Abstract:
Since the discovery of the KATP channel in 1983, numerous studies have revealed its physiological functions. The KATP channel is expressed in various organs, including the pancreas, brain and skeletal muscles. It functions as a “metabolic sensor” that converts the metabolic status to electrical activity. In pancreatic beta-cells, the KATP channel regulates the secretion of insulin by sensing a change in the blood glucose level and thus maintains glucose homeostasis. In 2004, heterozygous gain-of-function mutations in the KCNJ11 gene, which encodes the Kir6.2 subunit of the KATP channel, were found to cause neonatal diabetes. In some mutations, diabetes is accompanied by severe neurological symptoms [developmental delay, epilepsy, neonatal diabetes (DEND) syndrome]. This review focuses on mutations of Kir6.2, the pore-forming subunit and sulfonylurea receptor (SUR) 1, the regulatory subunit of the KATP channel, which cause neonatal diabetes/DEND syndrome and also discusses the findings of the pathological mechanisms that are associated with neonatal diabetes, and its neurological features.

Key words: neonatal diabetes, DEND syndrome, KATP channel, sulphonylurea

The Structure and Physiological Roles of the KATP Channel

The glucose-dependent insulin secretion is initiated by an increase in the plasma glucose concentration, which enhances the glucose metabolism in beta-cells. This enhanced glucose metabolism leads to an increase in the intracellular concentration of adenosine triphosphate (ATP). This leads to the closure of the KATP channel, which in turn induces membrane depolarization and triggers the opening of the voltage dependent Ca\textsuperscript{2+} channel, which stimulates the release of insulin (1, 2) (Fig. 1). However, the detailed mechanisms that are involved in glucose-dependent insulin secretion and the regulation of the KATP channel are more complicated than the above mechanism.

The electrophysiological findings of KATP channel property confused researchers in the early days of KATP channel research. From the early electrophysiological studies, it was clear that an increased ATP concentration inhibited the KATP channel, but the measurement of the ATP concentration in intact beta-cells revealed that the intracellular ATP concentration was so high, even under low glucose conditions (2-4 mM), that the KATP channel should be permanently closed (3, 4). However, this discrepancy was later explained by the finding that MgADP can activate the KATP channel (5, 6). At low glucose concentrations, the activation of the KATP channel by MgADP was found to be more dominant, while at high glucose concentrations the inhibitory effects of ATP were found to become more dominant as the intracellular ATP concentration increased. The regulation of KATP channel activity was therefore revealed to result from a balance between the inhibitory effects of intracellular ATP and the activation of the KATP channel by intracellular MgADP.

When the KATP channel was cloned in 1995, it was found to be a complex of two different proteins: pore forming subunit Kir6.2, a member of the inwardly rectifying potassium channel family; and sulfonylurea receptor (SUR) 1, a member of the ABCC family, and an ATP-binding cassette transporter (7, 8) (Fig. 2). Four Kir6.2 subunits compose a channel pore and four SUR1 subunits surrounding the Kir6.2 channel pore compose a 4:4 octameric complex (9). Each Kir6.2 and SUR1 subunit possesses an endoplasmic reticulum retention motif and since Kir6.2 and SUR1 mask each other’s motifs, none of the subunits can reach the cell...
membrane alone (10). The binding site for ATP lies on the Kir6.2 subunit while the MgADP binding site lies on the SUR1 subunit (11-14).

The Discovery of Neonatal Diabetes due to Gain-of-function Mutations in the K_{ATP} Channel

It is well known that K_{ATP} channel mutations can cause congenital hyperinsulinism. The underlying mechanisms of congenital hyperinsulinism include a total loss of the K_{ATP} channel in the plasma membrane or the impairment of K_{ATP} channel activation by MgADP, which modulates the closed state of the K_{ATP} channel, resulting in permanent membrane depolarization and insulin secretion (15-18).

On the other hand, the existence of genetic variance in residue 23 of Kir6.2 (E23K) has been reported to be common in patients with type 2 diabetes (the precise mechanism by which E23K contributes to the development of diabetes remains unclear) (19-21). In 2000, a gain-of-function mutation of the K_{ATP} channel was found to cause glucose intolerance in a mouse model (22). This report indicated the possibility that gain-of-function mutations in the K_{ATP} channel may decrease insulin secretion, leading to the development of diabetes in humans.

