



The effect of cystic fibrosis transmembrane conductance regulator modulators on impaired glucose tolerance and cystic fibrosis related diabetes

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ABSTRACT

Cystic fibrosis (CF) is an autosomal recessive disorder, with a prevalence of 1 in 2,500 live births. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. With the significant advancement in CFTR-directed therapies, life expectancy of CF patients has steadily increased. With improved survival, CF related co-morbidities have become more apparent. The most common endocrine complication includes Cystic fibrosis related diabetes (CFRD). Impaired glucose tolerance and insulin deficiency in CFRD leads to a decline in pulmonary function in CF patients. Here we review the underlying mechanisms involved in the pathogenesis of CFRD, focusing on the role of CFTR in the regulation of insulin secretion from the β -cell. We then discuss CFTR modulators and their effect on impaired glucose tolerance and CFRD.

Introduction

Cystic fibrosis (CF) is the most common autosomal recessive disorder in Caucasians. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, resulting in abnormal chloride transport in epithelial tissues. The most common endocrine complication of CF is cystic fibrosis-related diabetes (CFRD). Two percent of CF patients have CFRD in childhood, increasing to 20% of adolescents, eventually reaching 40–50% of CF patients in adulthood [1]. The implications of CFTR dysfunction resulting in CFRD are a rapidly evolving area of scientific interest. The purpose of this paper is to review the literature on the effect of CFTR modulators on glucose tolerance, insulin secretion and CFRD.

Mechanistic views on the pathogenesis of CFRD

Mutations of the CFTR gene result in reduced or absent protein function, leading to altered fluid and electrolyte composition of secretions, which ultimately leads to viscosity induced organ obstruction and fibrosis [2]. Consequences of CFTR protein dysfunction in the lung have been well studied since lung disease is the primary cause of morbidity and mortality in CF patients.

CFRD is the most common secondary complication of CF. Decreased

insulin secretion from the pancreas is the most prominent defect in CFRD, but the mechanism by which the CFTR influences insulin secretion remains debated. Furthermore, CFTR expression in islet cells has been a subject of some controversy. Two major hypotheses have been proposed for the pathogenesis of impaired insulin secretion in CFRD: (1) β -cell dysfunction due to intrinsic CFTR-dependent mechanisms of insulin secretion. (2) β -cell dysfunction resulting from pancreas-extrinsic CFTR defects.

A role for an intrinsic β -cell defect is supported by the results of experimental studies in human and mouse islets. Loss of CFTR function in cell lines, cultured rodent/ferret and human islets has been reported to impair insulin secretion [3–6] and augment glucagon secretion [6,7]. This suggests that loss of CFTR function in islets contributes to CFRD via intrinsic disruption of β and α cell stimulus-secretion coupling. CFTR plays a role in glucagon suppression; CFTR expression has been found in glucagon-secreting human and rodent α cells [6,8] and was implicated in the regulation of glucagon secretion via adenosine triphosphate-sensitive K^+ (KATP) channels. α cells have a KCl co-transporter which maintains a low level of chloride in the cell. The opening of CFTR, thus, induces chloride entry, causing membrane hyperpolarization, and inhibiting glucagon secretion. CFTR dysfunction results in impaired glucagon suppression, which is observed in CFRD patients [9]. Huang et al used a CFTR mutant mouse model to explore the role of CFTR in

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regulating glucagon secretion and showed that CFTR negatively regulates glucagon secretion by potentiating KATP channels [7].

Impaired first-phase insulin response reported in CF, is primarily due to the absence of functional CFTR in animal [5,10] and human [11] studies. Olivier et al [5] showed reduced first-phase insulin secretion and abnormal glucose tolerance in fasted newborn CFTR^{-/-} ferrets, a phenotype notably similar to CF human infants.

A previous study by Guo et al. [4] reported a functional role of the CFTR in β cells and insulin secretion. They found that the CFTR channel in β cells can be activated by glucose and its Cl⁻ efflux contributes to the glucose-induced membrane depolarization and action potentials, leading to Ca²⁺ influx required for insulin secretion. Glucose elicited membrane depolarization, calcium oscillations, and insulin secretion were abolished or reduced by inhibition or knockdown of CFTR in primary mouse β cells and β cell lines. These observations imply that CFTR Cl⁻ channel play an important role in glucose-induced membrane depolarization, which stimulates insulin secretion in pancreatic cells via the elevation of the cytosolic Ca²⁺ concentration.

