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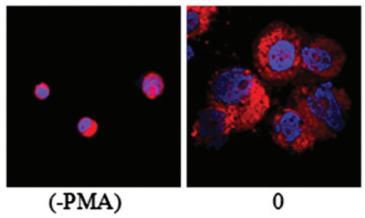
In This Issue of *Diabetes*

By Max Bingham, PhD

Metformin for Atherosclerosis

The widely used antidiabetic drug, metformin, may have a role to play in the management of atherosclerosis, according to a new investigation published in this issue of *Diabetes* (**p. 2028**). The study by Vasamsetti et al. investigated the role of the drug in both cell cultures and animal models of atherosclerosis and found that it is likely to inhibit monocyte-to-macrophage differentiation and may modify the inflammatory state of blood vessel walls. This is seen as a key step in plaque formation in atherosclerosis. While the complete molecular mechanism of metformin in diabetes is not totally understood, it is known to activate AMP-activated kinase (AMPK). And, it is via this route that the researchers now say it is likely to act in the attenuation of atherosclerotic plaque development. Specifically, they concluded that "the AMPK-STAT3 axis plays a pivotal role in regulating monocyte-to-macrophage differentiation and that by decreasing STAT3 phosphorylation through increased AMPK activity, AMPK activators [of which metformin is one] inhibit monocyte-to-macrophage differentiation." The experiments allude to a variety of molecular mechanisms that metformin might influence in atherosclerosis. Of note was the complete regression of plaque formation in the mice model and downregulation of a variety of inflammatory markers in both the cell cultures and animal models. Reduced aortic aneurysm and significant inhibition of LDL and triglyceride increases were also reported as being associated with metformin treatment. This also appears to be important from the perspective of proatherosclerotic effects. According to authors Srigiridhar Kotamraju and Jerald Kumar, the significance of this study is clear: "If these data can be confirmed in clinical studies, the significance for patients with type 2 diabetes and atherosclerosis could be considerable."



Phase contrast images indicate the inhibition of PMA-induced monocyte adherence by metformin treatment after 48 h.

Vasamsetti et al. Metformin inhibits monocyte-to-macrophage differentiation via AMPK-mediated inhibition of STAT3 activation: potential role in atherosclerosis. Diabetes 2015;64:2028–2041

Mechanisms in Support of Low-Dose IL-2 Therapy in Type 1 Diabetes

Low-dose interleukin-2 (IL-2) therapy is showing promise in type 1 diabetes as well as in a few other conditions. A phase 2 efficacy study of IL-2 therapy in type 1 diabetes is due to come out in the coming months. And yet, many of the mechanisms that underpin its use have remained largely theoretical–until now. According to a report by Yu et al. published in this issue of *Diabetes* (**p. 2172**), we now have the makings of an intricately balanced set of mechanisms that support low-dose IL-2 therapy usage in type 1 diabetes. In particular, the researchers demonstrated that a key reason for this responsiveness of regulatory T cells (Tregs) to IL-2 at low doses is that the cells express two parts of the IL-2 receptor (α and γ chains) at a higher level than $CD4^+$ and natural killer cells. The apparent wide gap between effects seen at low doses and those required to activate unwanted downstream gene expression (i.e., side effects) suggest a considerable therapeutic window might exist. This may be important since low and high responders to treatment might exist. According to author Thomas R. Malek, the implications of this research and the wider clinical work are considerable: "Boosting Tregs differs from most other approaches as this is aimed at restoring self-tolerance, rather than broadly suppressing the entire immune system. Our work quantifies a therapeutic window where relatively low levels of IL-2 selectively targets this key cell population. Particularly exciting is that low-dose IL-2 offers a straightforward approach to enhance Treg cells and represents a therapy that could be readily administered to many patients with type 1 diabetes or other autoimmune diseases, although additional testing is required to ensure safety and efficacy." While providing an overall model for the mechanisms behind low-dose IL-2 therapy in type 1 diabetes, this work supports previous findings and, importantly, the continuation of the phase 2 study, the results of which will be key for the continuation of this research area.

