Editorial

Medicinal Chemistry of Novel Anti-Diabetic Drugs

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Diabetes mellitus is a common metabolic disorder affecting millions of people worldwide. The prevalence of this chronic, endocrine condition continues to grow, from a world-wide prevalence of 221 million in 2010 to a projected 300 million in 2030 [1, 2]. The majority (~90%) of patients suffering from diabetes mellitus have type 2 while about 10% have type 1. Type 1 diabetes is caused by immunological destruction of pancreatic beta cells leading to absolute insulin deficiency. On the other hand, type 2 diabetes is associated with deficient insulin secretion and/or insulin resistance. The etiology of diabetes mellitus is multifactorial involving both genetic and environmental factors.

The multifactorial nature of the disease makes management of the diabetes difficult and in many cases multifaceted. While insulin might be nearly sufficient in the treatment of type 1 diabetes, a more diverse approach is needed for the amelioration of the signs and symptoms of patients suffering from type 2 diabetes.

Several non-pharmacological approaches have been employed to manage patients with type 2 diabetes. Physical exercise with or without weight loss have been shown to improve glycemic control [3, 4]. Physical exercise such as progressive resistance training has been reported to significantly lower blood glucose level in patients suffering from type 2 diabetes [4]. In addition, a low calorie diet with a low glycemic index is also useful in lowering glycemic level [5].

Since the etiology of diabetes mellitus is multifactorial, the pharmacological approach would warrant a multidirectional treatment as well. Several groups of pharmaceutical agents are used to target different phases of the metabolism of the pancreatic beta cell in order to generate an optimal secretion of insulin.

Oral hypoglycemic agents including, sulfonylureas, which induces the release of insulin after binding with the sulfonylurea receptors on pancreatic beta cell are widely used for the treatment of type 2 diabetes. The biguanides, a drug that does not necessarily induce insulin secretion but reduce hepatic glucose output [6] is also an 'old hand' in the pharmacotherapy of type 2 diabetes. Biguanides also increase peripheral uptake of glucose [7]. All of these actions of biguanides help to reduce blood glucose level in diabetic patients.

In spite of the success achieved with the use of the older generation of oral anti-diabetic agents, the severity and prevalence of diabetes complications continue to be high, hence the need for newer medications in the fight against the signs and symptoms of diabetes mellitus.

Research into ways of treating diabetes mellitus has led to the discovery of thiazolidinediones. These drugs bind to nuclear molecules, called peroxisome proliferator-activated receptor (PPAR). Stimulation of PPAR will in turn activate genes responsible for insulin release. The medicinal chemistry of this class of anti-diabetic drug is a subject of this Special Issue. The discovery of dual PPAR agonists is particularly interesting because it is capable of controlling diabetes mellitus and at the same time preventing the complications associated with it.

In addition, incretins such as GLP-1 and bioactive agents that block DPP-4 (vidagliptin) are relatively new, but promising tools in the arsenal of drugs used in the treatment of diabetes. DPP-4 is the enzyme that degrades GLP-1.The medicinal chemistry of this group of drug is addressed in this Issue.

Meglitinide analogues target pancreatic beta cell receptors to induce insulin release by attaching to the sulfonylurea receptor subunit and closing the K+ ATP channel concomitantly [8].

Alpha-glucosidase inhibitor (e.g. acarbose, miglitol) is yet another drug used in the treatment of diabetes mellitus. Alpha-glucosidase inhibitors delay the digestion of complex carbohydrates resulting in a decrease in blood glucose [9].

Amylin, which is released with insulin from pancreatic beta cell, is used after structural modification, as adjunct therapy in the treatment of type 1 diabetes. It is particularly favored in pediatric patients. The functions and medicinal chemistry of amylin is discussed in this Special Issue.

Insulin, given subcutaneously, comes in different preparations including short-, intermediate- and long-acting. Other forms of insulin preparation including nasal insulin spray have also been experimented. Further development of this type of insulin is under intense focus [10]. Other insulin preparation include thyroxyl-insulin, an insulin linked to thyroxin, binds strongly to plasma proteins via its thyroxyl

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molecule, resulting in a prolonged plasma half-life and little chance of diffusing through the vascular endothelium [5]. All of these result in a longer insulin action.

Studies examining the role of herbs in the treatment of diabetes have been gaining momentum in the last few decades and many herbs have been characterized as having hypoglycemic action [11]. One medicinal plant that has been getting a lot of attention is Mormodica charantia. The fruit juice of this plant has been shown to have hypoglycemic effect [12-14]. The medicinal chemistry of this plant is discussed in detail in this Special Issue.

FUTURE OUTLOOK

Improved knowledge of the chemical nature of bioactive agents, whether natural or synthetic will contribute to further discoveries of many more therapeutic agents for the treatment of diabetes in the near future. These developments will reduce the severity of the signs and symptoms of diabetes mellitus.

I would like to thank all contributors to this Special Issue. We hope that this Special Issue on the medicinal chemistry of novel anti-diabetic drugs will help in the development of more potent and optimal anti diabetic drugs in the not too distant future.

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