In 2004, the first case of neonatal diabetes with a gain-of-function mutation in the K_{ATP} channel was reported (23). The prevalence of neonatal diabetes is estimated to be 1 in 250,000. It is characterized by the onset of diabetes within 6 months after birth (24-29). Nearly half of the cases of neonatal diabetes are caused by Kir6.2 (KCNJ11) and SUR1 (ABCC8) mutations (23-32). Approximately 31% of the cases are due to KCNJ11 mutations, while 13% are due to ABCC8 mutations (33). Although the majority of these patients develop diabetes, only approximately 20% of patients with K_{ATP} channel mutations develop neurological symptoms. Neonatal diabetes is classified into the following four subtypes based on the severity of the symptoms: transient hyperglycemia (transient neonatal diabetes: TNDM); permanent hyperglycemia (permanent neonatal diabetes: PNDM); the presence of severe neurological symptoms such as developmental delay, epilepsy and muscle weakness (DEND syndrome); and DEND syndrome symptoms without epilepsy (intermediate DEND syndrome: iDEND) (24-28).
changes in the KATP channel activity, which occur due to a sent, the Po is increased in comparison to the wild-type KATP channel. Binding mutations do not usually affect the gating property involved in channel gating are considered to indirectly reduce (binding mutations). Mutations located in the regions in- 

Kir6.2 Mutations and the Pathophysiology of Neonatal Diabetes

The reported mutations of Kir6.2 are mostly dominant heterozygous (one homozygous mutation has been reported), whereas those in SUR1 are either dominant or recessively inherited (29, 32, 34).

The functional studies of neonatal diabetes-causing Kir6.2 mutations have shown that these mutations reduce the ability of ATP to inhibit the K_{ATP} channel (23, 25-30). These tiny changes in the K_{ATP} channel activity, which occur due to a small shift in ATP sensitivity, can alter the beta-cell electrical activity and insulin secretion to an extent that causes diabetes (34). The molecular mechanism underlying this reduced ATP sensitivity depends on the location of the Kir6.2 mutation (Fig. 3).

Mutations located in the predicted ATP binding site are considered to directly impair the binding of ATP to Kir6.2 (binding mutations). Mutations located in the regions involved in channel gating are considered to indirectly reduce the inhibition of channel activity by ATP (gating mutations). Binding mutations do not usually affect the gating property of the K_{ATP} channel. In single channel recordings of the K_{ATP} channel with binding mutations, the fraction of time that channels spend in the open state (open probability: Po) is similar to that of the wild-type K_{ATP} channel (25, 35-37). On the other hand, when K_{ATP} channel gating mutations are present, the Po is increased in comparison to the wild-type K_{ATP} channel, which indicates that these mutations shift the channel gating toward the open state. The shift of channel gating toward the open state will ultimately reduce the inhibition of the channel by ATP (37-40).

Although there are no correlations between the underlying mechanism (gating or binding) and the severity of patient symptoms, there is a clear correlation between the degree of ATP sensitivity and the severity of the disease. In compari-

SUR1 Mutations and the Pathophysiology of Neonatal Diabetes

The mechanism through which SUR1 mutations induce neonatal diabetes/DEND syndrome is complicated and poorly understood. SUR1 is composed of three transmembrane domains (TMDs), which are linked by a cytosolic linker region (CL3) and two nucleotide-binding domains (NBDs), NBD1 and NBD2. TMD 1 and 2 contain six transmembrane helices, while TMD0 contains five transmembrane helices (7, 32) (Fig. 2).

Each NBD contains Walker A and Walker B motifs, which are required for nucleotide binding. NBD1 and 2 dimerize to undergo MgATP binding, and NBD2 hydrolyses MgATP to MgADP and stimulates the K_{ATP} channel activity.

To date, more than 60 mutations that induce neonatal diabetes have been identified in SUR1. Most patients with SUR mutations only have diabetes; however, approximately 30% of patients with SUR mutation are reported to have neurological features (32). There are two possible mechanisms through which SUR1 mutations can induce an increase in the K_{ATP} channel activity. The first mechanism is through the actions of Kir6.2, such as reducing the binding of ATP to Kir6.2 or stabilizing the open state of the channel by impairing the gating mechanism of Kir6.2 (42). The second possible mechanism involves the enhancement of the activating effect of MgADP (43-48). How SUR1 is coupled to the total K_{ATP} channel activity remains unclear. However, because
very recent studies have clarified the structure of the $K_{ATP}$ channel in high resolution, it is expected that the details of the interaction of Kir6.2 and SUR1 will be revealed (47, 48).

### The Neurological Features of $K_{ATP}$ Channel Mutations Causing DEND Syndrome

The mechanism underlying the induction of hyperglycemia by $K_{ATP}$ channel mutations has been well investigated. However, the mechanisms underlying the development of the neurological features that are seen in patients with DEND syndrome are less understood (49). The $K_{ATP}$ channel is expressed in multiple types of neurons in the brain. Although numerous studies have reported on the $K_{ATP}$ channel and the brain function, the details of the physiological contribution of the brain $K_{ATP}$ channel remain to be elucidated. However, recent studies have clarified the physiological contribution of the brain $K_{ATP}$ channel to some extent. The neurons in the hypothalamus are known to sense changes in glucose concentrations through the $K_{ATP}$ channel, which ultimately regulates the food intake and glucose metabolism (49-52). It has also been reported that the $K_{ATP}$ channel contributes to the protection of neurons against stressful conditions such as brain infarction and hypoglycemia (53).

