Teaching an Old Drug New Tricks: Can Paroxetine Ease the Burden of Cardiovascular Disease in Diabetes?

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Diabetes doubles the risk of cardiovascular disease (CVD) independently of other risk factors (1). A 50-year-old with diabetes is likely to die, on average, 6 years earlier than a counterpart without diabetes, with vascular deaths being the major contributor to reduced survival (2). In keeping with the predicted rise in diabetes prevalence, the proportion of CVD deaths attributable to diabetes (currently 10% in developed countries [2]) is likely to increase substantially. Although intensive research efforts have identified the molecular mechanisms contributing to diabetes-related CVD, these discoveries have not been mirrored by major pharmaceutical advances. As a blockbuster drug to reduce CVD in diabetes has failed to emerge, other approaches need to be considered as a matter of urgency.

Although robust evidence supports the benefits of blood pressure reduction and lipid lowering in diabetes, the appropriateness of intensive glucose lowering as a tool to reduce cardiovascular risk is now questionable. In individuals newly diagnosed with diabetes, the UK Prospective Diabetes Study trial showed that intensive glycemic control with insulin or sulphonylurea resulted in a nonsignificant 16% risk reduction in myocardial infarction (3). Further, it was only after 10 years of follow-up that a 15% relative risk reduction emerged, suggesting a possible legacy effect of intensive control early in the disease process (4). In contrast, a series of large randomized trials investigating intensive glucose control in patients with diabetes of longer duration and/or established CVD has failed to demonstrate benefit. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation and Veterans Affairs Diabetes Trial studies reported no benefit from intensive glucose lowering on cardiovascular events or mortality (5,6). The Action to Control Cardiovascular Risk in Diabetes study, which randomized 10,251 diabetic patients at high risk for cardiovascular events, was terminated early because of increased mortality in the intensive intervention group (7). A high incidence of hypoglycemia associated with intensive glucose lowering is a likely explanation for the increased mortality (8). More recently, the Outcome Reduction with Initial Glargine Intervention study, which tested use of insulin glargine to normalize fasting plasma glucose, also failed to demonstrate a reduction in cardiovascular events (9).

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If intensive lowering of blood glucose is ineffective in reducing CVD events, what about targeting the cellular consequences of hyperglycemia rather than glucose per se? Might this approach deliver CVD prevention without the potentially unfavorable effects of hypoglycemia? Endothelial dysfunction (characterized by reduced bioavailability of nitric oxide and increased production of reactive oxygen species [ROS]) plays a critical role in the pathogenesis of diabetic vascular dysfunction. Although multiple cellular sources have been implicated in endothelial ROS generation (10), mitochondrial ROS is the principal contributor to hyperglycemic endothelial dysfunction (Fig. 1) (11). Cross-talk between mitochondria and NADPH oxidase facilitates a vicious feed-forward cycle of endothelial ROS generation (12), highlighting mitochondrial ROS as a suitable target for pharmacological inhibition (13).

In this issue of *Diabetes*, Gerö et al. (14) used a cell-based screening approach to identify potential inhibitors of hyperglycemia-induced endothelial ROS generation. They coupled this strategy with a drug repositioning approach, screening a library of existing clinical drugs and drug-like molecules to identify compounds that reduced mitochondrial ROS generation without jeopardizing cell viability. Of the handful of compounds so identified, the antidepressant paroxetine was selected for further study. Paroxetine reduced hyperglycemia-induced endothelial ROS generation, mitochondrial protein oxidation, and DNA damage without interfering with mitochondrial electron transport or cellular bioenergetics. To confirm a favorable effect on vascular phenotype, the investigators then showed that acute and chronic paroxetine treatment improved (though did not completely reverse) endothelial dysfunction in rat aortic rings exposed to hyperglycemia. Although these findings are persuasive, Gerö et al. acknowledged that certain questions remain unanswered. For example, although it is likely that the principal site of antioxidant action is within the sesamol moiety of paroxetine, the molecular mechanisms by which it inhibits mitochondrial ROS require further evaluation. Furthermore, the observation that paroxetine reduces xanthine oxidase–derived ROS in a cell-free system indicates that its antioxidant properties are not specific to mitochondria, thus arguing for detailed characterization of paroxetine's action on all cellular sources of ROS.

Drug repositioning offers an alternative to conventional drug discovery by finding new uses for existing medicines or compounds outside the scope of their original indication (15). The concept is not new: sildenafil is a well-known example of a drug identified serendipitously for erectile dysfunction following its original development as an antiangina medication. In the cardiovascular arena, systematic drug repositioning approaches have been used to identify drugs to prevent ischemia reperfusion injury or promote angiogenesis, but they have not previously been

