Research Perspective

Novel roles for JNK1 in metabolism

Bengt F. Belgardt[1,2], Jan Mauer[1,2], and Jens C. Brüning[1,2]

[1] Institute for Genetics, Department of Mouse Genetics and Metabolism, Center for Molecular Medicine, University of Cologne (CMMC), Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), 2nd Department for Internal Medicine University of Cologne 50674 Cologne, Germany
[2] Max Planck Institute for the Biology of Ageing, 50674 Cologne, Germany

Key words: *JNK1, obesity, insulin resistance, CNS*
Received: *07/05/10; accepted: 08/29/10; published on line: 08/31/10*
Corresponding author*: Jens C. Brüning, MD;* ***E-mail:*** *jens.bruening@uni-koeln.de*

Abstract: Activation of stress-kinase signaling has recently been recognized as an important pathophysiological mechanism in the development of diet-induced obesity, type 2 diabetes mellitus and other aging-related pathologies. Here, c-Jun N-terminal Kinase (JNK) 1 knockout mice have been shown to exhibit protection from diet-induced obesity, glucose intolerance, and insulin resistance. Nonetheless, the tissue-specific role of JNK1-activation in the development of the metabolic syndrome has been poorly defined so far. Recently, it was demonstrated that JNK1 signaling plays a crucial role in the central nervous system (CNS) and in the pituitary to control systemic glucose and lipid metabolism partially through regulation of hormones involved in growth and energy expenditure.

Insulin signalling and its negative regulators in aging-associated diseases

The insulin/insulin-like signalling pathway is highly conserved throughout the animal kingdom. Whereas its predominant role in mammals is the control of metabolic homeostasis and its deregulation leads to the development of diabetes mellitus, lowering insulin/insulin-like signalling in *c. elegans, d. melanogaster* and *m. musculus* has been implicated in lifespan extension [1-5].

The anabolic peptide hormone insulin is secreted from the pancreas in response to an increase of blood glucose concentrations. It acts on the liver to reduce hepatic glucose output and it promotes glucose and lipid uptake into peripheral tissues such as adipose tissue and skeletal muscle. Binding of insulin or insulin-like peptides to their receptor leads to recruitment of insulin receptor substrate (IRS) proteins, subsequently activating two major signalling branches: the phosphatidylinositol 3 kinase (PI3K)-pathway and the mitogen-activated protein kinase (MAPK)-pathway [6, 7]. PI3K activity mediates activation of the kinase AKT, which phosphorylates and thereby deactivates forkhead transcription factors (FOXOs). FOXOs are transcriptional regulators of genes involved in metabolism and growth [8]. Activation of the PI3K/AKT/FOXO axis mediates many of insulin's and insulin-like peptides' effects, including e.g. regulation of growth, glucose/fat metabolism, stress response and lifespan (Figure 1) [9]. Besides the expression and activation of this pathway in peripheral organs, the insulin/insulin-like signalling machinery is also expressed and active in the central nervous system (CNS) where it regulates fertility and body weight [10-12]. Furthermore, it was recently demonstrated that insulin action in the CNS also controls peripheral glucose and fat metabolism [13-15].

In the last decade, several studies have demonstrated that central as well as peripheral insulin signalling can be drastically impaired by a variety of obesity- and/or aging-associated parameters such as hyperlipidemia, hyperglycemia, endoplasmatic reticulum (ER) stress and inflammation [16-19]. Following this, the incidence

of numerous aging-associated diseases such as diabetes mellitus and obesity has created an urgent necessity to define the mechanisms underlying energy intake and expenditure, and to identify molecular targets for pharmacological intervention.

JNK1 and aging-associated diseases

In 2002, the group of Gökhan Hotamisligil revealed that mice deficient for the stress mediator c-Jun N-terminal Kinase (JNK) 1 are protected from the development of high fat diet-induced obesity and glucose intolerance, as well as insulin resistance [20]. Nonetheless, it remained unclear, in which tissue(s) JNK1 might act to impair energy and glucose homeostasis under conditions of diet-induced obesity.

