Intracellular ATP binds to Kir6.2 molecules to inhibit the channel activity, whereas MgADP binds to SUR1 to activate the channel. Therefore, channel activity is controlled by the ATP/ADP ratio within the cells.

In the endoplasmic reticulum, Kir6.2 and SUR1 associate with each other to form the channel that is transferred to the Golgi apparatus and to the cell surface. If Kir6.2 and SUR1 do not associate with each other, they cannot escape the endoplasmic reticulum and are degraded there.

Kir6.2 and SUR1 are encoded by *KCNJ11* (1 exon) and *ABCC8* (39 exons), respectively. These genes are located side-by-side with close proximity on 11p15.1.

Known etiologies of CHI (Table 2)

1. Transient and persistent CHI

There are two main types of CHI: transient CHI, which usually develops soon after birth and resolves spontaneously within the first 3–4 weeks of life and persistent CHI, which can develop later in life as well as in the neonatel period, and lasts longer. The distinction between transient and persistent CHI is not possible on the basis of laboratory test results. In our national survey in Japan, only shorter gestational age and lighter birth weight were predictors of transient CHI[20]. The incidence of persistent CHI is generally estimated as 1 in 50,000 live births[9] although the incidence could be higher in certain populations (e.g., 1 in 2,500 births in Saudi Arabia). On the contrary, the incidence of transient CHI is much higher. In the national survey in Japan, the incidence of transient CHI (1 in 17,000 births) was approximately twice as high as that for persistent CHI (1 in 35,400 births)[20].

1) Transient CHI

Transient CHI is believed to be caused mainly by nongenetic factors, e.g., small size for the infant's gestational age or stressful perinatal conditions such as cardiopulmonary disorders. An important exception is the monoallelic inactivating mutation in *HNF4A*[21-23]. Unlike other patients with transient CHI, patients with *HNF4A* mutations are often born large for gestational age. Importantly, a fraction of these patients develop a form of dominantly inherited diabetes, maturity-onset diabetes of the young type 1 (MODY1), later in life and therefore should be followed up after resolution of CHI (21-23). Because *HNF1A* is in the same pathway with *HNF4A* and its mutation is the cause of MODY3, researchers checked for mutations in *HNF1A* in patients with transient CHI, and indeed found some patients with mutations in *HNF1A*[24,25].

2) Persistent CHI

In contrast, persistent CHI is believed to have genetic etiologies. However, even with the most comprehensive analysis, the responsible genes can be identified in only 53% of diazoxide-responsive CHI patients[26] although in unresponsive patients, K_{ATP} channel mutations could be identified in most (87.6%–88%) cases[26,27].

2. Causes of persistent CHI

Table 2 lists known causes of CHI. The most common of these are inactivating mutations in one of the K_{ATP} channel genes, *ABCC8* or *KCNJ11* (K_{ATP}-CHI). The second most common is an activating mutation of glutamate dehydrogenase (GDH-CHI). Others are relatively rare. When confined to families with consanguinity, inactivating mutations in L-3-hydroxyacyl-coenzyme A dehydrogenase (HADH-CHI) are the most common cause[26,27].

1) K_{ATP}-CHI

Three distinct subtypes of K_{ATP}-CHI are known:

(1) Recessively-inherited K_{ATP}-CHI: Recessive K_{ATP}-CHI is caused by biallelic mutations in one of the K_{ATP} channel genes. This is the most severe form of K_{ATP}-CHI, and all β-cells in the pancreas present in abnormal (diffuse) form. Pathologically, recessive K_{ATP}-CHI is characterized by large β-cells with abnormally enlarged nuclei[28].

Table 2. Genetic causes of congenital hyperinsulinism

Gene	Protein	Chromosome	Inheritance	Note
K_{ATP} channel			AR, AD, Focal	Diazodixe unresponsive Usher CHI (contiguous deletion)
ABCC8	SUR1	11p15.1		
KCNJ11	Kir6.2	11p15.1		
GLUD1	Glutamate dehydrogenase	10q23.3	AD	Hyperammonemia
GCK	Glucokinase	7p15	AD	Diffuse/focal?
HADH	L-3-hydroxyacyl-coenzyme A dehydrogenase	4q22–q26	AR	
UCP2	Uncoupling protein 2	11q13	AD	
SLC16A1	Monocarboxylate transporter 1	1p12	AD	Exercise induced HI
HNF4A	Hepatocyte nuclear factor 4α	20q13.12	AD	Transient/persistent macrosomia
HNF1A	Hepatocyte nuclear factor 1α	12q24.2	AD	Variable onset glycogenosis renal tubular dysfunction

AR, autosomal recessive; AD, autosomal dominant; CHI, congenital hyperinsulinism; HI, hyperinsulinism

(2) Dominantly inherited K_{ATP}-CHI: Dominant K_{ATP}-CHI is caused by a monoallelic mutation in the K_{ATP} channel genes. The presentation is usually relatively milder, and patients often respond to diazoxide[29] although there are some refractory cases[30].

