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Identifying novel therapeutic targets for diabetes through improved understanding of islet adhesion receptors

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Adhesion receptors are transmembrane proteins that mediate cell–cell and cell–matrix communications. In addition to their adhesive role in maintaining islet architecture, they are also important for promoting islet cell survival, proliferation and secretory function. Their capacity for improving β-cell mass and insulin secretion suggest that they may be suitable targets for pharmacological intervention, and their interactions with extracellular matrix proteins hold promise in improving islet transplantation outcomes. In this review, we have focused on integrins, cadherins and adhesion GPCRs, and highlight recent advances in their roles in islet function and discuss whether they could be targeted for diabetes therapy.

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Introduction

Islets of Langerhans are heterogeneous cell clusters in the pancreas, consisting mainly of insulin-secreting β-cells, glucagon-secreting α-cells and somatostatin-secreting δ-cells, and there are also minority endocrine cell types that express the peptides pancreatic polypeptide and ghrelin. These cells are arranged in compact three-dimensional clusters and they work synchronously to maintain euglycemia. Earlier observations in which isolated β-cells secreted less insulin than β-cells within intact islets point to the importance of intercellular contacts and cellular organisation in islet function [1]. Moreover, there are several reports that islets exposed to extracellular matrix (ECM) proteins exhibit increased survival and improved insulin secretion [2••,3,4,5••], which is suggestive of an important role for islet–matrix interactions in appropriate regulation of glucose homeostasis.

The ECM consists of a fibrous mesh that contains proteins such as collagens, elastins, fibronectins and laminins, which provide structural support to cells and facilitate cellular elasticity, motility and adhesion. These ECM proteins can regulate cellular function by interaction with families of cell surface adhesion receptors that include integrins, cadherins and adhesion G-protein-coupled receptors (GPCRs). Islets express members of these adhesion receptors, which allow them to sense signals from the ECM and the islet microenvironment (Figure 1). This is of potential therapeutic interest for diabetes since drugs targeting adhesion receptors are in current use or are undergoing clinical trials to treat diseases such as multiple sclerosis, inflammatory bowel disease, cancer and asthma (Table 1) [6•]. However, despite the important roles that adhesion receptors play in islet function they have not yet been investigated as potential targets for diabetes therapy. This article reviews recently published data on islet adhesion receptors and considers the therapeutic implications for diabetes.

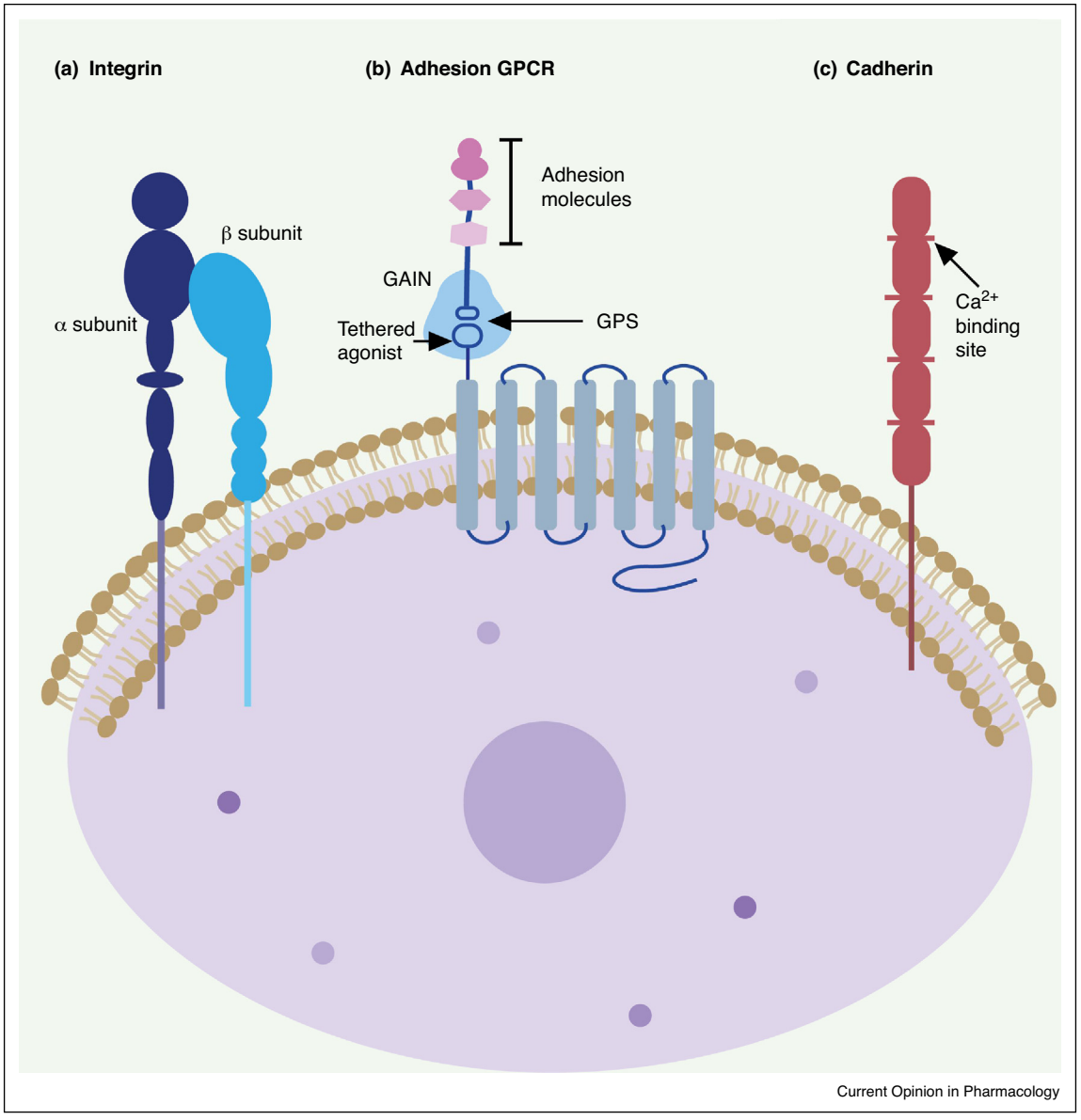
Diabetes epidemic: a case for additional therapeutic options