Using a CFTR mutant (DF508) mouse model and a CFTR-overexpressing AlphaTC1-9 cell line, Huang et al [7] explored the role of CFTR in the regulation of glucagon secretion by α cells. The results demonstrated that CFTR negatively regulates glucagon secretion by potentiating adenosine triphosphate-sensitive K⁺ (KATP) channels, a defect of which results in excessive glucagon secretion found in CFTR mutant (DF508) mice/islets. These results suggest that dysregulated glucagon secretion due to CFTR mutations in α cells may also contribute to the glucose intolerance in CF patients leading to CFRD.

Di Fulvio et al demonstrated heterogeneous CFTR expression in human, mouse and rat β -cells and provided evidence that pharmacological inhibition of CFTR influences basal and stimulated insulin secretion in normal mouse islets but not in islets lacking this channel, despite being detected by electrophysiological means in ~30% of β -cells. Their results demonstrated a potential role for CFTR in the pancreatic β -cell secretory response and allow us to hypothesize that a defect in CFTR function could lead to abnormal β -cell electrophysiological properties underlying insulin secretion [12].

Conversely, other studies of humans and CF animal models have suggested that CFRD results from CF-induced pancreatic autodigestion, inflammation, and reduction of β cell mass [13–16] causing insufficient islet hormone secretion [16,17]. These findings are supported by an association between CFRD, exocrine disease severity, and pancreatic insufficiency. Further investigations in an F508del mouse model confirm a significant reduction in glucose-induced insulin secretion in islets studied ex vivo. The authors concluded that the observed reduction in insulin secretion was directly proportional to the reduction in insulin content, and did not occur as a result of a CFTR-induced beta cell insulin secretory defect [10].

To elucidate the underlying causes of CFRD and the role of CFTR in islet cell function, Hart et al generated acute and chronic models of β cell-specific CFTR deletion and investigated the effects of CFTR loss on glucose tolerance and β cell function. They showed that CFTR does not intrinsically regulate α or β cell function and that the etiology of CFRD is largely dependent on islet loss and intra-islet inflammation in the setting of a complex and progressive multiorgan disease [18].

Sun et al investigated the CFTR-dependent islet-autonomous mechanisms affecting insulin secretion by using islets isolated from CFTR knockout ferrets. Total insulin content was lower and glucose-stimulated insulin secretion was impaired in neonatal CF islets, with reduced first, second, and amplifying phase secretion. Interleukin (IL)-6 secretion by CF islets was higher and IL-6 treatment of WT ferret islets produced a CF-like phenotype with reduced islet insulin content. Pharmacologic inhibition of CFTR reduced glucose-stimulated insulin secretion by WT ferret and human islets but similarly reduced insulin secretion and intracellular Ca²⁺ in CFTR knockout ferret islets, indicating that the mechanism of action is not through CFTR. Single-molecule fluorescence in situ hybridization on isolated ferret and

human islets and ferret pancreas, demonstrated that CFTR RNA co-localized within KRT7 + ductal cells but not endocrine cells. These results suggest that islet-associated exocrine cells express the majority of CFTR within islets and probably influence β -cell function through exocrine-derived factors such as IL-6 that alter properties of the islet, including insulin content [19]. White et al demonstrated that in situ CFTR mRNA expression was present in only a very small minority (<1%) of normal adult β -cells. This indicates that although CFTR is indeed expressed in a few β -cells in the adult human islet, but the expression is considered be low and unlikely to play a role on β -cell function [20].

Although the above mentioned studies support each of these hypotheses, the question of whether CFTR functions within the β -cell continues to be a subject of debate.