Yu et al. Selective IL-2 responsiveness of regulatory T cells through multiple intrinsic mechanisms supports the use of low-dose IL-2 therapy in type 1 diabetes. Diabetes 2015;64:2172–2183

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Insulin Resistance in Different Areas of the Brain Might Predict Progression Toward Alzheimer Disease

Progressive hypometabolism of glucose in a variety of brain areas is typical for the transition from normal cognitive function to mild cognitive impairment (MCI) and eventually the development of Alzheimer disease. However, in a report from Willette et al. in this issue of *Diabetes* (**p. 1933**), it now seems higher insulin resistance (IR) may predict relative hypermetabolism of glucose in various regions of the brain, including key structures for memory, when patients transit from MCI to overt Alzheimer disease. Using data from the Alzheimer's Disease Neuroimaging Initiative, the researchers calculated an index of peripheral IR (HOMA-IR) and assessed its relationship with glucose metabolism rates in brain regions typically affected by Alzheimer disease. This was completed with data from normal older individuals and patients with MCI or Alzheimer disease—an approach never previously reported. Taken together, the results suggest that both hyper- and hypometabolism of glucose in different areas of the brain and at different stages of disease progression are related to IR. According to author Dimitrios Kapogiannis: "The study demonstrates that IR is associated with hypermetabolism of brain structures critical for memory (hippocampus) at the critical stage of transition from MCI to Alzheimer's. This transient hypermetabolism may be considered as the unsuccessful effort of a brain structure under stress to compensate for its already failing function. This effort eventually fails, as is evident by the ensuing hypometabolism in Alzheimer's. This ties IR even more firmly into Alzheimer's pathogenesis and motivates the search for IR-related biomarkers and the repurposing of medications that decrease IR to treat the disease." This report mechanistically supports two ongoing clinical trials in Alzheimer's disease: the trial of exenatide, a drug commonly used in type 2 diabetes, and a trial of intranasal insulin. In both cases the clinical and biological significances are clear, if proven in the trials: a potential medication for the progression of Alzheimer disease.

Willette et al. Insulin resistance predicts medial temporal hypermetabolism in mild cognitive impairment conversion to Alzheimer disease. Diabetes 2015;64:1933–1940

Exercise, AICAR, and Insulin: There Is a Link

Exercise is a key intervention in the management of type 2 diabetes in part because uptake of glucose in skeletal muscle cells increases during and after exercise. This is achieved during exercise via a complex insulin-independent signaling cascade mediated by cellular GLUT4 translocation to the cell surface membrane. Furthermore, the ability of insulin to stimulate glucose uptake after a single bout of exercise remains enhanced. The molecular mechanisms behind these effects are poorly understood but appear to be related to a downstream target of both insulin- and exercise-induced signaling pathways—the target being TBC1D4. A report by Kjøbsted et al. in this issue of *Diabetes* (**p. 2042**) now confirms that acute AMPK activation increases skeletal muscle insulin sensitivity via an AMPK-TBC1D4 signaling axis, at least in ex vivo mouse hind-limb muscle. Using AICAR stimulation to induce the chemical equivalent of exercise, the researchers found that in wild-type mouse muscle, insulin sensitivity could be increased and glucose uptake was stimulated. The same effects could not be seen in mice with blunted or ablated AMPK signaling. The researchers also concluded that: "TBC1D4 phosphorylation may facilitate the effect of prior AMPK activation to enhance glucose uptake in response to insulin." These associations were again only seen in wild-type mouse muscle and were specifically related to phosphorylation of the Thr^{649} and Ser^{711} residues. Commenting on the research, author Jørgen F.P. Wojtaszewski said: "Apart from underlining that this research demonstrates the feasibility, at least in part, of using AICAR or other pharmacological AMPK activating agents as a mimic for exercise in mice, it supports the use of exercise as an intervention in type 2 diabetes. A range of recent observations suggests indeed that TBC1D4 is a point of convergence for signaling events elicited by exercise and insulin, also in humans. Thus, our data support the view that AMPK is also a potential pharmacological target in insulin-resistant skeletal muscle. Although globally expressed in all cells of the body, tissue selectivity might be achievable through the selective expression of the γ3 regulatory AMPK subunit in skeletal muscle."

Kjøbsted et al. Prior AICAR stimulation increases insulin sensitivity in mouse skeletal muscle in an AMPK-dependent manner. Diabetes 2015;64:2042–2055

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