Diabetes is rapidly becoming a global epidemic, with a current incidence of 425 million people worldwide (International Diabetes Federation; URL: https://www.idf.org/) and the global cost of diabetes is set to rise to $2.5 trillion by 2030 [7••]. There are currently a range of drugs available to treat type 2 diabetes (T2D), which accounts for approximately 90% of all diabetes cases, but approximately 50% of younger T2D patients cannot achieve their glycaemic target with the available drugs despite a good history of adherence [8•]. Potential T2D therapies targeting GPCRs such as GPR40 and GPR119 have largely had unsatisfactory outcomes in clinical trials [9•], and there is still a pressing need to identify additional therapeutic targets that may be used for appropriate glucoregulation in T2D.

Islet adhesion receptors

Adhesion receptors are plasma membrane proteins consisting of a 'sticky' extracellular domain, a transmembrane component and a cytosolic terminal domain, and the adhesion receptor superfamily consists of integrins, cadherins, immunoglobulin-like cell adhesion molecules, selectins and the more recently described adhesion GPCRs (aGPCRs). Selectins are not included in this short review because they are not expressed by islets

Figure 1



Islet adhesion receptors. **(a)** Integrins are transmembrane heterodimers composed of α-subunit and β-subunit. They provide adhesion through interaction of the extracellular domains with ECM molecules and they also recruit intracellular proteins that mediate cell signalling via their short cytoplasmic domains. **(b)** Adhesion GPCRs have adhesion molecules on their extracellular domain, which is joined non-covalently to the seven-transmembrane segment at the GPCR proteolytic site (GPS) within the GPCR autoproteolysis-inducing (GAIN) domain. Removal of the extracellular segment above the GPS exposes the embedded tethered agonist, which elicits downstream signalling. **(c)** Cadherins consist of five-extracellular repeats containing Ca^{2+} binding sites that enable them to participate in homophilic adhesion. The small cytoplasmic segment of cadherins regulates interaction with the actin cytoskeleton and intracellular signalling via binding to catenin proteins.

per se, but by infiltrating lymphocytes in type 1 diabetes (T1D) [10].

Defective communication between islet endocrine cells has deleterious consequences and contributes to the islet dysfunctions seen in T2D and neonatal diabetes mellitus [11,12]. In addition, impaired islet function has been observed following deletion or inhibition of adhesion receptors. For example, reduced β1 integrin expression in islets results in impaired glucose tolerance and reductions in insulin secretion and islet mass [13••], while inhibition of E-cadherin prevents the formation of pseudoislets, which are β-cell clusters that have been configured to resemble native islets and show improved insulin secretion compared to dispersed cells [14]. All adhesion receptors are involved in cell–cell or cell–ECM