lipolysis in adipose tissue, but not in muscle (18, 19). However, local administration of catecholamines to the muscle tissue induce muscle lipolysis which is more pronounced after epinephrine than norepinephrine stimulation (20). The autonomic innervations of fat tissue seem to influence insulin sensitivity by production of FFA and glycerol as well as gene expression of adipose tissue hormones such as resistin and leptin (21). Moreover, the lipolytic effects of catecholamines are more pronounced in visceral adipocytes while the antilipolytic effect of insulin is reduced, leading to higher FFA release from visceral fat. (22, 23).

An excess of FFA distribution to liver, skeletal muscle and pancreas promotes insulin resistance (24, 25) and insulin secretion deficiency (26, 27). Also, adrenergic stimulation with reduced capillary recruitment may contribute to the diminished peripheral muscle glucose uptake (28). Muscle sympathetic nerve activity is positively related to body fat and is increased in obese subjects in the fasting state (29). Type 2 diabetes subjects have higher resting muscle sympathetic nerve activity than both healthy obese and lean controls (30). In addition, type 2 diabetes subjects are proposed to be more sensitive to sympathetic stimulation i.e. they had an amplified increase of p-glucose after a noradrenalin load, mainly due to increased hepatic glucose output (31). A mechanistic link between high insulin levels and sympathetic activation is indicated in first-degree relatives to T2DM who have both higher fasting insulin and sympathetic nerve activity (32). Furthermore, elevated activation of the sympathetic nerve system has been shown in subjects with the metabolic syndrome and is proposed to be related to mental stress factors (33).

Chronic stress is proposed to lead to hypothalamic arousal resulting in both elevated cortisol secretion and sympathetic nervous activation leading to insulin resistance, visceral obesity, dyslipidemia, hypertension and type 2 diabetes (34). Persistent stress such as work stress or sleeping disturbances are also associated to the development of T2DM (35, 36). Therefore, stressful events leading to neurohormonal disturbances with enhancement of insulin-antagonistic hormones such as cortisol and catecholamines might be potential risk factors that may contribute to the development of T2DM.

The parasympathetic nervous system and insulin resistance

Heart rate variability is a surrogate marker for cardiac autonomic function and diminished heart rate variability is associated with the metabolic syndrome (37). Heart rate variability increases less in insulin resistant compared to insulin sensitive relatives to type 2 diabetes during hyperinsulinemia indicating an early disturbance in autonomic response in insulin resistant subjects (38). Also the normal decrease of sympathetic/parasympathetic activity during the night is reduced in T2DM relatives (38). An imbalance in the autonomic nervous system, with an increase sympathetic and decreased parasympathetic activity, is associated with insulin resistance both following stress (15) and insulin infusion (39). A high sympathetic vs. parasympathetic reactivity is also strongly related to visceral adiposity as well as insulin resistance (40). Blocking parasympathetic by cholinergic antagonist atropine or by hepatic parasympathetic denervation induced insulin resistance in animals (41) Activation of parasympathetic nerves to the liver lead to the release of a hormone named hepatic insulin sensitising substance (HISS). HISS accounts for about 50 % of insulin stimulated muscle glucose uptake in rats (42). Therefore, a disturbed parasympathetic activation with reduction of HISS release could be a contributing mechanism for insulin resistance.

Parasympathetic or vagal activation stimulates insulin secretion by release of acetylcholine. This vagus mediated insulin secretion can be blocked by atropine and is called the cephalic insulin response (43). Vagus also activates release of the gut hormone glucagon-like peptide-1 (GLP-1) that stimulates insulin release (44).

In adipose tissue, parasympathetic activity seems to stimulate anabolic processes in contrast to the known catabolic effects by sympathetic innervation (21). Fat specific vagotomy decreased insulin mediated fat and glucose uptake while the activity of the catabolic hormone sensitive lipase was increased (21). Thus, sympathetic activity increases FFA release while parasympathetic activity seems to decrease FFA output from adipose tissue.

In summary, a reduced parasympathetic nerve activity relative to sympathetic activity may result in higher FFA-release from adipose tissue, less HISS release from the liver resulting in decreased insulin stimulated glucose uptake and reduced insulin secretion from the β -cells in the pancreas which could all contribute to the development of type 2 diabetes. In addition, a cardiac autonomic imbalance reflected in diminished heart rate variability is linked to an increased cardiovascular risk. See fig 2.