However, these functions, which are already known, cannot fully explain the neurological symptoms of DEND syndrome. It is hypothesized that the underlying mechanism through which DEND syndrome patients develop epilepsy involves the deactivation of the inhibitory neurons, which is induced by the opening of the $K_{ATP}$ channel.

As previously mentioned, the neurological symptoms of patients with DEND syndrome were originally considered to be associated with developmental delay, epilepsy and muscle weakness. However, recent reports suggest the existence of psychiatric disorders. Some patients with causative mutations of DEND syndrome are reported to show signs of attention deficit hyperactivity disorder (ADHD), autism or sleeping disorder (54, 55). In a mouse model, mice with neural tissue with DEND-causing V59M mutations displayed hyperactivity, increased exploratory behavior and reduced anxiety, which is consistent with the symptoms of ADHD and autism (56). The precise mechanism underlying the development of these psychiatric disorders remains unclear. Because these psychiatric symptoms have a severe impact on both the patient and the patient’s family, an integrated and collaborative approach to clinical care is required.

### Implications for Therapy

Before the discovery of $K_{ATP}$ channel mutations, neonatal diabetes was considered to be a rare form of type 1 diabetes, and was therefore treated with insulin. However, numerous basic and clinical studies on mutations have revealed that many patients with neonatal diabetes due to $K_{ATP}$ channel mutations can be treated with sulphonylurea drugs, which bind to both Kir6.2 and SUR1 subunits (57, 58).

The low affinity-binding site in Kir6.2 is blocked by high concentrations of the sulphonylurea drugs and has no clinical relevance. The primary effect of the drug is mediated by the high affinity-binding site on SUR1 (59, 60). Clinically, sulphonylureas bind to the high affinity-binding site and induce the closure of the $K_{ATP}$ channel by suppressing the activating effect of MgADP and unmasking the inhibiting effect of ATP on Kir6.2 (59).

Studies of the $K_{ATP}$ channel mutations using the Xenopus oocyte expression system have revealed that many (if not all) mutations were found to be close to some extent by sulphonylurea drugs (27, 35, 37, 38, 58). Based on these findings, more than 90% (87.5% in Japan) of patients with neonatal diabetes were successfully switched from insulin injection treatment to oral sulphonylurea (glibenclamide) therapy (57, 58, 61). Because a high dose of glibenclamide is required for the treatment of neonatal diabetes, the risk of inducing hypoglycemia should be considered. However, clinical studies have shown that sulphonylurea therapy induces fewer fluctuations in blood glucose, and a marked decrease in HbA1c levels in comparison to insulin injection therapy (57).

It is suggested that sulphonylureas can also improve the neurological features of patients with DEND syndrome (26). Hashimoto et al. reported the successful improvement of the neurological features in patients with T293N and R50P mutations, which are associated with DEND syndrome (61). However, the patients’ neurological symptoms did not completely recover after treatment with sulphonylureas. This may be because the concentration of sulphonylurea is not sufficient to close the $K_{ATP}$ channel in the brain. Whether sulphonylureas can cross the blood brain barrier (BBB) remains unclear. A previous study showed that when glibenclamide was administered peripherally in mice, the drug concentration in the cerebral spinal fluid was not high enough to block the mutated $K_{ATP}$ channel, which affected the neural electrical activity (62). However, an increase in the blood flow in the cerebellum was observed in patients with DEND syndrome after they switched to sulphonylurea therapy (63). This shows that sulphonylureas have an effect on the brain, and that the improvement of the motor function by the initiation of sulphonylurea therapy may be explained by the improved cerebellum function; however, further study is required to test this hypothesis.

Generally, sulphonylurea treatment is more effective when it is started at an early stage of life. Age and prolonged poor glycemic control seem to be important predictors of responsiveness to sulphonylureas in neonatal diabetic patients. Effective transfer is less likely in elderly patients with poor glycemic control (64-66). Because insulin therapy does not improve the neurological symptoms of DEND syndrome, an early-stage diagnosis is critical, as it enables sulphonylurea therapy to be initiated as quickly as possible.

Minor side effects of high-dose sulphonylurea treatment
have been reported in patients with neonatal diabetes. Transient diarrhea was reported by some patients after switching to sulphonylurea treatment (67). Furthermore, approximately 7.5% of sulphonylurea-treated patients experienced tooth discoloration (68). The severity of discoloration varies from a mild color change to a loss of enamel. The mechanism responsible for this symptom is unclear but thought possibly to be related to the direct exposure of the teeth to high doses of the drug, because the patients with discoloration either chewed the drug or took it in solution (68).

The increased activity of the $K_{ATP}$ channel due to mutations leads to reduced insulin secretion and the development of neonatal diabetes. Some mutations cause severe neurological symptoms. Recent studies have shown that many patients with neonatal diabetes and $K_{ATP}$ channel mutations can be effectively treated using sulphonylurea drugs. Functional studies on $K_{ATP}$ channel mutations provide novel therapeutic options for patients with neonatal diabetes; thus, it is important to make a precise diagnosis at an early stage of the disease.

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