(3) Focal K_{ATP}-CHI:

i) Pathogenesis

In patients with focal K_{ATP}-CHI, abnormal β-cells are confined to a restricted region in the pancreas. In close proximity with the K_{ATP} channel genes at chromosome 11p15.1, an imprinted region at 11p15.5 harbors maternally expressed tumor suppressors, *H19* and *CDKN1c*, and a paternally expressed growth factor gene, *IGF2*. The focal lesion arises in an individual with a paternally inherited, monoallelic mutation in one of the K_{ATP} channel genes. When segmental paternal uniparental disomy occurs as a somatic mutation during the development of the pancreas, that particular cell loses K_{ATP} channel activity. At the same time, the tumor-suppressor activities of *H19* and *CDKN1C* are lost, and the activity of *IGF2* is doubled. This leads to a growth advantage for the abnormal β-cells and eventually leads to formation of a focal lesion[31-34]. Histologically, the focal lesion is characterized by the presence of large β-cells with enlarged nuclei similar to those of the diffuse lesion, and β-cells outside the focus have normal histology[35-37].

ii) Clinical implication

Although 96.2% of focal lesions are unresponsive to diazoxide[3], when the focal lesion is identified preoperatively, partial pancreatectomy can cure the patient without postoperative complications. Therefore, the identification and localization of focal lesions are extremely important. However, because they are generated during the normal organogenesis of the pancreas, they cannot usually be detected using conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging, and angiography. The focal lesions can be preoperatively identified using molecular analysis and ^{18}F-fluoro-L-DOPA positron emission tomography (^{18}F-DOPA PET) scans, thereby enabling surgeons to plan the surgical procedure and to find the lesion intraoperatively.

iii) ^{18}F-DOPA PET scan

^{18}F-DOPA is incorporated into β-cells by DOPA-decarboxylase, which is abundant in β-cells. Following the initial description of its role in identifying the focal lesion[38], its usefulness has been reported in a number of publications[39,40]. ^{18}F-DOPA PET detects focal lesions as small as 5 mm and is better preformed as PET-CT. However, there are some challenges in interpreting the results. First, artifact uptakes tend to be found in the head of the pancreas because the head has a larger mass than the rest of the pancreas and because ^{18}F-DOPA is excreted into the bile duct. Second, ^{18}F-DOPA PET does not necessarily show the exact size of the lesion, especially when the lesion extends so-called tentacles out of the central lesion. These problems appeared more pronounced in our experience in Japan[41].

iv) Epidemiology of focal K_{ATP}-CHI

Previously, it was reported that approximately 40%–60% of surgically treated patients had focal CHI[31,42,43]. However, recent molecular analysis has revealed a racial disparity in the frequency of paternally inherited monoallelic mutation in K_{ATP}-CHI patients. For example, the percentage of patients with a paternally inherited monoallelic K_{ATP}-channel mutation is 20.6% in Spain[44], 33% in Norway[45], 84.2% in Japan[46], 37.7% in Germany[47], 58% in China[48], and 25% in the UK[27]. Obviously, these figures could be affected by ascertainment biases and by small sample sizes. In Japan, we have presently identified 46 patients with K_{ATP}-CHI, and 37 (80.4%) have paternal mutations. Therefore, combined with the report from China[48], it appears that Asians tend to have a higher frequency of paternally inherited mutation, suggesting the presence of focal CHI. The identification of focal CHI, therefore, is even more important for Asian patients.

v) Discordant molecular and ^{18}F-DOPA PET results

Not all patients with a paternally inherited K_{ATP} channel mutation have focal uptake by ^{18}F-DOPA PET, and some of these actually show diffuse histology. For example, Banerjee et al.[49] reported that 31% of patients with a paternal monoallelic mutation showed diffuse uptake on 18F-DOPA PET. Similarly, Kapoor et al.[27] reported that 26% of patients with paternal mutation appeared to have a diffuse lesion on PET. These results may indicate that not all maternal mutations were identified by the molecular analysis. However, when monoallelic mutations were identified in patients with K_{ATP}-CHI, the majority were paternal mutations: 79.3% and 65% in two UK series[27,49], 84.2% in Japan[46], and 83.3% in Norway[45]. Selectively missing the maternal allele during the molecular analysis is statistically highly unlikely. Another possibility, therefore, is that these patients have unusually scattered focal CHI that resembles true diffuse CHI. Further analysis is necessary to address this problem.

2) Non-K_{ATP} channel CHI

Most other persistent CHI are caused by excessive anaplerosis (replenishment of metabolic intermediate) into the GSIS pathway. With the exception of *GCK* and *SLC16A1* mutations, these non-K_{ATP}-channel CHI are usually responsive to diazoxide.

(1) GDH

GDH is encoded by *GLUD1* at chromosome 10q23.3. GDH mediates conversion of glutamate to α-ketoglutarate and ammonia, which is one of the major anaplerotic pathways in the Krebs cycle. An activating mutation in the *GLUD1* gene then supplies excess α-ketoglutarate into the Krebs cycle. The resulting overproduction of ATP causes CHI associated with hyperammonemia (hyperinsulinism–hyperammonemia syndrome)[50]. Both dominantly inherited and sporadic cases have been reported. Hypoglycemia is responsive to diazoxide, but hyperammonemia is resistant to conventional treatment.