The HPA axis – glucocorticoids and insulin resistance

The hypothalamic-pituitary-adrenal (HPA) axis controlling cortisol secretion and the sympathoadrenergic systems both originate in the hypothalamus and they are interlinked, and overactivity in one of them can cross-activate the other (3). Elevated activity in both these systems has been reported in individuals with the metabolic syndrome, and this has been proposed to be triggered by psychosocial factors (33). Repeated stress will lead to neuroendocrine responses that, if prolonged, might be important in the development of visceral adiposity and type 2 diabetes. There are now several studies that link psychosocial factors to visceral adiposity, metabolic syndrome and type 2 diabetes (13). For example, low educational level, low sense of coherence and work stress and low emotional support in women and sleeping disorders in men are stress factors that have been associated with development of type 2 diabetes (13). However, in individuals exposed to a high psychosocial stress level there are no unequivocal alteration in levels of the candidate hormones involved, e.g. cortisol, adrenaline and noradrenaline. Interestingly, P. Björntorp suggested that a hypothalamic

arousal leads to insulin resistance via excess cortisol production, but later on there is a shift to a “burn-out” phenomenon with low secretion of cortisol as well as growth hormone and sex steroids (3, 34).

The clinical syndrome of glucocorticoid excess, i.e. Cushing’s syndrome, is associated with insulin resistance, glucose intolerance, dyslipidemia, central adiposity and hypertension. Pharmacological treatment with high doses of glucocorticoids produces a similar clinical picture. Some studies suggest elevated cortisol levels in situations such as work stress and unemployment (45), and this is expected to lead to accumulation of abdominal fat. Taken together, most previous studies do, however, not support major alterations in the overall HPA activity in insulin-resistant individuals, e.g. in obesity or type 2 diabetes (10, 46, 47). Accordingly, subjects with metabolic syndrome have been reported to have normal average cortisol levels, but a decreased diurnal variability (48). There is now much interest in potential alterations in local tissue levels of cortisol, that is the major glucocorticoid in humans, and the interconversion between inactive cortisone and active cortisol is reported to be altered in obesity.

The metabolic effects of cortisol are largely explained by its ability to antagonize the actions of insulin. Cortisol exerts its metabolic effects via effects on gene transcription, and the glucocorticoid receptor belongs to the family of nuclear hormone receptors acting as transcription factors in the cell nucleus. Cortisol impairs glucose uptake in peripheral tissues like fat and muscle and this can involve impaired translocation to the plasma membrane of glucose transporter 4 (GLUT4) (13). Previous results on human fat cells suggest that there are differences in glucocorticoid effects between the visceral and subcutaneous adipose depots (49). Insulin action on glucose transport was impaired only in visceral fat cells and this might be attributed to defects in the insulin-signaling pathway (49). Moreover, cortisol also stimulates gluconeogenesis in the liver and this is mainly mediated by enhanced expressions of gluconeogenic enzymes, e.g. phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. Some of the insulin-antagonistic effects, both at the liver and in skeletal muscle may be secondary to a lipolytic effect exerted by glucocorticoids. In addition to their effects on insulin

sensitivity, glucocorticoids may also inhibit insulin secretion and increase apoptosis of pancreatic β -cells (50), and that may obviously contribute to the diabetogenic potential of excess cortisol.

Albeit insulin resistance and type 2 diabetes are not typically associated with altered levels of circulating cortisol, there may be an increased HPA-drive as suggested by elevated amounts of glucocorticoid metabolites excreted in urine (49). Moreover, in type 2 diabetes the level of hyperglycemia can influence circulating glucocorticoids. Thus, with increasing hyperglycemia cortisol levels become elevated, both in the basal state and following ACTH challenge (51). Interestingly, there are similar findings with high FFA levels that can activate both the HPA axis and the sympathoadrenergic system (52).

In obesity, there are indications of an enhanced local conversion of cortisone to cortisol in adipose tissue via the enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD-1) (46). This may contribute to the development of alterations in glucose and lipid metabolism as well as to adiposity itself (46). Cortisol produced by the adrenal cortex is to some extent converted to the inactive form, cortisone, through 11 β -HSD-2 action in the renal tubular cells. Cortisone reenters the circulation and is available for conversion to cortisol, in tissues with high 11 β -HSD-1 expression, in particular adipose tissue and liver. It is of interest to explore whether there are differences in expression of 11 β -HSD-1 in visceral and subcutaneous adipose tissue, but there are reports suggesting a higher expression in visceral tissue as well as no difference (53-55). Nonetheless, it seems that both depots display elevated 11 β -HSD-1 expression in obesity (54, 55). Genetic animal models give support for the link between adipose tissue 11 β -HSD-1 activity and metabolic phenotype (56, 57). Interestingly, a high cortisol regeneration in visceral adipose tissue could spill over into the portal circulation and contribute to systemic cortisol levels (58).

