Adipokines and central control in adenosine A1 receptor dependent glucose metabolism

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Keywords: adenosine A1 receptor, adipokines, orexin, ghrelin, glucose metabolism, insulin resistance, diabetes, knock out mouse model

Abbreviations: A1AR, adenosine A1 receptor; WAT, white adipose tissue; GLUT4, glucose transporter 4; RBP4, retinol binding protein 4; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; TNFα, tumor necrosis factor alpha; IL-6, interleukin 6; PAI-I, plasminogen activator inhibitor-1; IA-2/IA-2β, islet-associated proteins 2 and 2β

Submitted: 12/09/11
Revised: 01/06/12
Accepted: 01/06/12
http://dx.doi.org/10.4161/adip.19285
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Commentary to: Faulhaber-Walter R, Jou W, Mizel D, Li L, Zhang JH, Kim SM, et al. Impaired glucose tolerance in the absence of adenosine A1 receptor signaling. Diabetes 2011; 60:2578–87; PMID:21831968; http://dx.doi.org/10.2337/db11-0058

A1AR deficient mice develop a phenotype of insulin resistance and grow fat. Participating pathophysiological pathways are not understood in detail yet, as discussed in our recent manuscript. This commentary further explores possible pathophysiological mechanisms with emphasis on the roles of the adipokines resistin, retinol binding protein 4, adiponectin and the function of the gastric hormone ghrelin in adenosine mediated central regulation of energy balance. The postulate of an important function of ghrelin/A1AR axis provides a good hypothetical basis for further investigations to clarify the mechanism of A1AR-dependent metabolic homeostasis.

The incidence of diabetes is rising rapidly and its complications are of major clinical and socioeconomic impact. Investigating possible treatment strategies need to be pursued with high priority. Recently we reported that adenosine A1 receptor (A1AR) signaling contributes to insulin-controlled glucose homeostasis and insulin sensitivity in C57Bl/6 mice and is involved in the metabolic regulation of adipose tissue.1 To our knowledge, our study was the first to systematically define the diabetogenic phenotype of A1AR deficiency under in vivo conditions. Earlier studies using pharmacological treatment strategies have yielded conflicting results. Nevertheless, the pro-diabetic effects were largely attributed to adenosine A2b receptor activation rather than A1AR blockade.2 The focus of this commentary is to provide additional information about possible mechanisms participating in metabolic control after loss of A1AR signaling. Our data show that in addition to causing insulin resistance lacking A1AR also leads to a profound disturbance of body composition. A1AR−/− mice grow fat even when fed a standard diet.1,3 Since adult A1AR−/− mice seem to resemble the phenotype typically seen in type 2 diabetes, one could argue that the disturbed glucose homeostasis might just evolve as an epiphenomenon in mice that grow fat, comparable perhaps to other mice models of type 2 diabetes such as the db/db mouse.4 However, the fact that high fat feeding eliminated the difference in growth without influencing the difference in glucose tolerance suggests an alternative mechanism of action. Our findings revealed a significant decrease of net glucose uptake in A1AR−/−, especially in white adipose tissue (WAT) and only to a lesser extent in muscle tissue. The underlying mechanism involves a reduced Akt activation but an increased Akt expression. Glucose transporter 4 (GLUT4) is a common downstream factor in the Akt signaling pathway contributing to muscle glucose uptake after induction of its expression and trafficking to the membrane.5 However, no differences in overall GLUT4 expression could be detected by western blot of muscle tissue in adult A1AR-deficient mice (Faulhaber-Walter R; Jahrestagung der Deutsche Diabetes Gesellschaft 2008; oral presentation). Furthermore, muscle glucose uptake of A1AR-deficient mice was not significantly different from controls in clamp studies, strengthening our conclusion that the phenotype of A1AR deficiency is not influenced by GLUT4 to a major extent. Therefore alternative mechanisms explaining the involvement of A1AR signaling in...
Adipokines

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Effects of Peripheral Adipokines

Our glucose clamp study revealed a significant impairment in whole body glucose uptake and specifically a significantly decreased glucose uptake in white adipose tissue (WAT). WAT is the dominant adipose tissue in the adult body of mice, and it is known to be actively involved in maintaining glucose homeostasis by the production of a variety of hormones such as adipokines. Adipokines are being secreted into the systemic circulation and thus can affect energy metabolism and body composition. Leptin has been reported frequently to play a leading role in this regard. However, as discussed in detail in our study, leptin does not seem to play a major role in the A1AR-dependent effects so that other adipokines may be considered as major contributing factors.