Because GDH is allosterically activated by leucine, GDH-CHI presents with the typical leucine-sensitive CHI.

3) HADH

HADH—previously known as short-chain hydroxyacyl CoA dehydrogenase—is encoded by *HADH* at 4q22–q26. HADH functions in the mitochondrial matrix to catalyze the oxidation of straight-chain 3-hydroxyacyl-CoAs as part of the β-oxidation pathway. Unlike other proteins in the β-oxidation pathway, HADH is abundant in pancreatic β-cells and inhibits the activity of GDH. Biallelic HADH mutation then causes activation of GDH and hyperinsulinemia[51-53].

4) Glucokinase

Glucokinase is encoded by *GCK* at chromosome 7p15. Patients with GCK-HI have an activating mutation in *GCK*. This leads to overactivity in the GSIS pathway and oversecretion of insulin[54-56]. On the contrary, inactivating monoallelic mutation is a cause of MODY2 or GCK-MODY[57]. Recently, a somatic activating mutation in GCK has been proposed as a cause of a novel form of diazoxide-responsive focal CHI[58].

5) Uncoupling protein 2

Mitochondrial uncoupling protein 2 (UCP2) is encoded by *UCP2* at chromosome 11q13. UCP2 protein leaks protons across the inner mitochondrial membrane, thereby uncoupling the oxidative phosphorylation from ATP generation. Patients with a monoallelic mutation in UCP2 have excessive ATP production leading to HI[59].

6) Monocarboxylate transporter 1

Monocarboxylate transporter 1 (MCT1) encoded by *SLC16A1* at 1p12 is in the cell membrane and transports extracellular lactate and pyruvate into the cells. In pancreatic β-cells, the activity of MCT1 is normally suppressed to prevent lactate influx during exercise. In patients with exercise-induced HI, researchers identified mutations in the promoter of *SLC16A1* that activate the transporter. During exercise, extracellular lactate is fluxed into the β-cells and is converted to pyruvate, which fuels the GSIS pathway. The resulting increase in ATP production leads to HI[60].

3. Syndromic CHI

A variety of syndromes are reportedly associated with CHI. Because CHI is not a common feature of these syndromes, some of these associations may be coincidental. Nevertheless, CHI is frequently associated with Beckwith-Wiedemann syndrome, Sotos syndrome, Kabuki syndrome, Costello syndrome, mosaic Turner syndrome, or congenital deficiency of glycosylation[61]. In these syndromes, the association may have biological implications more than by-chance association. Of note is the Usher-CHI syndrome[62,63] in which CHI is associated with the symptoms of Usher syndrome, i.e., hearing loss and retinitis pigmentosa. This association is caused by biallelic deletions encompassing the K_{ATP} channel genes at 15p11 and the adjacent *USH1C* gene at 11p14.3, which is responsible for Usher syndrome.

Current treatment strategies

Current treatment strategies are summarized in Table 3 and are reviewed below.

1. Diazoxide

Diazoxide is a benzothiazine derivative that acts on the SUR1 subunit of the K_{ATP} channel, activating it. Diazoxide is used orally in three divided doses (5–15 mg/kg/day) and is effective for a variety of CHI subtypes[64]. However, it is generally ineffective for the most severe, neonatal-onset, recessive, and focal forms of K_{ATP}-CHI. Dominant K_{ATP} channel CHI often responds to diazoxide, although some unresponsive cases have been reported[32]. Hypertrichosis occurs in most patients and could be a serious concern. Other side effects include water retention, which could cause serious problems such as congestive heart failure or reopening of the ductus arteriosus[65,66]. This side effect may be of particular concern in patients with a low birth weight, as in transient CHI. Routine coadministration of diuretics is advised.

2. Octreotide

Octreotide is a somatostatin analog that acts on the somatostatin receptors SSTR2 and SSTR5 and inhibits secretion of a variety of hormones, including gastrin, cholecystokinin, glucagon, growth hormone, secretin, pancreatic polypeptide, thyroid stimulating hormone (TSH) vasoactive intestinal peptide, and insulin. Although its use for CHI has not been licensed in any country, it has been used for nearly 20 years for both short- and long-term control of diazoxide-unresponsive CHI[67,68]. It is administered as multiple daily subcutaneous injections (3–4 times/day) or by continuous subcutaneous infusions using an insulin pump. In our experience, many

Table 3. Treatment for congenital hyperinsulinism

Nutritional
Hypertonic glucose infusion
Cornstarch
Glycogen storage disorder formula
Enteral feeding (nasogastric tube feeding, gastrostomy)
Medical
Diazoxide, 5–20 mg/kg/day, po
Nifedipine, 0.25–2.5 mg/kg/day, po
Octreotide, 5–25 μg/kg/day, sc
Glucagon, 1–20 μg/kg/hr, sc, iv, im
Surgical
Pancreatectomy (partial, subtotal, neartotal)

po, per oral; sc, subcutanetous; iv, intravenous; im, intramuscular.

patients with K_{ATP} channel CHI can be maintained on long-term treatment until spontaneous remission at 2–5 years of age[69]. Common adverse events include gastrointestinal symptoms, white stool, dilated gall bladder with or without gall stones, and growth deceleration after 2 years of age. Rarer, but more serious side effects, include hepatitis[70], necrotizing enterocolitis[71] and long QT syndrome[72].

