Selective Insulin Receptor Modulators (SIRM): A New Class of Antidiabetes Drugs?

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Diabetes is a complex disease that causes life-threatening complications and often requires life-long treatment. In the last few decades, drugs with different antidiabetes mechanisms have become available. These drugs include insulin-sensitizers (metformin and glitazones), secretagogues (sulphonylureas and incretins), and insulin-mimetics (both short- and long-acting analogs). These therapeutic tools have facilitated more tailored and efficacious therapy. When pancreatic insulin secretion is insufficient or absent, the injection of exogenous insulin or an insulin analog is the only available treatment to activate insulin receptors and restore the biological effects of insulin on target cells. This treatment, however, is associated with hypoglycemia, weight gain, and excess mitogenic activity that may promote the progression of pre-existing subclinical cancers. In these patients, an ideal treatment would activate the insulin receptor and replicate the beneficial metabolic actions of insulin, without causing adverse effects.

In an innovative approach to treatment of insulin-dependent diabetes, a study by Bhaskar et al. (1) in this issue of *Diabetes* introduces this type of drug. Using phage display technology, the authors identified a human monoclonal antibody (XMetA) that binds with high-affinity (ED_{50} 0.10 nmol/L) to the insulin receptor (IR) and has full glucoregulatory activity as well as a reduced risk of hypoglycemia and weight gain. XMetA is a partial IR agonist because it does not exert the full activity of insulin. Structurally unrelated to insulin, this antibody binds the IR at a different site than the hormone and does not interfere with insulin binding. Moreover, it does not bind to the IGF-I receptor. Although this antibody binds the IR with an affinity similar to that of insulin, XMetA activates IR autophosphorylation in vitro with a sevenfold reduced affinity and fivefold lower maximal activation. In addition, XMetA selectively triggers pathways downstream of the IR: XMetA activates Akt with a maximal effect that is 40% that of insulin but, in contrast to insulin, does not activate the mitogen-activated protein kinase (MAPK)/extracellular signal–related kinase pathway, which is responsible for insulin's mitogenic activity. Consequently, XMetA promotes glucose uptake in 3T3 cells but not the proliferation of MCF-7 cells. In vivo, in ICR mice made diabetic with streptozotocin, XMetA given intraperitoneally twice per week for 6 weeks nearly normalized fasting hyperglycemia and blood glucose levels after a glucose challenge and reduced HbA_{1c} from ~12 to 9%. In XMetA-treated animals, food and water intake decreased, and ketone levels normalized. In addition, nonfasting glucose, non–HDL cholesterol, and free fatty acid levels were also reduced. Neither hypoglycemia nor weight gain was observed. This allosteric human antibody appears to be a selective modulator of the IR that apparently reproduces only the favorable effects of insulin and not insulin's potential adverse effects.

Do we have the magic bullet to treat insulin-dependent diabetes with an ultra-long-acting drug that avoids the risks of insulin treatment? Certainly not yet, but this study introduces a novel approach to searching for this bullet. The data of Bhaskar et al. must be considered preliminary because of the short duration of the in vivo study, and the few in vitro models that were presented require appropriate confirmation. The major limitation of the study, however, is the lack of a mechanistic explanation for some of the observed data. Not only is the mechanism involved in the biological effects of the allosteric activation of the IR unclear, but why hypoglycemia does not occur if the antibody is continuously present (even during the fasting state) has not been explained. This is even more puzzling given that insulin levels (but not C-peptide levels) are clearly increased in mice treated with XMetA. Finally, the long-term consequences of the unbalanced activation of the Akt pathway versus the MAPK pathway and how this imbalance may affect gene expression in different tissues have not been evaluated and may be matters of concern.