Retinol-binding protein 4 (RBP4) is a recently described adipokine that has been identified as a possible link between obesity, insulin resistance and type 2 diabetes. In contrast to leptin, no direct involvement of adenosine in RBP4 regulation has been described yet. Moreover, the link between RBP4, insulin resistance and obesity has been identified as an impaired glucose metabolism of the liver, where our clamp studies did not show a difference in glucose uptake between control and mutant animals. In addition, lack of A1AR signaling did not lead to reduced glycolysis or gluconeogenesis in the liver (Gavrilova O, personal communication). Therefore it seemed unlikely that A1AR play a crucial role in the physiological effects regulated by RBP4. Regarding adenosine effects on net glucose metabolism in the liver, in vitro experiments using rat hepatoma cells showed that these effects were mostly conferred by A2b signaling leading to glycogenolysis and gluconeogenesis.

Another adipokine, resistin, initially also was linked to obesity and insulin resistance. Resistin is increased in obesity and rises during feeding. Experimental evidence however led to contradicting conclusions about its role in metabolic control. Banerjee et al. reported that in a mouse model lacking resistin, fasting glucose was low and that this was due to reduced hepatic glucose production after activation of AMP-kinase. Lacking resistin suppressed a post-fast hyperglycemia that is usually linked to obesity. On the other hand, chronic resistin infusion was accompanied by reduced fat mass and improved insulin resistance and involved the activation of the Akt pathway. Since, as shown in our paper, the A1AR-dependent metabolic control seems to involve the Akt pathway, it could not be excluded that resistin somehow participates in exerting downstream effects after A1AR activation. Tullin et al. reported that growth hormone, a potent inducer of resistin expression in WAT of spontaneous dwarf rats, is rapidly induced by adenosine via A1AR in vivo—although the authors failed to demonstrate the same effects in vitro. Thus, growth hormone may be feasible as a link between A1AR and resistin expression. However because hepatic effects were rather negligible in our model, and because resistin has not been reported as being regulated directly through adenosine receptor signaling, resistin does not seem to be of central importance for the A1AR-dependent regulation. Nevertheless, investigating the role of resistin in more detail might be worthwhile in future studies looking into the specific downstream mechanisms of A1AR-dependent metabolic regulation.

Adiponectin is another important adipokine derived from WAT. Reduced levels of adiponectin have been associated with obesity and diabetes in mammals. Szkudelski et al. reported that adiponectin secretion was effectively reduced by the A1AR antagonist DPCPX (8-cyclopentyl-1,3-dipropylxanthine) in rat adipocytes in vitro. In contrast, we did not detect differences in protein expression levels of adiponectin when comparing adult A1AR−/− with wild-type mice in vivo. Hence adiponectin did not appear to contribute in a major way to the phenotype of A1AR deficiency. Another group however, Marecki et al., very recently studied another in vivo rodent hyperinsulinemic model by overfeeding young prepubertal rats. Their results suggest an age-dependent role of adiponectin in metabolic dysregulation, as well as an organ-specific differentiation (e.g., hepatic vs. muscle) and an adiponectin-independent ectopic fat deposition. The A1AR−/− phenotype in our study parallels these symptoms in that it also presents with an age- and diet-dependent exaggeration of disturbed metabolic control. Hence in view of these latest findings on adiponectin and the role of A1AR, it seems worthwhile to perform longitudinal measurements of serum adiponectin levels in the A1AR−/− mice at different ages.