3. Glucagon

Glucagon stimulates glycogenolysis and gluconeogenesis to increase hepatic glucose output. It is administered by intravenous, subcutaneous, or intramuscular routes, and has been used mainly for short-term control of diazoxide-unresponsive patients who are not adequately controlled by other means. However, as is the case for octreotide, its long-term use until spontaneous remission has been reported[73,74]. Apart from its gastrointestinal side effects, its crystallization in the infusion tubes has been a major practical problem during long-term use. Part of this problem may be ameliorated by the development of a water-soluble formulation that is in a phase 2 clinical trial (ClinicalTrials.gov Identifier: NCT01972152).

4. Pancreatectomy

When patients are not responsive to medical treatment and cannot be weaned off treatment with intravenous glucose infusions, pancreatectomy should be considered. When a focal lesion is identified preoperatively, partial pancreatectomy is the treatment of choice. However, the lesion is not always visible or palpable at the site indicated by ^{18}F-DOPA PET. Although intraoperative sonography can aid in identification[75], repeated intraoperative biopsy may be necessary to help surgeons determine the extent of pancreatectomy. Such a treatment is made possible only by a multidisciplinary team composed of surgeons, radiologists, pediatric endocrinologists, and pathologists who are well experienced in the treatment of CHI[76,77]. When a focal lesion is identified in the body or tail of the pancreas using ^{18}F-DOPA PET, resection is relatively easy; even if the exact location of the focal lesion cannot be identified, distal pancreatectomy of <70% typically cures the patient without a risk of postoperative diabetes. On the contrary, when the lesion is identified in the head of the pancreas, resection may be difficult without damaging important adjacent structures such as the main pancreatic duct or the common bile duct. In those cases, pancreatic head resection with Roux-en-Y reconstruction of distal pancreatojejunostomy has been proposed[78]. For patients with diazoxide-unresponsive diffuse CHI, extended resection of the pancreas is still needed. Even in these cases, near-total pancreatectomy should be avoided as much as possible in order to reduce the development of postsurgical diabetes[79,80]. A 70%–90% resection may be considered to reduce the pancreatic mass and to facilitate medical management.

Other unsolved questions and future perspectives

1. Causes of the remaining 50% of persistent CHI

At present, even with the most comprehensive molecular analysis, mutations in known causative genes cannot be identified in 21.3% of patients[26]. When confined to diazoxide-responsive cases, mutations are not identified in 53%. Therefore, if we assume that all persistent CHI is genetic in origin, there must be unidentified causative genes. In an effort to address this issue, Proverbio et al.[81] analyzed 17 families with CHI who lacked mutations in *ABCC8/KCNJ11* using a combination of transmission disequilibrium tests and whole-exome sequencing and reported 21 novel genes as possible candidates. Although none of these have been confirmed as causative, further efforts employing next-generation sequencing may answer these questions.

Using next-generation sequencing, Flanagan et al.[82] took a different approach of sequencing the entire genomic region of the *ABCC8* and *HADH* genes[82]. By this strategy, they identified deep intronic mutations of both genes causing CHI, c.1333-1013A>G in *ABCC8* and c.636þ471G>T *HADH*. Surprisingly, these mutations were common in the Irish and Turkish populations, accounting for 14% of focal hyperinsulinism cases and 32% of subjects with HADH mutations.

2. Causes of transient CHI (a hypothesis)

Transient CHI is common in infants who were born small for their gestational ages (SGA) or in those with perinatal stress. However, little is known about its cause. SGA infants are in a hypoxemic condition in utero[83]. Because β-cell function is inhibited by hypoxia-inducible factor 1α (HIF1α)[84,85], a sudden increase in the oxygen tension at delivery may downregulate HIF1α leading to hyperinsulinemia. In line with the observation that oxygenation of fetal blood improves with gestational ages[83], it has been reported that blood insulin levels at birth correlate with the gestational age of the infants: 9.2 μIU/mL for full term; 10.3 μIU/mL for early term; 13.2 μIU/mL for late preterm; and 18.9 μIU/mL for early preterm[86]. Hyperinsulinemia at birth, therefore, is a common finding in newborns with a lower birth weight.

3. Mechanism of spontaneous remission of CHI

Both diffuse and focal HI resolve spontaneously over time[87]. A previously proposed mechanism for spontaneous remission of CHI is apoptotic death of insulin-oversecreting β-cells[88]. However, the initial event could be functional shutdown of insulin secretion rather than apoptotic cell death because the abnormal β-cells could still be observed by ^{18}F-DOPA PET at an early stage of the spontaneous remission of focal K_{ATP}-CHI[89]. Manipulating the process of functional shutoff could be an

attractive treatment option for CHI.