In type 2 diabetes and glucose intolerance, there is no convincing support for an altered 11 β -HSD-1 activity in adipose tissue and data on skeletal muscle are inconsistent (59)

(60, 61). In the liver no alterations were found in type 2 diabetes whereas a down-regulation was found in obese individuals (62). Even though there are many questions to resolve about regulation of 11 β -HSD-1, it may be an attractive drug target for future treatments of obesity and diabetes.

Other neuroendocrine pathways

Growth hormone is known to have insulin-antagonist effects by counteracting insulin mediated glucose uptake and patients with acromegaly are at high risk of developing visceral obesity, impaired glucose tolerance or type 2 diabetes. On the other hand, patients with growth hormone deficiency also have visceral obesity and an increased insulin resistance even when correcting for body fat (63). Thus, both an excess of, and a deficiency in GH can result in insulin resistance. Furthermore, abdominal obesity is associated with blunted GH-secretion and GH treatment have been shown to reduce abdominal fat mass in both abdominally obese men (64) and women (65). Also, hypothalamic-pituitary disturbances affecting sex-steroid levels can interact with insulin action in peripheral tissues (59) since physiological sex-steroid levels seem to be most favourable for normal insulin-sensitivity. Both castration and administration of supraphysiological doses of testosterone resulted in insulin resistance in rats (66). In women with T2DM, free testosterone levels are associated with insulin resistance (67). Reduced testosterone levels in men may contribute to the development of visceral obesity and testosterone replacement seem to decrease abdominal fat and improve glucose and lipid abnormalities (68). On the other hand, estrogen replacement improved glucose levels and lipid profile in post-menopausal women with T2DM (69).

RAS in insulin resistance

The renin-angiotensin system (RAS) is yet another neuroendocrine pathway that can be involved in the development of insulin resistance (15). Renin catalyses the conversion of angiotensinogen to angiotensin I and angiotensin converting enzyme (ACE) promotes the onward conversion into angiotensin II. Angiotensin II has many effects including blood pressure elevation, fluid and sodium retention and urinary potassium excretion. RAS appears to interact with insulin effects as antihypertensive medications that activate RAS, e.g. thiazide diuretics (70) cause insulin resistance whereas those that reduce

effects of RAS, e.g. ACE inhibitors and angiotensin receptor blockers (ARB), display a positive or neutral effect on insulin sensitivity (71). One possible mechanism relating to insulin resistance in this context is local RAS action in adipose tissue that can lead to impaired adipocyte recruitment and differentiation, and this can be prevented by ACE inhibitors or ARBs (72).

Apart from the importance of RAS with respect to diabetes risk with antihypertensive medications, there is also a possibility that endogenous RAS dysregulation could be a general mechanism in the early development of insulin resistance (73). The major regulation of systemic RAS activity is exerted via renin levels that are governed by sympathetic nerve activity (74). Thus, it is likely that stress responses elicited via the sympathetic nervous system will occur not only by direct neural signals and adrenaline production, but also through RAS activation. It could be speculated that perturbations in endocrine and paracrine RAS action can contribute to the early development of the metabolic syndrome, and studies addressing a primary role of endogenous RAS activation in metabolic disease are warranted.

Adipose tissue as a target for stress factors

There is a clear relationship between central fat storage, i.e. visceral obesity, and features of the metabolic syndrome as well as risk for type 2 diabetes (48). A link between central obesity and HPA axis dysregulation has also been suggested, and it is proposed that high glucocorticoid levels will promote lipid storage in visceral rather than subcutaneous adipose tissue. Moreover, an altered balance in the activity of the sympathetic and parasympathetic nervous systems, respectively, appears to be associated with visceral obesity (40). Interestingly, in humans visceral adipose tissue seems to have a greater propensity for inflammation than subcutaneous adipose tissue, as supported by higher intratissue cytokine levels as well as by a greater number of adipose tissue macrophages (75). Visceral compared to subcutaneous adipocytes are reported to be more sensitive to the lipolytic effects of catecholamines, and to the insulin-antagonistic action of glucocorticoids, but they are less sensitive to the

antilipolytic and lipogenic effects of insulin (22). In visceral adiposity, this could, in turn, result in diverting fatty acids to other tissues, e.g. muscle and liver.