CFTR mutations

There are six classes of mutations frequently found on the CFTR gene that are involved in the absence or altered expression of the CFTR protein responsible for the CF pathology [Fig. 1]. Class I mutations leads to lack of functional CFTR protein synthesis due to nonsense, frame shift or splicing mutations. Class II mutations lead to a misfolding protein that fails to achieve conformational stability in the endoplasmic reticulum and transport to the plasma membrane, resulting in severe reduction of CFTR activity [21]. This class includes Phe508del, the most prevalent mutation in the CFTR gene in Western countries. CF patients homozygous for class II mutations have severe pancreatic insufficiency and are considered at a higher risk to develop CFRD [2]. Class III mutations, referred as “gating” mutations lead to gating Cl channel defect [21]. G551D is the most common CFTR gating mutation. Class IV mutations reduce CFTR dependent Cl transport due to channel conductance defect, but still permit a degree of residual function. Class V mutations results in reduction of functional CFTR protein due to decreased synthesis and/or inefficient protein maturation. Class VI mutations affect CFTR stability at the plasma membrane level, thus reducing the protein expression and recycling at the apical surface [21]. Mutations in classes I, II, and III are usually associated with more severe disease, whereas others are related to milder phenotypes [21].

CFTR modulators

CFTR modulator are drugs that can enhance and/or restore the expression, function, as well as stabilize the defective CFTR protein. These include potentiators (ivacaftor), that increase conductance of the CFTR channel, and correctors (lumacaftor, tezacaftor, elexacaftor), that improve CFTR trafficking to the cell surface [22]. The use of CFTR modulators have shown to improve pulmonary function while reducing CF exacerbations. Currently, it is debated whether CFTR modulators have an effect on glucose tolerance and insulin secretion.

Ivacaftor, a novel CFTR activator, is specifically used to treat patients with the G551D mutations. Known as the “gating” mutation, this results in failure of the CFTR channel to open at the cell surface. G551D mutations have a prevalence of approximately 4% to 5% in the CF population [22].

A small pilot study by Bellin et al [23] shows that correction of CFTR activity with Ivacaftor administered over 4 weeks improved insulin secretion in patients with CFRD. This study consisted of 5 participants, ages 6–52. 2 participants had CFRD, 1 had impaired glucose tolerance and 2 had normal glucose tolerance. The insulin response to oral glucose improved in four of the five participants. The significant increase in insulin secretion in response to oral glucose was seen in 2 pediatric subjects ages 6 and 14 yr. Acute insulin secretion in response to intravenous glucose improved in four of the five subjects, including partial restoration in two subjects who previously had no measurable acute insulin response. This suggests that pediatric population with CF are able to compensate for CFTR defect since their beta cell mass is largely intact. As islets are lost over time due to exocrine pancreatic fibrosis and