4. Novel medications for diazoxide–unresponsive CHI

1) Novel somatostatin analogues

Novel somtatostatin analogues have been successfully used for CHI or other forms of HI, including lanreotide[90,91] or long-acting octreotide[92] for CHI. In addition, pasireotide has been tested for severe postgastric bypass HI[93]. Although octreotide and lanreotide have affinities for somatostatin receptors SSTR2 and SSTR5, pasireotide has a broader spectrum of activity for other types of SSTRs[94].

2) Small molecule corrector of K_{ATP}-channel CHI

The search for small molecules to treat CHI is fueled by previous efforts to correct the trafficking defect of the cystic fibrosis transmembrane conductance regulator, which is deficient in patients with cystic fibrosis. The idea is to use small molecules as pharmacological chaperones to correct the trafficking defect and help their expression to the cell surface[95]. This strategy is applicable to certain mutations of the K_{ATP}-channel genes. Thus far, sulfonylureas[96] and carbamazepine[97] have been successfully used to correct the trafficking defects of mutations within the transmembrane domains 0 and 1 (TMD0, TMD1) of *ABCC8*.

3) Glucagon-like peptide 1 (GLP1) receptor antagonist

GLP1 is secreted from the L-cells of the small intestine and binds to the GLP1 receptors in pancreatic β-cells, thereby stimulating the secretion of insulin (the incretin pathway). This pathway has a role in the amplification of postprandial insulin secretion and has been the target of novel treatments for type 2 diabetes. An antagonist of the GLP1 receptor, exendin[9-39], has been shown to be effective for the treatment of CHI in an open-label, randomized clinical trial[98]. Although the effect was not complete, and monotherapy of CHI with this class of medication appears impractical, GLP1 receptor antagonists may have a role in adjunctive treatment of CHI.

4) Mammalian target of rapamycin (mTOR) inhibitors

mTOR is a member of the serine/threonine kinase family and is induced by amino acids (arginine and branched-chain amino acids), stress, high-energy status, oxygen, and growth factors. mTOR is complexed with regulatory-associated protein of mTOR (Raptor), mammalian LST8/G-protein β-subunit–like protein (mLST8/GβL), PRAS40, and DEPTOR to form the mTORC1 complex. Alternatively, mTOR is complexed with mLST8/Gβ, rapamycin-insensitive companion of mTOR (Rictor), and mammalian stress-activated protein kinase-interacting protein 1 (mSIN1) to form mTORC2 and is active in a variety of cellular mechanisms, including protein synthesis, cell proliferation, or cell survival. Therefore, mTOR inhibitors have been widely used to treat neoplasms. In terms of glucose metabolism, activation of mTORC1 is known to cause increased glucose uptake and glycolysis via HIF1. In addition, mTORC2 is known to play an important role in maintaining the β-cell mass through the phosphotidylinositol-3-kinase/mTORC2/AKT signaling pathway[99]. Sirolimus, one of the mTOR inhibitors, was successfully used to treat patients with diazoxide unresponsive CHI[100]. These classes of medications therefore may have a role in the treatment of CHI as well.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Review Article

Congenital hyperinsulinism: Global and Japanese perspectives

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Abstract Over the past 20 years, there has been remarkable progress in the diagnosis and treatment of congenital hyperinsulinism (CHI). These advances have been supported by the understanding of the molecular mechanism and the development of diagnostic modalities to identify the focal form of ATP-sensitive potassium channel CHI. Many patients with diazoxide-unresponsive focal CHI have been cured by partial pancreatectomy without developing postsurgical diabetes mellitus. Important novel findings on the genetic basis of the other forms of CHI have also been obtained, and several novel medical treatments have been explored. However, the management of patients with CHI is still far from ideal. First, state-of-the-art treatment is not widely available worldwide. Second, it appears that the management strategy needs to be adjusted according to the patient's ethnic group. Third, optimal management of patients with the diazoxide-unresponsive, diffuse form of CHI is still insufficient and requires further improvement. In this review, we describe the current landscape of this disorder, discuss the racial disparity of CHI using Japanese patients as an example, and briefly note unanswered questions and unmet needs that should be addressed in the near future.

Key words 18F-dihydroxyphenylalanine, congenital hyperinsulinism, potassium channel.

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and infants before weaning. Other terms for CHI, such as "nesidioblastosis" or "persistent hyperinsulinemic hypoglycemia in infancy," are currently less frequently used. "Nesidioblastosis" is a pathological term indicating the continuous proliferation of islet cells from the pancreatic ducts, which is a common finding in healthy newborns and in obese subjects,[1–4] and the term "persistent hyperinsulinemic hypoglycemia in infancy" is no longer favored because symptoms of CHI could develop after infancy or even in adulthood.[5]

Persistent severe hypoglycemia could lead to permanent brain damage, so appropriate and timely treatment is extremely important for the prognosis of patients with CHI.[6–9] Patients resistant to medical treatment previously often underwent near-total pancreatectomy, which involves removal of more than 95% of the total volume of the pancreas. The results, however, were frequently unsatisfactory because many patients remained hypoglycemic after surgery and most patients without hypoglycemia eventually developed postsurgical insulin-dependent diabetes mellitus.[9–11]

Fortunately, during the past decade, there has been major progress in the understanding and treatment of CHI, and many cases are now curable without postsurgical complications. However, there are still unanswered questions about the cause of CHI and unmet needs of patients that need to be addressed. Importantly, current diagnostic and therapeutic strategies are not uniformly available and applicable throughout the world.

