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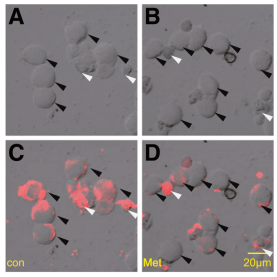
In This Issue of *Diabetes*

By Max Bingham, PhD

Metformin/AICAR for Pain Relief in Diabetic Neuropathy: Underlying Mechanisms Proposed

A potential molecular mechanism involving AMPK and an ion channel (TRPA1) that is involved in pain and stress sensing has been linked to diabetic peripheral neuropathy, which Wang et al. (**p. 98**) say might be a therapeutic target for the painful version of diabetic neuropathy. The experiments they describe initially focus on dorsal root ganglion (DRG) neurons and the effects of two AMPK activators, metformin and AICAR, in decreasing TRPA1 activity. In particular, they say treatment with the two AMPK activators decreases levels of membrane-associated TRPA1, which in turn inhibits calcium influx. Given these results and also parallel experiments with HEK293 cells, the authors considered a role for AMPK in painful diabetic neuropathy and specifically the hypothesis that AMPK is reduced in DRG neurons. They report that in diabetic *db/db* mice, AMPK activity was indeed impaired and associated with an increase in TRPA1 and allodynia (pain associated with normally nonpainful stimulation). Treatment with either metformin or AICAR then normalized both AMPK and TRPA1 levels. In subsequent experiments with cultured DRG neurons, the authors report that exposure to high levels of glucose decreased AMPK levels but that the effect could be reversed with short-term metformin addition. Turning back to experiments in mice, they go on to show that both prolonged systemic and short-term topical treatment with AMPK activators normalized membrane expression of TRPA1 and prevented mechanical allodynia. Author Yi Dai told *Diabetes*: "Our study has revealed a link between the cellular energy sensor AMPK and the pain sensor TRPA1. This means that metabolic disorders with AMPK changes may be involved in sensory problems. Activators such as metformin then may have considerable potential for use as a drug against these types of sensory disorders. Standing at a translational perspective, we expect our findings may attract much interest from clinicians to perform further studies in humans using clinical end points."

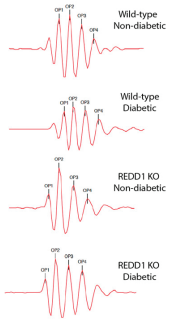


Representative images acquired using a confocal microscope showing rat DRG neurons under bright field (*A* and *B*) and the corresponding images with membrane TRPA1 immunofluorescence (*C* and *D*). Membrane TRPA1 expression was lower in rat DRG neurons treated with metformin (500 mmol/L) for 2.5 min (*D*) than in nontreated DRG neurons (control; *C*). Black and white arrowheads indicate analyzed and nonanalyzed neurons, respectively.

Wang et al. Negative regulation of TRPA1 by AMPK in primary sensory neurons as a potential mechanism of painful diabetic neuropathy. Diabetes 2018;67:98–109

Deletion of REDD1 Prevents Vision Problems in a Mouse Model of Type 1 Diabetes

The protein REDD1 may play a central role in diabetes-related retinal cell death and loss of vision, according to Miller et al. (**p. 110**). Elevated in response to hyperglycemia, the protein appears to be an important regulator of Akt and mTOR and, if this finding is proven to be correct, suggests that therapies targeting these pathways might help prevent diabetes-induced visual problems. Initially focusing on R28 retinal cells, the authors report that in cell culture conditions mimicking hyperglycemia, REDD1 (Regulated in Development and DNA Damage 1) protein expression was elevated at the same time as caspase activation and cell death. However, after using CRISPR/Cas9 technology to produce REDD1-deficient retinal cells, they found that hyperglycemia conditions did not promote cell death as before. Turning to wild-type mice with streptozotocin-induced diabetes (i.e., mimicking type 1 diabetes), they found elevated retinal apoptosis in comparison to nondiabetic controls. However, in equivalent REDD1-deficient mice, there was no retinal damage in mice with streptozotocin-induced diabetes or their equivalent controls. Using retinograms and tests for visual acuity and contrast sensitivity, wild-type mice with diabetes reportedly had abnormalities, whereas REDD1-deficient mice with diabetes did not. Taken together with previously published evidence, the authors say that diabetes likely promotes REDD1 expression and that this contributes to retinal cell death and the visual issues. They go on to discuss likely pathways involved but in particular tackle whether therapeutic options might be possible for the vision issues associated with diabetes. They highlight the small interfering RNA PF-04523655 that can reportedly reduce REDD1 mRNA expression in the retina of rodents with diabetes and improve visual acuity in patients with diabetic macular edema. Author Michael D. Dennis said: "Current therapeutics for addressing diabetes-induced vision loss focus on a single cytokine that contributes to late-stage microvascular complications; however, our study suggests that targeting REDD1 has the potential to prevent neuronal cell death in retina that occurs early in the course of diabetes."