The family of JNK kinases can not only be activated by cytokines, but also by endoplasmatic reticulum (ER) stress and hyperlipidemia, all of which are elevated in obesity and/or diabetes mellitus [21]. Previous data indicated that upon activation, JNK1 mediates inhibitory serine phosphorylation of IRS proteins, thereby impairing insulin action [22]. Interestingly, it was recently reported that mutation of the most frequently investigated JNK1 phosphorylation site, Ser307, augments (and not blocks) insulin resistance in obese mice, possibly pointing to either adaptive mechanisms during development or additional parallel pathways by which JNK1 can affect metabolism [23].

JNK1 and CNS insulin sensitivity

In the last year, JNK1 has been conditionally inactivated in several peripheral classically insulin-sensitive tissues including adipose tissue, muscle and liver [24-26] (Figure 1). Nevertheless, none of these mouse models fully recapitulated the protection from obesity and diabetes observed in conventional knockout mice opening the possibility that JNK1 activation also in the CNS may contribute to its effects on energy and glucose metabolism.

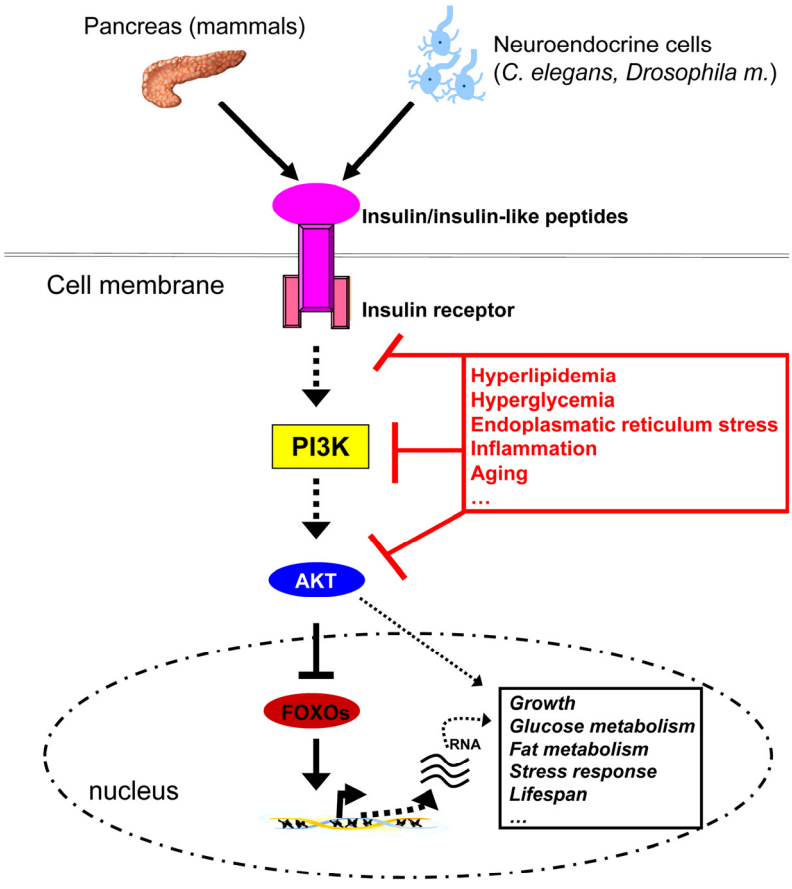

Figure 1. Insulin-like signalling plays a central role in growth, metabolism and the aging process. Insulin, derived from pancreatic beta-cells in mammals or insulin-like peptides derived from neuroendocrine cells in invertebrates signals via binding to and activation of the membrane bound receptors. This event subsequently activates PI3K, which through phosphorylation of membrane lipids (phosphor-inositides) regulates activity of the downstream kinase AKT. AKT eventually phosphorylates forkhead transcript-tion factors such as FOXO1, which are then exported from the nucleus and degraded. FOXOs regulate transcription of many genes involved in glucose and lipid metabolism, growth, stress response and the aging process. Thus, insulin-like signalling is able to control all of these processes through FOXO regulation and other signalling cascades, in the end impinging on crucial physiological processes and lifespan itself. Nonetheless, chronic intake of energy-dense food coupled with little physical activity leads to hyperlipidemia and hyperglycemia, which through several mechanisms (including JNK1 activation) reduce cellular insulin sensitivity, thereby disrupting metabolic homeostasis.