We have studied CHI in Japan over the past several years and found that there are regional biological and social differences in this disorder from what has been reported globally. In this review, we describe the current global landscape of CHI and discuss an example of CHI in Japan that differs from the global trend.

Mechanism of glucose-induced insulin secretion

Glucose-induced insulin secretion

To facilitate the understanding of the pathophysiology of CHI (Fig. 1), the following is a brief summary of the pathway of glucose-induced insulin secretion. After a meal, blood glucose is at an elevated level and is transported into the cells by glucose transporters. The transporter for the pancreas is glucose transporter 2 (GLUT2), which has a low affinity and high capacity for glucose, galactose, or fructose and transports them within the range of physiological concentrations.[12] The transported glucose is then phosphorylated by glucokinase, a member of the hexokinases. This enzyme has a low affinity for glucose and is not inhibited by its end product, glucose-6-phosphate. Therefore, it generates glucose-6-phosphate in a wide range of physiological glucose concentrations and is considered the glucose sensor of the pancreas.[13] Glucose-6-phosphate is metabolized through glycolysis to form pyruvate, which is then transported into mitochondria. Within mitochondria, pyruvate is further metabolized through the Krebs cycle and the oxidative phosphorylation

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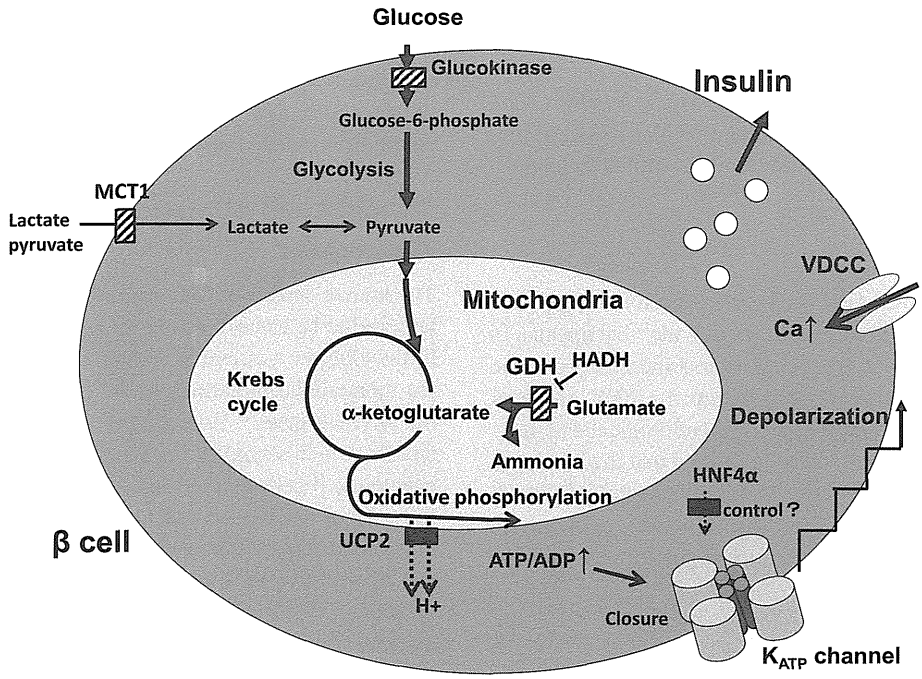

Fig. 1 Glucose-induced insulin secretion pathway is shown together with molecules relevant to congenital hyperinsulinism. ADP, adenosine diphosphate; ATP, adenosine triphosphate; GDH, glucose dehydrogenase; HADH, L-3-hydroxyacyl-coenzyme A dehydrogenase; HNF4α, hepatocyte nuclear factor 4α; K_{ATP} channel, adenosine triphosphate–sensitive potassium channel; MCT1, monocarboxylate transporter 1; UCP2, uncoupling protein 2; VDCC, voltage-dependent calcium channel.

pathway. During this process, one molecule of glucose generates 38 molecules of adenosine triphosphate (ATP). The increased intracellular ATP/adenosine diphosphate (ADP) ratio then leads to the closure of the ATP-sensitive potassium channel (K_{ATP} channel) in the cell membrane, which prevents the potassium current through the channel and causes depolarization of the cell membrane. The change in the membrane potential opens the voltage-gated calcium channel, leading to influx of extracellular calcium into the cells. The increased intracellular calcium concentration then facilitates exocytosis of the insulin-containing vesicles and secretion of insulin.[14]