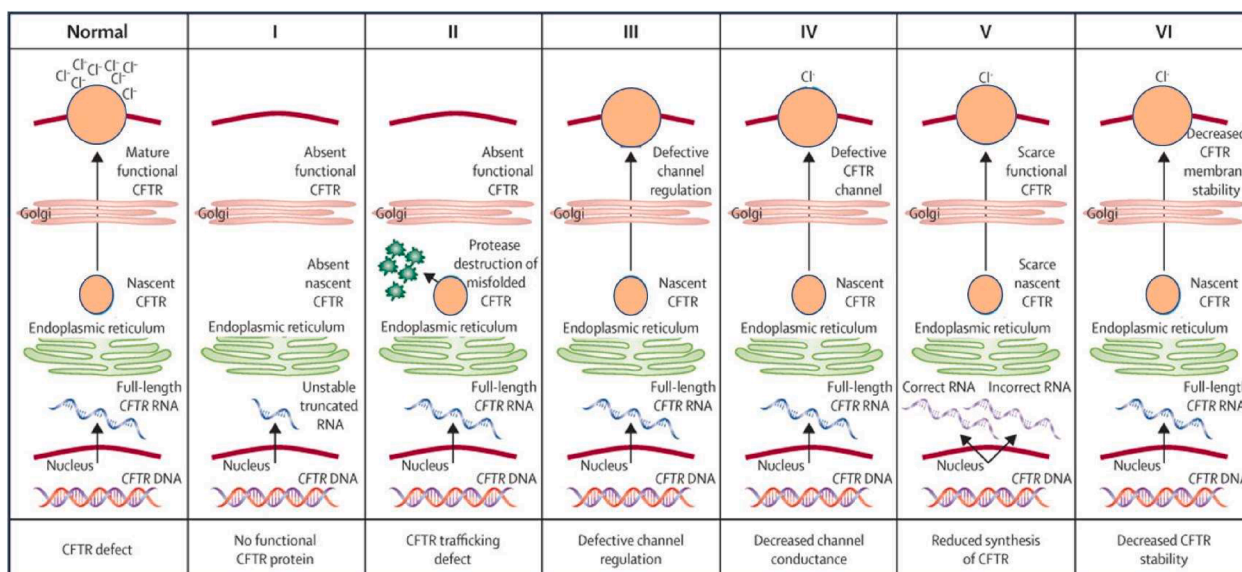


Fig. 1. Classification of CFTR mutations Note: Reproduced from *Advances in Genomics and Genetics*, Vallières E, Elborn J. Cystic fibrosis gene mutations: evaluation and assessment of disease severity, 161–172 [31] Copyright © 2014, with permission from Dove Medical Press. Abbreviation: CFTR, cystic fibrosis transmembrane regulator.

chronic beta cell stress, the impact of CFTR on insulin secretion becomes more critical. This pilot study served as proof of concept that CFTR plays a reversible role in insulin secretion abnormalities. The primary limitation of this study was the small sample size, in addition to short study duration and the wide age range of the subjects.

Tsbari et al [24] investigated the effect of Ivacaftor treatment on insulin secretion in CF patients with CFRD. The study consisted of 2 patients (ages 22 and 24 yrs.) treated with Ivacaftor over 16 weeks. One patient (patient 1) had indeterminate glycemia and the other patient (patient 2) had CFRD. Neither patient was on oral hypoglycemic medications or insulin treatment. Pre-Ivacaftor treatment OGTT for patient 1 demonstrated indeterminate glycemia. Ivacaftor treatment led to an improvement from indeterminate glycemia to normal glucose tolerance. The AUC for glucose decreased by 12.35% after ivacaftor treatment. Insulin secretion post treatment was approximately 40% higher by the 30 min point, it was lower during the rest of the OGTT. Pre-Ivacaftor treatment OGTT for patient 2 demonstrated CFRD with fasting hyperglycemia. After Ivacaftor treatment, this patient had indeterminate glycemia. When comparing OGTT pre and post Ivacaftor treatment, the AUC for insulin increased by 77% and the AUC for glucose decreased by 16%. In conclusion, this case series showed beneficial effect of 4 month Ivacaftor treatment on glucose metabolism with an improvement in the first phase insulin secretion.

Sustained improvement in glycemic control with long term Ivacaftor treatment has been reported by Christian et al [25] in a case of an adult patient with CFRD. This patient was diagnosed with CFRD at age 20. He was started on insulin therapy the year following diagnosis. Eight years after being diagnosed with CFRD, he started Ivacaftor 150 mg orally. Within 6 months of starting Ivacaftor, he developed recurrent hypoglycemic episodes, prompting cessation of insulin therapy. The episodes of hypoglycemia were almost always after meals, and rarely during periods of fasting. This indicated that Ivacaftor had an effect on insulin secretion in response to a meal. He had resolution of CFRD (A1c- 5.6%) and remained off insulin while on Ivacaftor therapy (3 years), despite weight gain of 15 kg during that time frame.

Kelly et al [26] evaluated the impact of 4 months of Ivacaftor treatment on islet hormone in young individuals with CF (median age 13.5 yr.). Their study consisted of 12 subjects, 5 had abnormal glucose tolerance and 7 had normal glucose tolerance prior to treatment. After treatment, glucose tolerance normalized in one abnormal glucose

tolerance subject. Ivacaftor treatment did not alter meal responses except for an increase in early phase C-peptide ($P = 0.04$). First-phase ($P = 0.001$) and glucose potentiation of arginine-induced ($P = 0.027$) insulin secretion assessed by acute C-peptide responses improved after Ivacaftor treatment. The disposition index relating the amount of insulin secreted for insulin sensitivity also improved ($P = 0.04$). In conclusion, early insulin secretion improved four months after starting Ivacaftor therapy. Whether insulin secretion would further improve with long duration of Ivacaftor therapy in young individuals with CF is not known.

Dual therapy

Lumacaftor/Ivacaftor (Orkambi) is a combined CFTR modulating therapy including a corrector (Lumacaftor) and a potentiator (Ivacaftor). This combination therapy was approved for treatment of CF patients with delta 508 mutations, which comprise approximately 70% of all mutations [26].