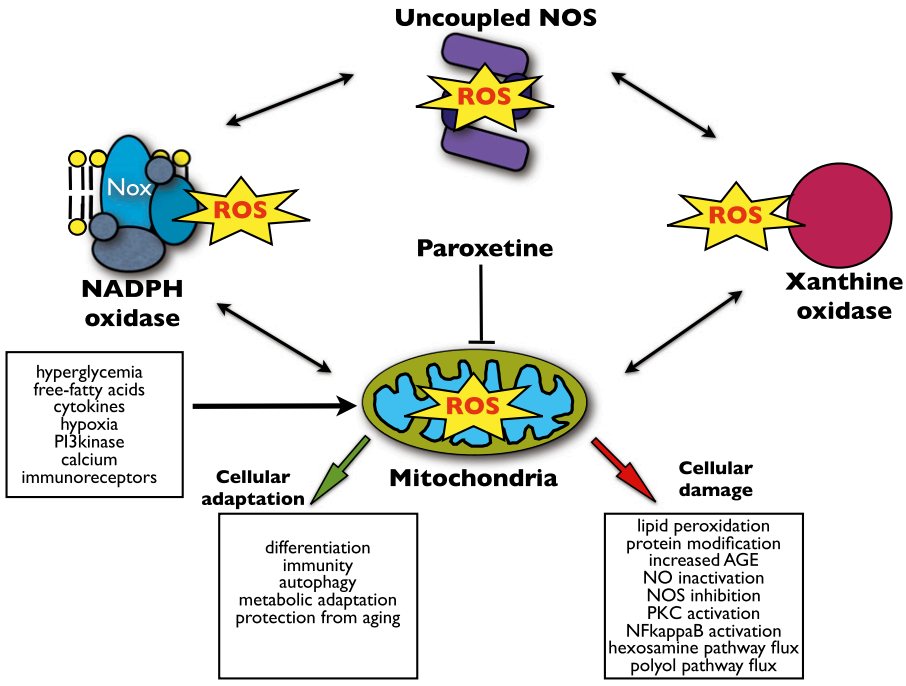

FIG. 1. Feed-forward interactions between endothelial sources of ROS and their contribution to diabetes-related vascular pathology. Mitochondria, NADPH oxidase, uncoupled endothelial nitric oxide synthase, and xanthine oxidase are among the cellular sources of ROS, which contribute to endothelial dysfunction and diabetic vasculopathy. Mitochondrial ROS generation predominates in hyperglycemic environments. ROS derived from each cellular source may activate ROS generation from other sources, driving a vicious feed-forward cycle by "ROS-induced ROS" generation. In addition to toxic effects resulting in cellular damage and contributing to vascular pathology, mitochondrial ROS also play physiological roles and modulate cellular adaptation to stress. In this issue of *Diabetes*, Gerö et al. used a novel cell-based screening approach of known pharmacological compounds to identify a new property of paroxetine as a potent inhibitor of mitochondrial ROS generation. AGE, advanced glycosylation end product; NFkappaB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthase; Nox, NADPH oxidase; PKC, protein kinase C.

reported for diabetes-specific vascular dysfunction. As the safety profiles of repositioned drugs are often known, time-to-market is potentially reduced and less risky than de novo drug development. This is pertinent to the diabetes field, where requirements for preauthorization of cardiovascular risk assessment introduced by the U.S. Federal Drug Administration after safety concerns emerged over rosiglitazone may be restricting drug development (16).

Identification of paroxetine as a novel mitochondrial ROS inhibitor warrants its further evaluation in other experimental models, in particular its ability to reduce atherosclerosis. However, identifying new roles for other drugs by this approach comes with important caveats. First, the phenotypic screen carried out by Gerö et al. discounted statins because they reduced cell viability—contrasting with the unequivocal evidence for cardioprotective effects in diabetes. Second, insulin resistance, which usually precedes the development of hyperglycemia, is associated with ROS generation that is mediated by exposure to circulating cytokines and free fatty acids. Focusing exclusively on hyperglycemia-induced ROS will miss opportunities for ROS inhibition in this critical early phase of atherogenesis. Finally, it is now apparent that low-level mitochondrial ROS generation is critical to endothelial physiology by modulating cell differentiation, immunity, autophagy, and metabolic adaptation (Fig. 1) (17). The divergent functions of mitochondrial ROS to promote cell damage and promote cellular adaptation render it a potentially challenging therapeutic target and may explain why nonselective antioxidant strategies failed to prevent CVD and increased mortality (18).

With paroxetine, we have the reassurance of many years of clinical experience with no signal for harm. An association between selective serotonin uptake inhibitors and reduced cardiovascular risk in depression (19,20) provides a springboard to pursue the drug repositioning strategy initiated by Gerö et al. Paroxetine should now continue its journey from identification as a mitochondrial ROS inhibitor through further preclinical studies to clinical trials in individuals with diabetes. Ultimately, the new trick of this old drug might ease the burden of CVD in diabetes.

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REFERENCES

1. Sarwar N, Gao P, Seshasai SRK, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215–2222
2. Seshasai SRK, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
5. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572

6. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
7. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
8. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 2010;33:1389–1394
9. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
10. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res 2010;107:1058–1070
11. Nishikawa T, Edelstein D, Du XL, et al. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 2000;404:787–790
12. Dikalova AE, Bikineyeva AT, Budzyn K, et al. Therapeutic targeting of mitochondrial superoxide in hypertension. Circ Res 2010;107:106–116
13. Dikalov S. Cross talk between mitochondria and NADPH oxidases. Free Radic Biol Med 2011;51:1289–1301
14. Gerö D, Szoleczky P, Suzuki K, et al. Cell-based screening identifies paroxetine as an inhibitor of diabetic endothelial dysfunction. Diabetes 2013;62:953–964
15. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 2004;3:673–683
16. Viereck C, Boudes P. An analysis of the impact of FDA's guidelines for addressing cardiovascular risk of drugs for type 2 diabetes on clinical development. Contemp Clin Trials 2011;32:324–332
17. Sena LA, Chandel NS. Physiological roles of mitochondrial reactive oxygen species. Mol Cell 2012;48:158–167
18. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 2007;297:842–857
19. Taylor CB, Youngblood ME, Catellier D, et al.; ENRICHD Investigators. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Arch Gen Psychiatry 2005;62:792–798
20. Sauer WH, Berlin JA, Kimmel SE. Effect of antidepressants and their relative affinity for the serotonin transporter on the risk of myocardial infarction. Circulation 2003;108:32–36