K_{ATP} channel

The K_{ATP} channel is an octameric structure composed of four molecules of Kir6.2 subunits, which form the inner pore, and surrounded by four molecules of SUR1 subunits, which control the channel activity. Increased levels of intracellular ATP are sensed by the Kir6.2 subunits to limit the channel current. In contrast, increased Mg-ADP is sensed by the SUR1 subunits to increase the channel current. Therefore, an increased ATP/ADP ratio leads to a decreased open probability of the channel leading to secretion of insulin.[14,15]

Diagnosis of CHI

CHI is diagnosed on the basis of inappropriately elevated serum insulin levels in the presence of hypoglycemia. However, it is difficult to set distinct cut-offs for diagnosis. First, there are no confirmed age-dependent cut-offs for the diagnosis of hypoglycemia. Traditionally, blood glucose levels < 2.5 mmol/L (45 mg/dL) in children and <3.0 mmol/L (54 mg/dL) in adults have been widely accepted as cut-offs for hypoglycemia. These cut-offs were derived from physiological responses against hypoglycemia,[16] but they should probably differ depending on the clinical status of the individual patient.[17] Second, the cut-off for an "inappropriately high" insulin level is also unknown. A serum insulin level of >3 μU/mL in the presence of hypoglycemia is probably sufficient to diagnose hyperinsulinism. However, not all "detectable insulin" in the presence of hypoglycemia indicates a diagnosis of hyperinsulinism but instead depends on other factors, such as the assay sensitivity or the state of insulin resistance. To circumvent these difficulties, criteria such as the need for a higher glucose infusion to maintain euglycemia or the response to glucagon injections, are also used as adjuncts to help diagnose hyperinsulinism.[18] Table 1 shows the diagnostic criteria for hyperinsulinemic hypoglycemia proposed as a diagnostic guideline by a workgroup from the Japanese Society for Pediatric Endocrinology (http://jspe.umin.jp/).

Table 1 Diagnostic criteria for hyperinsulinemic hypoglycemia from the Japanese Society for Pediatric Endocrinology

Laboratory data during hypoglycemia (critical sample):
Blood insulin level >2–5 μIU/mL
Blood free fatty acid level <1.5 mmol/L
Blood β-hydroxybutyrate level <2.0 mmol/L
Glucose infusion rate to maintain normoglycemia:
>6–8 mg/kg/min

Epidemiology of transient and persistent CHI

Transient and persistent CHI

CHI can be categorized as: transient CHI, which develops soon after birth and usually resolves within the first 3–4 weeks of life; and persistent CHI, which could develop later and lasts longer.

Epidemiology

Persistent CHI

The incidence of persistent CHI has been reported to be approximately one case per 50 000 live births worldwide[19] but appears to vary depending on the gene frequency of mutant alleles and the marital habitus of the particular population. In 2009, we conducted a national survey to explore the epidemiological and treatment status of CHI in Japan; the results showed that the incidence of persistent CHI was one case per 35 400 live births.[20] In Saudi Arabia, where consanguineous marriage is more common, the incidence of CHI is reported to be much higher at one case per 2675 live births.[21]

Transient CHI

The incidence of transient CHI appears to be much higher than that for persistent CHI. The estimated incidence of transient CHI in Japan has been reported to be twice as high as that of persistent CHI at one case per 17 000 live births.[20] However, the incidence is probably underestimated because milder transient CHI that resolves within 1 week with a glucose drip infusion is probably not diagnosed or reported properly.

Differentiation of transient and persistent CHI

In the aforementioned survey in Japan, we identified 61 patients with persistent CHI and 127 patients with transient CHI who were born between 2007 and 2009.[20] Interestingly, the only clinical indices that could differentiate transient from persistent CHI were shorter gestational age and lower birthweight SDS in the transient CHI group. No other parameters, such as insulin/glucose ratio, total ketone bodies, or total free fatty acid levels, could differentiate these two groups with statistical significance.

Transient and persistent CHI: Known causes

Transient CHI

The known causes of CHI are listed in Table 2. Transient CHI is believed to be caused mostly by non-genetic factors, such as low birthweight or a stressful perinatal period. Important exceptions are monoallelic mutations in the *HNF4A* gene[22–25] and possibly the *HNF1A* gene.[26] Both of these genes code for transcription factors, which stimulate transcription of a variety of genes in the pancreatic β cells and the hepatocytes. Mutations in these genes have been shown to cause forms of dominantly inherited monogenic diabetes, maturity-onset diabetes of the young types 1 and 3, respectively. Exactly how mutations in these genes cause transient CHI is currently unknown. However, recent findings indicate the presence of gene–gene interaction between the *HNF4A* and *KCNJ11* genes.[27] The presentation of hyperinsulinism related to an *HNF1A* mutation appears to be different from that of typical transient CHI in that the patient could develop hypoglycemia later in infancy or in childhood.[26] Patients with *HNF4A* or *HNF1A* mutations could develop diabetes mellitus later in life and therefore should be followed up after remission of hypoglycemia.

