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EDITORIAL

Glucose-responsive insulin delivery systems☆

Sistemas de liberación de insulina sensibles a la glucosa

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Diabetes is a highly prevalent condition characterized by defective insulin action leading to elevated blood glucose concentrations. Replacement therapies are very imperfect: they only achieve stable control of blood glucose values in a few cases, do not adequately adapt to disturbing factors (intake, exercise, etc.), cause hypoglycaemic episodes, and require continuous effort on the part of patients (self-monitoring, dietary restrictions, subcutaneous insulin administration, etc.).

The development of systems, usually polymers, that release insulin or other drugs in response to environmental changes such as a decrease in pH, hypoxia, etc. started several years ago. There has been recent progress in our understanding of the so-called ''intelligent insulins'', an inappropriate term because of its connotation with ''cognitive capacity''. It therefore appears more adequate to call them ''glucose-responsive insulins''.

These are actually polymers that can experience structural changes as the result of environmental changes which result in insulin release. Unlike classical closed-loop systems, these materials do not contain a specific sensor or effector. A polymer or gel in which insulin is integrated plays this dual role. To be effective, the response to significant glucose increases should be rapid, limited in time, and repeatable as often as required. Treatment should be applied continuously over a long period of time, and systems have therefore to be highly biocompatible and not induce an inadequate inflammatory or immune response. These systems may be implantable devices, or gel may be directly injected in subcutaneous tissue or, as discussed below, applied on the skin as a patch.

Glucose detection mechanisms may be natural (enzymes or proteins able to bind glucose) or synthetic.[1] Glucose oxidase is the enzyme used in almost all systems, but each system uses different changes caused by glucose oxidation such as pH decrease, hypoxia, electrostatic repulsion, the complementary action of catalase on hydrogen peroxide, etc. Among glucose binding proteins, also called lectins, concanavalin A, a protein with four glucose binding sites, is the most commonly used. This protein was used many years ago as a glucose sensor in a continuous monitoring system based on the change of viscosity resulting from glucose binding. Concanavalin A may also competitively bind to insulin, so that it releases insulin when the glucose concentration increases. However, the main problem of systems based on concanavalin A is its potential toxicity.

Among synthetic molecules, phenylboronic acid (PBA) is the most commonly used. The response of a synthetic insulin with PBA as a sensor to repeated hyperglycaemic episodes during a period of 13 h has recently been shown.[2] Although this is one of the most promising systems, its disadvantages include its lack of specificity (it also binds other monosaccharides) and its requirement of an alkaline pH in order to act.

There are various insulin release mechanisms,[3] but they may be summarized as transient changes in membrane porosity, hydrogel swelling, hydrogel contraction and shrinking,[4] and membrane dissolution.

The most promising study was published earlier this year in the journal *Proceedings of the National Academy of Sciences* by Yu et al.,[5] from North Carolina University. It is based on an ingenious system of nanovesicles that contain glucose

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oxidase and insulin, the wall of which is formed by hyaluronic acid conjugated with 2-nitroimidazole. When glucose is exposed to glucose oxidase, this oxidizes and consumes oxygen, so that local hypoxia occurs. Under hypoxic conditions, the lipophilic 2-nitroimidazole bound to hyaluronic acid becomes hydrophilic, and nanovesicles therefore dissolve and release insulin. This is new, as it is the first time that hypoxia generated by glucose oxidation has been used as an inducer of insulin release. This method allows for a faster response than in systems based on pH changes. An additional innovation is the use of patches, prepared also from a crosslinked hyaluronic acid matrix. These patches have microneedles, and glucose-responsive insulin nanovesicles are inside them. Each patch (6 mm) contains 121 conic 600 μ-long microneedles, which are painlessly inserted by means of a retractile injector into the subcutaneous tissue, becoming immersed in interstitial fluid. Tests have shown that microneedles do not break upon insertion. This highly biocompatible patch has been successfully tested in mice with streptozotocin-induced diabetes. In the first in vivo experiment, a single patch responded to hyperglycemia and stopped insulin release when hyperglycemia was corrected. In a final experiment, the authors showed that serial patch administration achieved long-term control of blood glucose levels minimizing the risk of hypoglycemia. Insulin release kinetics may be adjusted by changing the concentration of insulin and enzyme in the microneedles.

If their efficacy, tolerance and safety are confirmed, patches with microneedles containing glucose-responsive insulin could replace closed-loop systems or artificial pancreas, even before their routine implantation.

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