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Editorial Open Access

Application of Modern Drug Discovery Techniques in the Context of Diabetes Mellitus and Atherosclerosis

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Editorial

Diabetes is one of the most extensive diseases among the industrialized countries and implicates a high health care expense, not only because of the disease itself but also because of other associated serious health complications including blindness, kidney failure and lower-extremity amputations. In addition, it is an important independent risk factor for cardiovascular disease (CVD) such as coronary artery disease (CAD) resulting from accelerated atherosclerosis [1] which is one of the worst complications for patients with diabetes [2].

Despite the good results of intensive glycaemic control reducing the risk of any CVD event in patients with type 1 diabetes [3], there is a risk of hypoglycemia caused by an excess of insulin intake due to medication [4]. Nowadays, several studies have reported that β-cells generated from embryonic and adult stem cells are able to normalize blood glucose values secreting insulin in a glucose-regulated manner when transplanted into diabetic animal models [5,6]. This is a promising therapy for insulin-dependent diabetic patients. For this purpose, it is critical to identify novel differentiation factors for its use in the design of a protocol that combines several strategies for the differentiation of β-cells, such as soluble factors released during pancreas embryogenesis to induce β-cell differentiation from stem cells [7].

In addition, it is well known that, in pancreatic β-cells, K-ATP channels link changes in blood glucose concentration to insulin secretion and some drugs, such as sulfonylureas, module those channels [8].

There are other proteins involved in insulin secretion, such as glucagon-like peptide-1 receptor (GLP-1R) which stimulates postprandial insulin secretion and dipeptidyl peptidase IV (DDP4), involved in the degradation of GLP-1 [9]. Drugs that act as agonists and antagonists of these proteins respectively are candidates for the treatment of diabetes. Moreover, it has been suggested a possible role of GLP-1R agonists in reducing some cardiovascular effects [10].

On the contrary, it is not clear whether strict control of hyperglycemia reduces CV problems in (non insulin-dependant) type 2 diabetes [11-13]. However, it is been described a close relationship between insulin resistance and prothrombotic and proinflammatory factors linked to atherothrombotic disease [14]. Mainly three cellular components, platelets, monocytes and endothelium, have been suggested to modulate the inflammatory and thrombotic responses that occur in atherosclerosis [15]. Whilst the pathogenesis of the atherothrombosis is not fully understood, cell receptors are main actors in the network, conferring novel targets for drugs development [16]. Some compounds, like peroxisome proliferator-activated receptor (PPAR) agonists, can increase insulin sensitization and, as it has been recently described, have an antiplatelet action highlighting them as both antidiabetic and antithrombotic agents [17].

There are many other drugs approved for the treatment of diabetes but, unfortunately, all of them show some serious side effects. For example drugs of the thiazolidinediones class, full agonists of PPARγ, cause significant problems as weight gain and peripheral edema [18], insulin and sulfonylurea drugs administration can produce hypoglycemia [19] or DPPA-4 antagonists cause some immune-mediated dermatological effects [10].

Thus, we are still in the need of finding new drugs for the optimal treatment of diabetes taking into account other medical problems frequently associated with the disease, specially CVD and CAD.

Unfortunately, drug development timeline is time consuming and expensive. Modern drug discovery computational techniques save time and reduce costs in the process of selection of new compounds with drug like properties. During the last decade many studies have been performed using structure-based virtual screening of proteins playing a key role in the processes of glycemic homeostasis, insulin resistance or accelerated atherosclerosis [20,21]. These molecular simulation approaches, which are nowadays vastly applied to study the structure-activity relationship of characterized natural compounds within the potential cell receptors, has gained tremendous interest in recent years since it provides unique spatial information about these interactions and how they influence the cell phenotype [22].

Although virtual screening is a well established technique in the hit finding steps, it has some limitations, and for obtaining more accurate results it is usually necessary to apply complementary methods simulataneously. Ligand based virtual screening can be used to reduce the pool of drug candidates, via 2D or 3D structure and pharmacophore features similarity selection, and the time saved can be invested in more exhaustive docking simulations [23].

Another important limitation is set by the scoring function of the docking simulation. In order to improve this accuracy it is being proven useful the exploitation of machine learning methods, such as support vector machines [24] or fuzzy clustering, which have been used in many different research fields, and they have clearly proved they success in contexts of biological relevance such as bioinformatics and biomedicine [25-27].

Current trends in drug discovery bring us to the conclusion that future medicinal chemistry, in both academia and industry will rely

strongly on computational and cheminformatics approaches. This urges the academy to prepare competent medicinal chemists who have the capacities of both lab and computational chemists. Extension of pharmacological space to more promising chemical entities such as peptides and mRNA modulating agents; and developing targeted delivery systems for these "against the rule-of-five" molecules will still be hot topics in the near future [28-31].

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