In a situation of chronic calorie overload, subcutaneous adipose tissue finally reaches its upper limit for triglyceride storage, and this may lead to adipose inflammation as well as lipid 'spill-over'. This means that energy storage will be partitioned towards the visceral fat depot and subsequently into ectopic fat depots, i.e., intrahepatocellular and intramyocellular lipids (IHCL and IMCL), both of which will directly impair insulin action in these tissues (76). Interestingly, enlargement of human fat cells can be a robust marker of filled adipose energy stores, and it is independently associated with insulin resistance both in vitro and in vivo (77). High leptin levels, in turn, are independently correlated to fat cell hypertrophy and might be used as a sign of subcutaneous lipid overfill (77).

Neuroendocrine effects on endothelial function and muscle glucose uptake

In healthy subjects acute stress increases muscle glucose uptake and decreases systemic vascular resistance (78, 79). The decrease in vascular resistance during mental stress in healthy volunteers is mediated by β_2 -adrenoreceptor-mediated vasodilatation involving nitric oxide release (80). However, lipid infusion inhibited both insulin mediated glucose uptake and decrease in systemic vascular resistance during mental stress (81). Hence, lipids seem to abolish the insulin-stimulated glucose uptake during acute stress through endothelial dysfunction (81). Also, in obese subjects the effect of mental stress on vasodilatation and insulin action is abolished (79, 82). Obese subjects also have an impaired sympathetic and blood flow response to insulin in skeletal muscle tissue (29) as well as a diminished capillary recruitment (83). Endothelial dysfunction in obesity is partly due to diminished NO-availability (84), which may explain the reduced vasodilatory response not only to insulin but also to stress. A transient impaired endothelial function has also been reported after acute stress in healthy subjects (85).

Stress also increase cytokine response (86) especially in abdominal obese subjects (87). Insulin resistance is characterized by low-grade inflammation and adipokines such

as TNF α decrease both insulin signalling, glucose uptake (88) and capillary recruitment (89).

Thus, during chronic stress, neurohormonal disturbances such as increased cortisol and sympathetic activity with increased lipolysis can decrease insulin signalling as well as capillary recruitment and hence contribute to diminished muscle glucose uptake.

Cellular stress in insulin resistance

At the cellular level there are mechanisms that can constitute final common pathways for various factors causing insulin resistance. First, elevated glucose and FFA levels are hallmarks of type 2 diabetes and they can exert 'metabolic stress' designated as glucotoxicity and lipotoxicity, respectively. Second, in states of inflammation cytokines will induce insulin resistance via NF κ B, which is a master switch mechanism in cytokine signalling, leading to further cytokine production and also to insulin resistance via interaction with insulin signalling. Third, cellular oxidative stress may occur as a result of intracellular accumulation of reactive oxygen and nitrogen compounds, mainly the so-called reactive oxygen species (ROS). Interestingly, high ROS levels lead to insulin desensitisation probably via activation of various stress kinases, e.g. JNK, p38-MAPK, NF κ B and PKC isoforms. ROS are generated in the electron transport chain, as a by-product in the ATP generating process (5), and this occurs in situations of enhanced oxidation of energy substrates such as glucose and FFA. Inflammatory cytokines can increase oxidative stress, and there are results suggesting that this can be mediated via ceramide formation that stimulates mitochondrial ROS production. In adipose cells, TNF- α can thus increase ROS levels that will activate the stress kinase JNK that in turn may increase IRS-1 serine phosphorylation (8, 90). Thus, metabolic as well as inflammatory cellular stress can converge into a final pathway of oxidative stress.

Moreover, there is now evidence suggesting that neuroendocrine factors causing insulin resistance also have a common pathway in the excessive formation of ROS (8). It was previously reported that dexamethasone-induced insulin resistance in adipose cells is

associated with ROS formation (90). Interestingly, insulin resistance was prevented by overexpression of ROS-metabolizing enzymes. RAS-induced insulin resistance may also involve ROS accumulation and ARB treatment seem to attenuate oxidative stress in parallel with inflammation and insulin resistance (91, 92). Recent data suggest that angiotensin II directly promotes ROS accumulation, NF-kappaB activation and TNF-alpha production in skeletal muscle and that insulin action is impaired in parallel (93). The convergence of neuroendocrine pathways into cellular stress is summarized in Fig 3.