Other adipokines that play a role in metabolic control and/or regulation of endothelial function and vascular tone are part of the metabolic syndrome, such as visfatin, omentin, apelin, vaspin and/or pro-inflammatory molecules like TNFα, IL-6, PAI-I or serum-amyloid A among others have not been studied with specific reference to A1AR signaling in metabolic control. In summary, the peripheral adipokines each occupy a well-defined role in energy metabolism. However, none of them appears to be a satisfying candidate to explain the phenotype of the A1AR−/− in vivo.

Ghrelin, Adenosine and the Hypothalamic Axis

Varying receptor expression and/or activation patterns permit differential effects of adenosine in the brain. A1AR receptor dependent signals for instance play a role for the sleep-wake cycle controlled by hypothalamic neurons. Adenosine A1 activation exerts pleiotropic central effects as a neurotransmitter; mostly such as cognition, motor function and a role in cyclic regulation. As reported in more detail in our manuscript, disturbances of the central regulation of cyclic control in humans suffering from narcolepsy can be inflammatory toward increased eating behavior. In line with the hypothesis deduced in our study, Yang et al. very recently reported that the release of ghrelin from the mouse stomach seems to be disinhibited when missing the A1AR-stimulus. Ghrelin is a peptide hormone that exerts a potent appetite-stimulating activity, which is "supposed to play a role
in long-term regulation of energy balance, as chronic administration of ghrelin causes weight gain by reducing fat utilization as an energy source.\textsuperscript{21} Of interest, ghrelin Reports on This periodicity of the hypotalamic orexin/hypocretin expression is negatively controlled by A1AR signaling.\textsuperscript{25,26} Mice lacking A1AR therefore might develop a disturbed metabolic control first by disinhibition of gastric ghrelin, followed by orexin stimulation, which is also directly disinhibited centrally because of the missing A1AR-signaling. Often synergistic mechanisms in biological systems lead to more than purely additive effects. On this premise, the main contribution of A1AR signaling in homeostasis of metabolism could be to play an inhibitory part as tonic negative “controller.” Without doubt the central nervous system is involved in the fine tuning of the energy metabolism and maintenance of body weight. Lee et al. summarize that even the slightest disturbance of the hypothalamic control can possibly deflect the metabolic pendulum toward inappropriate appetite and reduction in energy expenditure which then can result in a progressive and significant weight gain over subsequent years.\textsuperscript{27,28} Interestingly, orexin/hypocretin action is associated with the central nervous dopaminergic reward system and the possibility of an orexin-stimulated hedonic feeding in rodents has been suggested.\textsuperscript{29} Another hint supporting the influence of central nervous system control of glucose metabolism in the A1AR\textsuperscript{27} can be derived from the IA-2/IA-2\β double knockout mouse model. Islet-associated proteins 2 and 2\β (IA-2 and IA-2\β) are major autoantigens in type 1 diabetes and transmembrane proteins in dense core secretory vesicles of neuroendocrine cells. Mice deficient in IA-2 and IA-2\β completely lack the first-phase insulin response after glucose stimulus, a finding that exactly matches the insulin response of adult A1AR-deficient mice during high fat feeding which display the most diabetogenic phenotype of all our study groups (see Fig. 4C in our original article).\textsuperscript{30} Later studies have shown in addition that IA-2 and IA-2\β have a global effect on the secretion of certain brain neurotransmitters including dopamine.\textsuperscript{31} Our group demonstrated that central effects of IA-2/IA-2\β include cyclic control of basic body functions, such as the circadian rhythm of body temperature and arterial blood pressure.\textsuperscript{32} Reports on the hypothalamic regulation of temperament specifically by A1AR were conflicting, but the participation of adenosine per se was clearly demonstrated and also reproduced by our group (Eisner C; FASEB J 21:A1312, 2007; abstract).\textsuperscript{33,34} This possible connection certainly needs further experimental evidence, but it seems reasonable to accept the basic connection between insulin function, glucose metabolism and hypothalamic cyclic control.

In summary, the postulate of a ghrelin/A1AR/orexin axis may serve well to provide the base of a model to explain the metabolic phenotype of the A1AR\textsuperscript{27} mice. This model provides a good hypothetical basis for further research.

Acknowledgments

I am indebted to Jurgen Schnerrmann, Oksana Gavrilova and Limeng Chen for valuable support.

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