The theory that there exist receptor modulators that fine-tune classical biological responses to hormones is not new. The functional selectivity of a partial agonist can be the result of the partial agonist inducing conformational changes in the receptor that are different from those induced by the orthosteric ligand, with differential activation of the downstream signal transduction cascades (2). For the IR, this possibility has already been demonstrated, even with two ligands binding at the orthosteric site, such as insulin and the cognate ligand IGF-II. The IR isoform A, in fact, is differently activated by these two ligands, as is the postreceptor signaling and gene expression (3). In addition, through the IR, the synthetic insulin mimetic peptide S597 initiates different signaling responses than insulin (4). Remarkably, like XMetA, this peptide activates the MAPK pathway and the genes involved in cell proliferation and growth in a different manner than insulin. Selectivity can also be the consequence of the predominant activation of diverse receptor subtypes that are differentially expressed in different tissues, as demonstrated with receptor-selective modulators that have already reached clinical application. There are currently receptor-selective modulators that target adenosine receptors (5,6), estrogen receptors (7–9), and other receptors (10,11). Receptor-selective modulation can also potentially occur with the two isoforms of the insulin

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receptor, which are differentially expressed in different tissues (12). Finally, the ligand-receptor interaction can be influenced by coregulators that enhance or repress specific receptor functions and result in selectivity (13). Recently, glucose and GLUT-I have been reported to bind to isolated IRs (14). If ligand binding to the IR is glucose sensitive, glucose-mediated allosteric control of the IR function is an additional possibility.

Currently, our understanding of these processes is still incomplete and insufficient, but the paradigm of modulating IR activity according to specific requirements of the disease or of the patient must now be considered, similarly to what has already been demonstrated for other receptors. Selective insulin receptor modulators may therefore provide a novel and promising strategy for better and safer treatment of diabetes. More studies are warranted that better exploit the various possibilities for selective modulation of the IR and to produce a new generation of antidiabetes drugs.

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REFERENCES

1. Bhaskar V, Goldfine ID, Bedinger DH, et al. A fully human, allosteric monoclonal antibody that activates the insulin receptor and improves glycemic control. Diabetes 2012;61:1263–1271
2. De Meyts P. The insulin receptor: a prototype for dimeric, allosteric membrane receptors? Trends Biochem Sci 2008;33:376–384
3. Pandini G, Medico E, Conte E, Sciacca L, Vigneri R, Belfiore A. Differential gene expression induced by insulin and insulin-like growth factor-II through the insulin receptor isoform A. J Biol Chem 2003;278:42178–42189
4. Jensen M, Palsgaard J, Borup R, de Meyts P, Schäffer L. Activation of the insulin receptor (IR) by insulin and a synthetic peptide has different effects on gene expression in IR-transfected L6 myoblasts. Biochem J 2008;412:435–445
5. Göblyös A, Ijzerman AP. Allosteric modulation of adenosine receptors. Biochim Biophys Acta 2011;1808:1309–1318
6. Szentmiklósi AJ, Cseppento A, Harmati G, Nánási PP. Novel trends in the treatment of cardiovascular disorders: site- and event- selective adenosinergic drugs. Curr Med Chem 2011;18:1164–1187
7. Pickar JH, Mirkin S. Tissue-selective agents: selective estrogen receptor modulators and the tissue-selective estrogen complex. Menopause Int 2010;16:121–128
8. Leitman DC, Paruthiyil S, Vivar OI, et al. Regulation of specific target genes and biological responses by estrogen receptor subtype agonists. Curr Opin Pharmacol 2010;10:629–636
9. Arevalo MA, Santos-Galindo M, Lagunas N, Azcoitia I, Garcia-Segura LM. Selective estrogen receptor modulators as brain therapeutic agents. J Mol Endocrinol 2011;46:R1–R9
10. Higgins LS, Depaoli AM. Selective peroxisome proliferator-activated receptor gamma (PPARgamma) modulation as a strategy for safer therapeutic PPARgamma activation. Am J Clin Nutr 2010;91:267S–272S
11. Williams DK, Wang J, Papke RL. Positive allosteric modulators as an approach to nicotinic acetylcholine receptor-targeted therapeutics: advantages and limitations. Biochem Pharmacol 2011;82:915–930
12. Sciacca L, Prisco M, Wu A, Belfiore A, Vigneri R, Baserga R. Signaling differences from the A and B isoforms of the insulin receptor (IR) in 32D cells in the presence or absence of IR substrate-1. Endocrinology 2003;144:2650–2658
13. Schwartz TW, Holst B. Allosteric enhancers, allosteric agonists and ago-allosteric modulators: where do they bind and how do they act? Trends Pharmacol Sci 2007;28:366–373
14. Root-Bernstein R, Vonck J. Glucose binds to the insulin receptor affecting the mutual affinity of insulin and its receptor. Cell Mol Life Sci 2009;66:2721–2732