Conclusion

The mechanisms causing insulin resistance in type 2 diabetes and the metabolic syndrome are yet not fully understood. The complex interplay between genetic and acquired factors is fundamental in the pathobiology of these disorders. It is likely that stressors in various forms hit the organism at many different levels and that this with time adds up to a pathogenic process leading to insulin resistance and, eventually, diabetes. Such stress factors may to a great extent be channelled into various biological responses via neurohormonal pathways. The autonomic nervous system, HPA axis and RAS are likely to be involved, and they all profoundly affect nutrient metabolism and insulin action in various tissues. A hypothetical scheme of 'multiple hits' leading to insulin resistance along with hypothalamic dysregulation is depicted in Fig. 4. Future research should include elucidate potential new mechanisms, biomarkers and pharmacological targets related to neuroendocrine dysregulation in the pathobiology of insulin resistance. This would improve our understanding of the complex underlying disease mechanisms.

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Figure legends

Fig 1.

Indirect and direct pathways linking stress to metabolic disease.

Fig 2.

A schematic illustration on how decreased parasympathetic in relation to sympathetic nerve activity could influence insulin sensitivity, insulin secretion and heart rate variability. FFA, free fatty acids; PaSy, parasympathetic nervous system; SNS, sympathetic nervous system

Fig 3

Accumulation of reactive oxygen species as a common mechanism for insulin resistance caused by neuroendocrine factors. Ang II, angiotensin II; FFA, free fatty acids; IR, insulin receptor; IRS insulin receptor substrate; PaSy, parasympathetic nervous system; SNS, sympathetic nervous system; ROS, reactive oxygen species; Ser-P, serine phosphorylation

Fig 4

A multiple-hit hypothesis. Additive insults exerted by various stress mechanisms contribute to hypothalamic dysfunction, insulin resistance and type 2 diabetes.