REDD1 ablation prevents attenuated oscillatory potential (OP) amplitudes in response to diabetes. At 4 weeks after streptozotocin administration, scotopic electroretinogram responses were recorded from diabetic and nondiabetic wild-type and REDD1 knockout (KO) mice after overnight dark adaptation. Shown are representative OPs elicited from 21.0 cd-s/m² log flash intensity.

Miller et al. Deletion of the Akt/mTORC1 repressor REDD1 prevents visual dysfunction in a rodent model of type 1 diabetes. Diabetes 2018;67:110–119

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Fructosamine-3-Kinase Activity Associated With the Glycation Gap and Potential Diabetes Complications

A lot of studies use HbA_{1c} as the main measure of treatment outcomes. However, it is not the only measure of diabetes risk and HbA_{1c} has received some pretty serious criticism as a "main" diagnostic value for many years. Dunmore et al. (**p. 131**) explore the controversial glycation gap and why it might be a good basis for explaining the gap between average glycemia as measured by other methods (e.g., fructosamine) and those measured by HbA_{1c}. In particular, they focus on the role of fructosamine-3-kinase (FN3K) activity and the association with the glycation gap. They say that a positive glycation gap is likely associated with a variety of indicators for microvascular complications of diabetes. They found that erythrocyte FN3K activity was three times (323%) higher in volunteers with diabetes who had a negative gap as opposed to a positive gap between the two measures. The authors compared 81 versus 67 individuals with negative versus positive glycation gaps, respectively. They found that volunteers with a negative gap had a lower measure for advanced glycation end products and lower indicators of inflammation and other measures. They suggest that an individual's glycation gap and FN3K status might be important for diagnosing and managing diabetes, particularly for assessing risk of diabetes complications. Author Simon J. Dunmore commented: "We have previously shown that the glycation gap has potentially important implications for clinical judgements relating to a significant minority (around 10%) of patients with diabetes and to the incidence of diabetic complications. We believe that this latest study suggests that a huge difference in FN3K activity may play a role in the glycation gap and implies that clinicians should be aware of the gap and FN3K status of patients and also that there may be a potential for therapeutic intervention by modifying FN3K activity."

Dunmore et al. Evidence that differences in fructosamine-3-kinase activity may be associated with the glycation gap in human diabetes. Diabetes 2018;67:131–136

Undiscovered Genetic Mutations Likely Explain Multigenerational Diabetes of Adulthood

Multigenerational (>3 consecutive generations) diabetes of adulthood is a mostly overlooked form of diabetes, which is usually diagnosed as type 2 diabetes. Although juvenile forms of monogenic diabetes have had a number of genetic loci identified, multigenerational diabetes of adulthood has had very few loci identified. Pezzilli et al. (**p. 137**) report that among probands from 55 families with multigenerational diabetes of adulthood and an apparent autosomal dominant inheritance, just 23.6% carried mutations in known monogenic diabetes genes. This implies that in ~76% of cases, the genetic background of hyperglycemia remains to be discovered. The authors used targeted next-generation sequencing of 27 known monogenic diabetes genes in family probands and Sanger sequencing of identified mutations to verify their presence in family relatives. They report that they identified nine variants in eight of the probands after filtering strategies were applied. Further quality control procedures meant that six variants could be confidently linked to diabetes. That meant they had identified known monogenic diabetes genes in the minority (23.6%), but not the majority. Reportedly, the patients will now be the subject of further research aimed at uncovering mutations in novel genes. Author Sabrina Prudente said: "We have recently described familial diabetes of adulthood (FDA), which in the routine clinical set of adult individuals is simplistically diagnosed as type 2 diabetes. Such misdiagnosis involves at least 3% of adult patients among those defined as having type 2 diabetes with no evidence of autoimmune disease. Our study evidenced that only a small fraction of the genetics underlying FDA is explained by mutations in known monogenic diabetes genes. It is conceivable that thanks to next-generation sequencing the mostly yet unknown genetic background of FDA will be unraveled and probably the dream of precision medicine for some adult patients with diabetes will become reality as it is already the case for some young patients affected by MODY or neonatal diabetes."

Pezzilli et al. Insights from molecular characterization of adult patients of families with multigenerational diabetes. Diabetes 2018;67:137–145

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