Thomassen et al [27] investigated the effect of Lumacaftor/Ivacaftor on glucose metabolism and insulin secretion in CF patients. This was a small study consisting of 5 participants, ages 13–33 years. Prior to initiating treatment, two participants had impaired glucose tolerance, two had indeterminate glucose tolerance and one had normal glucose tolerance. After 6–8 weeks of Lumacaftor/Ivacaftor therapy, the fasting plasma glucose levels were normal in all participants. In response to OGTT, three had indeterminate glucose tolerance, one had normal glucose tolerance whereas, and one progressed to CFRD. In response to the IVGTT, only two participants were noted to have an improvement in insulin secretion as measured by AUC, while the remaining three had decreased insulin secretion. In conclusion, this study failed to demonstrate that Lumacaftor/Ivacaftor had a consistent impact on glucose tolerance and insulin secretion.

Misgault et al [28] investigated the effects of 1-year Lumacaftor/Ivacaftor treatment correcting glucose intolerance. This was a prospective, observational study, which included 40 CF patients with glucose intolerance or newly diagnosed CFRD. Patients were 24 years old on average with an age distribution of 12–61 years. Prior to treatment, 78% ($n = 31$) patients had glucose intolerance and 22% ($n = 9$) had CFRD. After one-year of Lumacaftor–Ivacaftor treatment, 50% ($n = 20$) of patients had normal glucose tolerance, 40% ($n = 16$) had glucose intolerance, and 10% had diabetes ($n = 4$). In the entire cohort, two-hour

glucose levels were significantly lower after one year of treatment but there was no difference in fasting or one-hour glucose levels. There was no difference in the one- and two-hour OGTT C-peptide and insulin levels between pre- and post-treatment, suggesting that no significant effect was observed on acute insulin secretion. However, significant increase was noted in BMI and albumin levels, suggesting improved nutritional status. This study had the largest number of CF patients reported so far in comparison to previous studies discussed above. While the majority of patients had impaired glucose tolerance, the study represented a relatively small number of patients with CFRD.

Recently, Moheet et al [29] examined the impact of lumacaftor/ivacaftor therapy on glucose tolerance and insulin secretion in patients with CF who were homozygous for the F508del mutation. This study consisted of 39 subjects, 9 subjects with normal glucose tolerance, 15 abnormal glucose tolerance and 15 had CFRD. They assessed OGTTs at baseline, 3, 6 and 12 months after starting therapy. There was no improvement in fasting, 2 h glucose levels, glucose or insulin area under the curve pre and post treatment demonstrating that Lumacaftor/Ivacaftor did not improve β cell function or glucose tolerance in this population.

Similarly, Colombo et al [30] reported no improved in glucose tolerance, insulin secretory parameters, clearance and sensitivity after one-year lumacaftor/ivacaftor treatment in a retrospective case-control study of 13 subjects with CF. The likely explanation for why there was no observed impact of lumacaftor/ivacaftor on OGTT or insulin level is that there is insufficient improvement in CFTR activity to make a measurable difference in islet function [29].

To date, there have been no studies focusing on the effect of Tezacaftor/Ivacaftor (Symdeko) on glucose metabolism and/or CFRD.

Triple therapy

Elexacaftor/Ivacaftor/Tezacaftor (Trikafta) was the first triple therapy approved by the FDA in October 2019. It is indicated for the treatment of CF patients age 6 years and older who have at least one F508del mutation. PROMISE is an ongoing, prospective, multi-center study that aims to investigate the biological and clinical effects of significantly corrected CFTR function using Elexacaftor/Ivacaftor/Tezacaftor. In the endocrine sub study, glucose tolerance, insulin secretion, hepatic insulin clearance, and incretin secretion will be evaluated. The results of this study will help us determine the effect of triple therapy on glucose metabolism and insulin secretion and whether early initiation of this modulator could prevent or delay the development of diabetes in CF.

Conclusion

CFRD is becoming an increasingly common diagnosis as CF patients are living longer. Although, the primary treatment is insulin however, CFTR modulators have shown a positive effect on improving glucose tolerance. The challenge with studies to date have been relatively short treatment duration, and failed to show conclusive evidence regarding the effect of CFTR modulators on glucose metabolism and insulin secretion. Large, prospective, long term studies are warranted to determine the effect of early initiation of CFTR modulator in preventing or delaying CFRD development.

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