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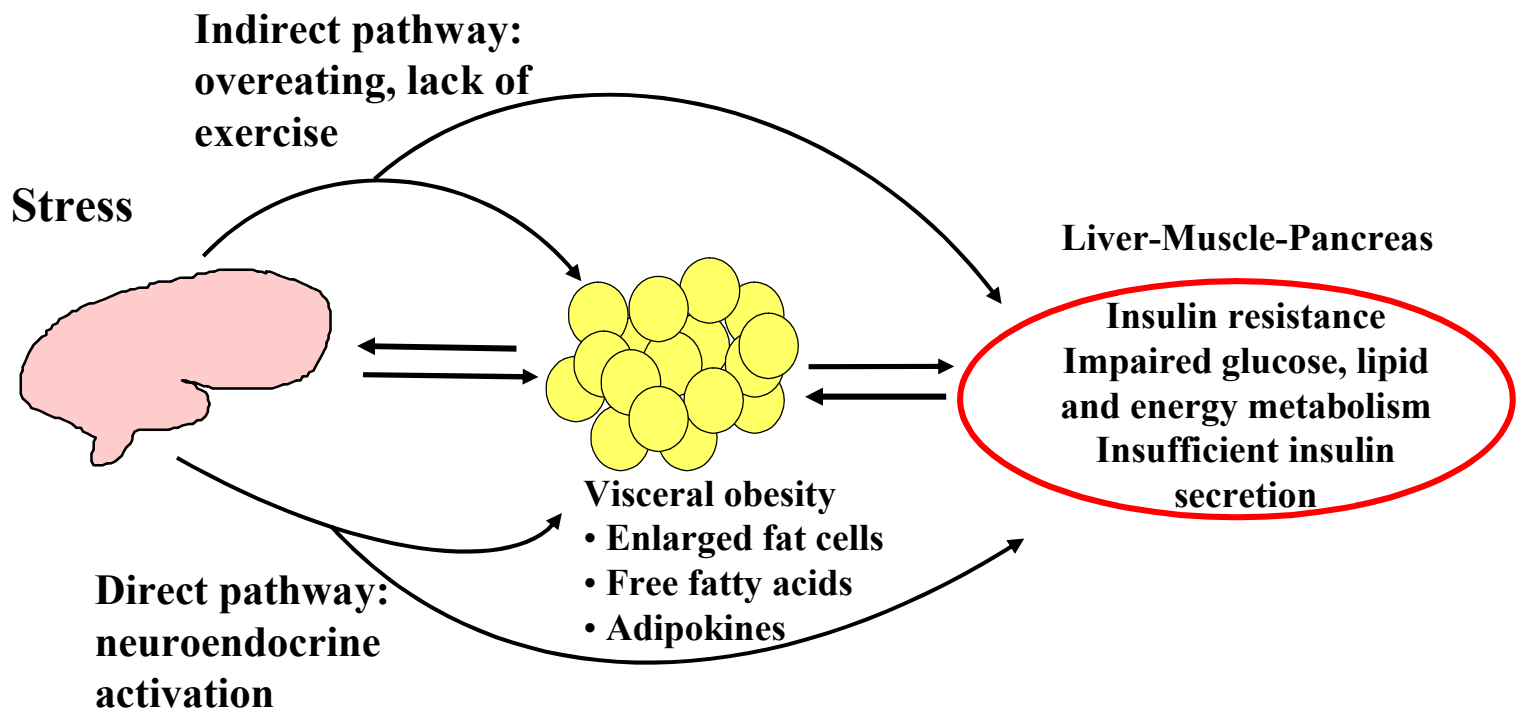
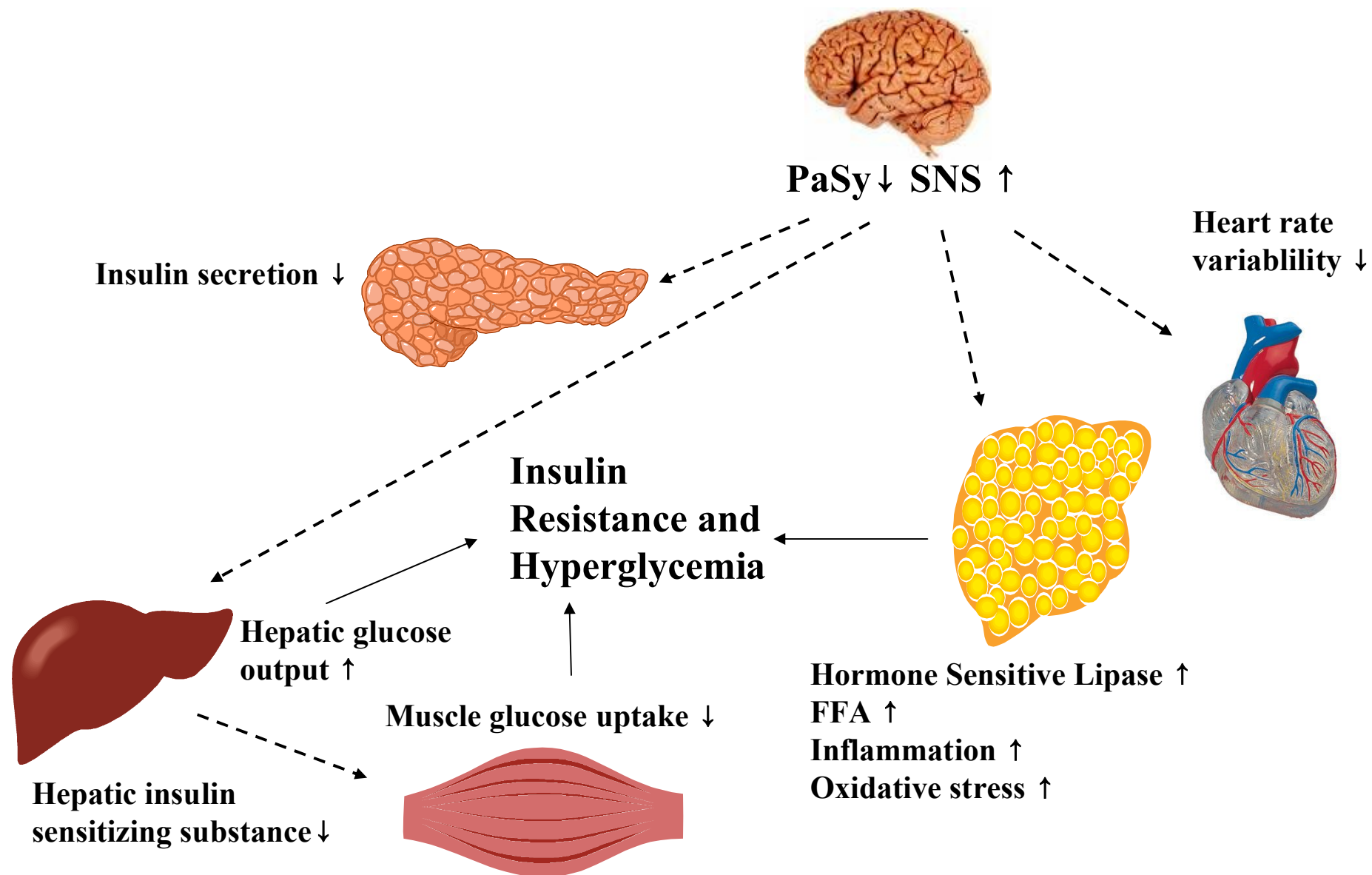


