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Review

Effects of non-steroid immunosuppressive drugs on insulin secretion in transplantation

Effets des immunosuppresseurs non stéroïdiens sur l'insulinosécrétion en transplantation

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Résumé

Le diabète post-transplantation (DPT) représente une complication importante des greffes d'organe. Il s'associe à un risque accru de dysfonction du greffon, mais surtout de morbidité et de mortalité cardiovasculaire. L'incidence du DPT est corrélée à l'âge, à l'ethnie non caucasienne, aux antécédents familiaux de diabète, au poids, à la présence d'une infection à VHC, et aux bolus de corticoïdes administrés en cas de rejet. Différents mécanismes peuvent expliquer ces troubles du métabolisme glucidique après transplantation. Les lésions d'ischémie reperfusion, quel que soit l'organe greffé vont favoriser une insulinorésistance, aggravée par la corticothérapie postgreffe. Le rôle délétère des immunosuppresseurs non stéroïdiens sur l'insulinosécrétion est également mis en cause, notamment celui des inhibiteurs des calcineurines. Les études in vivo et in vitro ont montré l'effet inhibiteur du tacrolimus sur l'insulinosécrétion, tandis que ces effets sont moins nets pour la ciclosporine et surtout mis en évidence in vitro. Le mycophénolate n'a pas d'effet démontré sur l'insulinosécrétion. Les travaux sur les inhibiteurs de mTOR, sirolimus et éverolimus, montrent des résultats controversés. Les effets du sirolimus, principal inhibiteur des mTOR étudié, pourraient dépendre de la concentration testée, du type cellulaire (cellules β ou lignées), de l'espèce humaine ou animale et également de facteurs nutritifs d'environnement. À concentrations thérapeutiques, sur des cellules humaines, un effet stimulant sur l'insulinosécrétion a été signalé, ce qui pourrait participer au succès du protocole d'Edmonton, en greffe d'îlots pancréatiques. Globalement, les stéroïdes sont essentiellement délétères du fait d'une augmentation de l'insulinorésistance, tandis que les anticalcineurines, et principalement le tacrolimus induisent une diminution de synthèse d'insuline.

Abstract

Post-transplantation diabetes (PTD) is a serious complication in organ transplantation: not only does it increase the risk of graft dysfunction; it also increases cardiovascular morbidity and mortality. *PTD incidence is correlated with age, non-Caucasian ethnic background, a family history of diabetes, excess weight, hepatitis C infection and steroid boluses for potential rejection*. Different mechanisms might explain post-transplantation glucose metabolism disorders: ischemia–reperfusion disorders, whether renal, hepatic or cardiac, are responsible for insulin-resistance, which is increased by post-transplantation steroids; the detrimental effect of non-steroid immunosuppressive drugs on insulin-secretion could also be involved, especially with calcineurin inhibitors. In vivo and in vitro studies have shown that tacrolimus has inhibitory effects on insulin-secretion, while these effects are less obvious for cyclosporin, and were mainly demonstrated in vitro. Mycophenolate has no overt effect on insulin-secretion. Sirolimus and everolimus, two mTOR inhibitors, have shown controversial results in this realm. The effects of sirolimus (most often studied mTOR inhibitor) appear to depend on serum levels, cell type (ß cell or cell line), species (human or animal) and

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also environmental nutrients. At therapeutic concentrations, a stimulatory effect on insulin secretion was observed on human β cells. This might explain the success of islet cell transplantation with the Edmonton protocol. Finally, steroids are mainly detrimental because they accentuate insulin resistance whereas anticalcineurins, in particular tacrolimus, lower insulin synthesis.

Mots clés : Immunosuppresseurs ; Insulinosécrétion ; Cellule β ; Ciclosporine ; Tacrolimus ; Mycophénolate ; Sirolimus ; Inhibiteurs des calcineurine ; Inhibiteurs des mTOR

Keywords: Immunosuppressive drugs; Insulin-secretion; β cell; Cyclosporine; Tacrolimus; Mycophenolate; Sirolimus; Calcineurins inhibitors; mTOR inhibitors

1. Introduction

Post-transplantation diabetes (PTD) is a severe complication, in particular after kidney transplantation [31]. Not only does it correlate with higher rates of organ dysfunction, but it also increases cardiovascular morbidity and mortality by as much as 3.27 after 8 years of graft survival [23]. PTD costs an additional 21 500 US$ per patient over the first two post-transplant years [64]. PTD incidence correlates with age, non Caucasian origin, a family history of diabetes [13,31,40], excess weight [34] and VHC infection [3]. Some of these risk factors often cause complications immediately after transplantation on account of immunosuppression, even more so when steroids are used concomitantly [39].

PTD incidence is extremely variable from one study to another, from 2% in some reports to as much as 53% in others [39]. Fluctuations are due to the difference in populations and the variety of immunosuppressive regimens used, but also to the definition of diabetes that is at the very least hazy, and often not even provided [8]. Last, age is important to consider, as the risk of developing diabetes increases with age, just as in the non-transplanted population, and not with the number of years post-transplantation [7].

The effect of immunosuppressive drugs on insulin secretion might also modulate the loss of insulin independence observed after islet transplantation in type 1 diabetes [52,54]. Indeed, metabolic studies after islet graft have shown that the early post-glucose insulin-secretion peak decreases and tends to disappear after 3 years despite persisting insulin-independence and normal hemoglobin A1c [54].

Different mechanisms can explain post-transplantation glucose metabolism disorders: ischemia/ reperfusion disorders after organ transplantation can cause insulin-resistance, which is accentuated by post-transplantation steroid treatments. Non-steroid immunosuppressors might also be detrimental to insulin secretion. Calcineurin inhibitors, in particular tacrolimus, have been pointed out as particularly detrimental.

The object of our study was to review in vivo and in vitro studies on the effects of calcineurin inhibitors (tacrolimus and ciclosporin A), mTOR inhibitors (sirolimus and everolimus) and mycophenolate on insulin secretion in pancreatic β cells. We deliberately omitted epidemiology studies on the prevalence of PTD in different types of transplantation according to immunosuppressive regimen.

2. Tacrolimus

2.1. Clinical cases

Les effets délétères du tacrolimus sur l'insulinosécrétion ont été suspectés dès 1996 avec la publication de cas cliniques de diabètes apparemment induits par le tacrolimus. [59].

2.2. In vivo studies in man

Based on these clinical cases, clinical trials were designed to test the effect of tacrolimus on insulin secretion after kidney, pancreas and liver transplantation (Table 1). PTD after kidney transplantation has been more often studied, though on smaller patient groups. Results tend to show that glycemia and insulinemia are more markedly increased with tacrolimus [4,10,61]. Only one study including 136 type 1 diabetic patients with a kidney-pancreas transplantation reported no significant difference in metabolic parameters between patients initially treated with tacrolimus or sirolimus [9]. Metabolic data after liver transplantation, though more delicate to interpret, showed that insulin clearance increased [35]. In addition to trials with transplanted patients, a small group of 7 non-transplanted, non-diabetic patients was studied with euglycemic hyperinsulinemic clamps before and after beginning tacrolimus treatment for an auto-immune disease. Results showed that insulin secretion decreased, regardless of glucose tolerance. Tacrolimus did not, however, modify insulin sensitivity [57]. Actually, when tacrolimus was used without steroids, PTD incidence was little different from that observed in patients treated with cyclosporin, except for those with a VHC infection [3,51]. PTD incidence is highly dependent upon tacrolimus serum concentrations [39]. But immunosuppressors have also been studied in animals.

2.3. In vivo studies in animals

2.3.1. In rodents

Human islets were transplanted under the renal capsula of nude diabetic mice, and increasing doses of intra-peritoneal tacrolimus (0.03, 1 and 3 mg/kg of FK506 for 1 week) were injected. As a result glucose tolerance deteriorated and E-peptide response to intra-peritoneal glucose decreased when tacrolimus doses increased [48]. Similar findings were reported in rat treated with increasing doses of tacrolimus (1.5 and