Fig 1

*Fig 3*

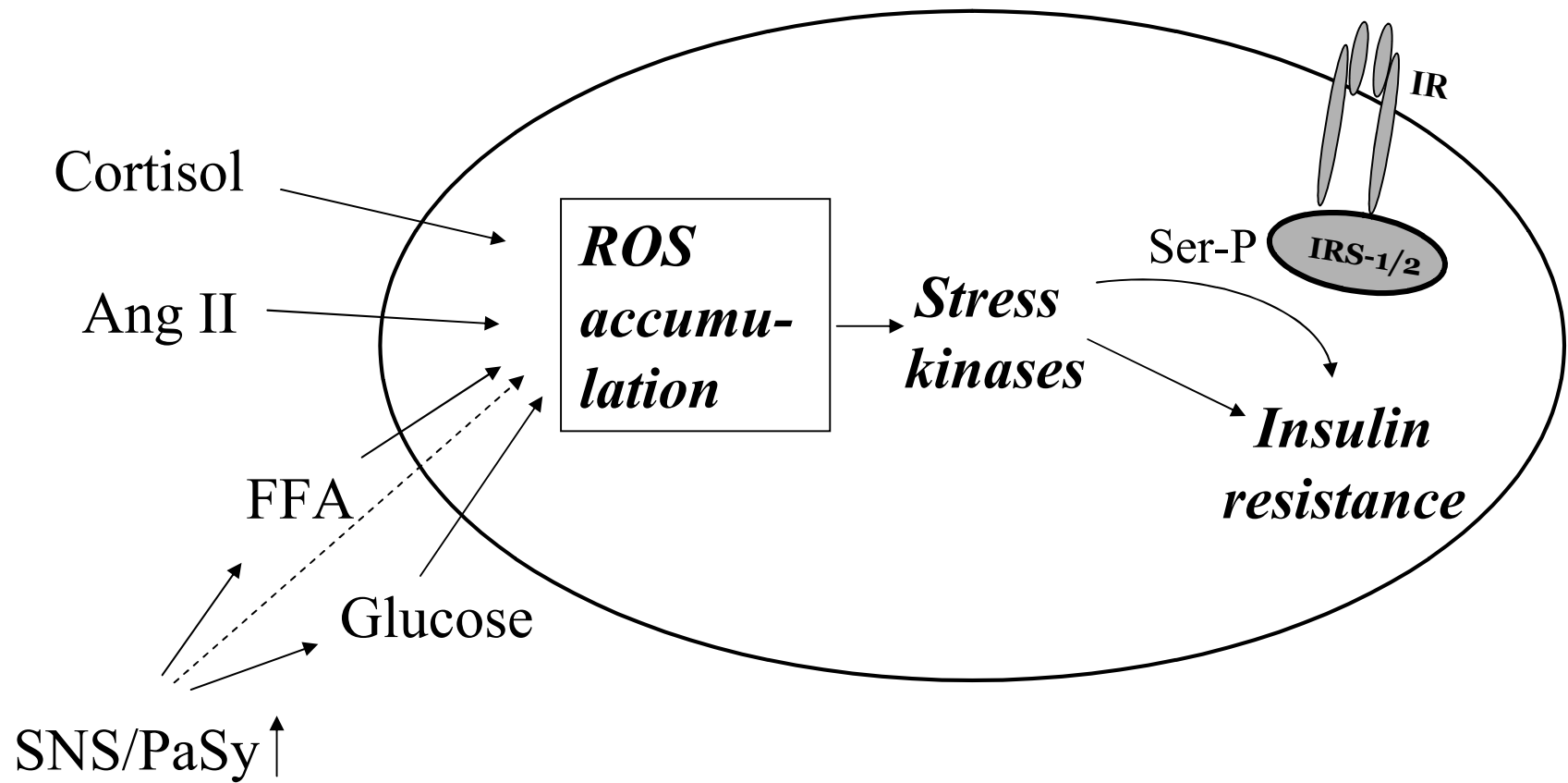
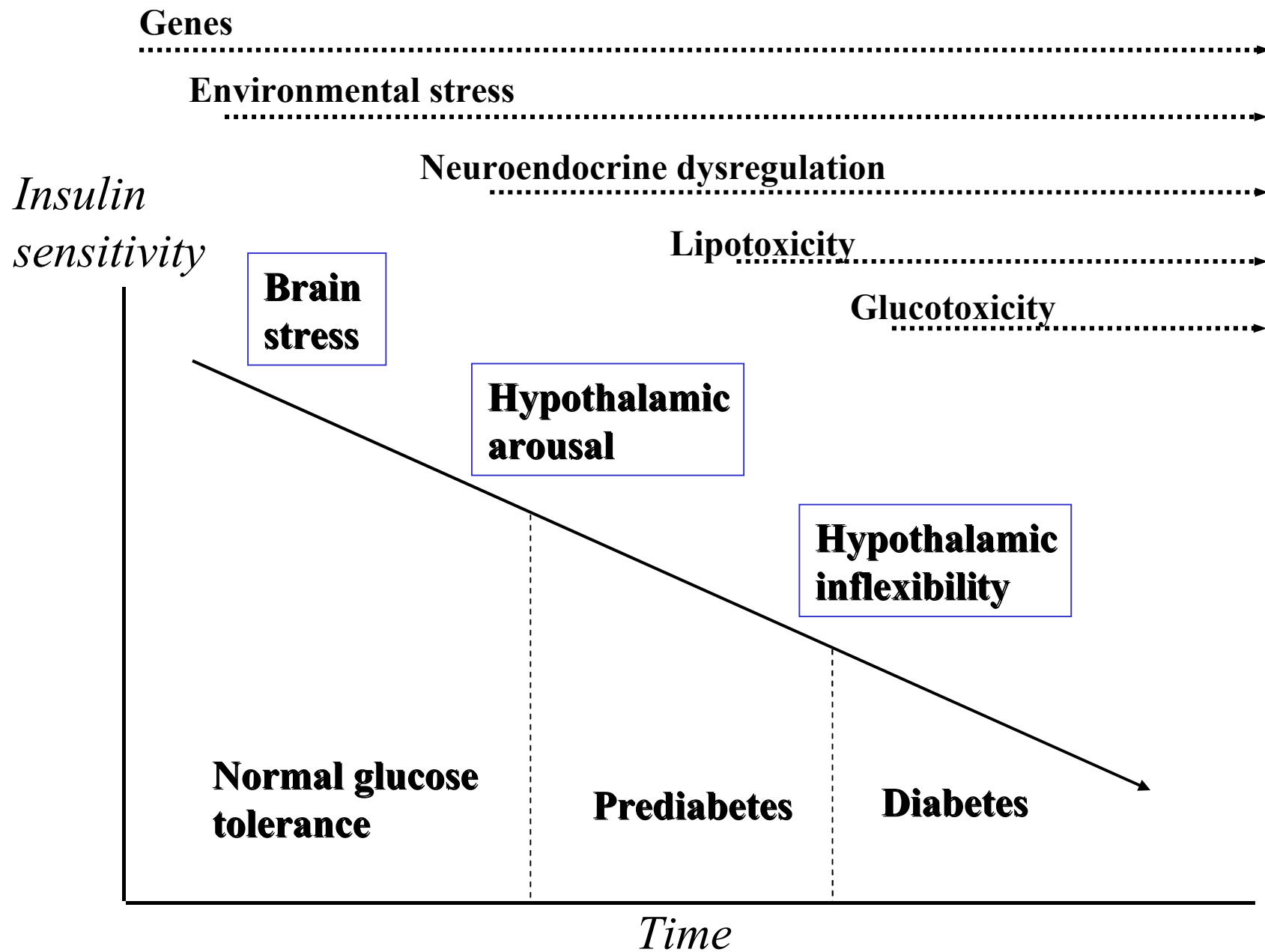


Fig 3

*Fig 4*