Persistent CHI

In contrast to transient CHI, most cases of persistent CHI are believed to be caused by genetic factors; however, causative gene mutations have been identified in only 45.3–79% of patients.[28,29]

Table 2 Known causes of congenital hyperinsulinism

Persistent	Nonsyndromic	K_{ATP} channel genes	AR, AD, focal (monoallelic paternal + paternal uniparental disomy)
		ABCC8 (SUR1)	
		KCNJ11 (Kir6.2)	
		GLUD1 (glutamate dehydrogenase)	AD, hyperammonemia
		GCK (glucokinase)	AD, focal?
		HADH (L-3-hydroxyacyl-coenzyme A dehydrogenase)	AR
		UCP2 (uncoupling protein 2)	AD
		INSR (insulin receptor)	AD
		SLC16A1 (monocarboxylate transporter 1)	AD
	Syndromic	*ABCC8, KCNJ11, USH1C*: Usher-CHI syndrome	AR
		Beckwith–Wiedemann syndrome	
		Congenital deficiency of glycosylation 1a, 1b, 1c	AR
		Kabuki syndrome	AD
		Mosaic Turner syndrome	
		Other	
Transient		Infant of diabetic mother	
		Small for gestational age	
		Stress-induced	
		Maternal medication (e.g. ritodrine hydrochloride)	
		HNF4A	AD
		HNF1A	AD

AD, autosomal dominant; AR, autosomal recessive.

Genetic causes of persistent CHI

K_{ATP} channel CHI. The most commonly known genetic cause of persistent CHI is in activating mutations in the K_{ATP} channel genes, *KCNJ11* and *ABCC8*.[30–32] Although the overall mutation detection rate for persistent CHI is slightly more than 50%, when confined to diazoxide-unresponsive cases, mutations in the K_{ATP} channel genes could be identified in 87.6–91% of cases.[28,29]

The mode of inheritance of K_{ATP} channel CHI could be both autosomal dominant and recessive. In addition, a specific mode of paternally inherited monoallelic mutation leading to the focal form of CHI is known. In general, recessively inherited K_{ATP} channel CHI presents with a more severe phenotype that is unresponsive to diazoxide, often necessitating near-total pancreatectomy.[30,33] In contrast, dominantly inherited K_{ATP} channel CHI presents with a milder phenotype, is mostly responsive to diazoxide, and rarely requires pancreatectomy.[34–37] It is generally assumed that the dominantly inherited form is relatively rare compared with the recessive form, but this could be an underestimate because mild dominant CHI may go unrecognized clinically. Pathological features of recessive K_{ATP} channel CHI include the presence of enlarged islet cell nuclei throughout the pancreas.[3,38–42] Basically, all β cells in the pancreas are abnormal in both recessive and dominantly inherited forms (diffuse lesion).

Usher-CHI syndrome. Usher-CHI syndrome is a specific form of recessively inherited K_{ATP} channel CHI. The *USH1C* gene is located at chromosome 11p15.1, with close proximity to the K_{ATP} channel genes, and is responsible for Usher syndrome. Usher-CHI syndrome is caused by the homozygous deletion spanning the *USH1C* gene and the K_{ATP} channel genes and is characterized by CHI associated with hearing loss and retinal degeneration.[43,44]

Focal form of K_{ATP} channel CHI

In contrast to the recessive and dominant forms of K_{ATP} channel CHI, the focal form of CHI is distinct in that abnormal β cells are confined to a restricted area of the pancreas. This is of enormous clinical significance because if the focal lesion is identified and localized before surgery, the patient can be cured of hypoglycemia by partial pancreatectomy without postoperative complications (see the section on "Treatment strategies for CHI" below).

The focal form of CHI occurs in patients who have a paternally inherited monoallelic mutation in one of the K_{ATP} channel genes.[45,46] Adjacent to the K_{ATP} channel genes at chromosome 11p15.1, there is a cluster of imprinted genes, *H19, IGF2*, and *CDKN1C*, at 11p15.5. *H19* and *CDKN1C* are tumor suppressor genes expressed exclusively from the maternal allele, whereas *IGF2* is a growth factor gene expressed from the paternal allele. When segmental paternal uniparental disomy occurs as a somatic event during the development of the pancreas in a person with a paternally inherited K_{ATP} channel mutation, that particular cell loses the K_{ATP} channel activity. In addition, the cell loses the tumor suppressor activity of H19 and CDKN1C and receives a double dose of IGF2, leading to a growth advantage during embryogenesis that eventually results in the formation of a focal lesion of insulin-overproducing cells.[45,46] The focal lesions are usually up to 1 cm in size, although a giant focal lesion that covers almost the whole pancreas has been reported.[47] The boundaries of the focal lesion, however, are often not very clearly demarcated because of the presence of numerous "tentacles" extending from the main lesion. Unfortunately, unlike insulinomas, these lesions are usually not identifiable by conventional imaging modalities, such as computed tomography, magnetic resonance imaging, or angiography.

18F-fluoro-L-dihydroxyphenylalanine positron emission tomography

Together with the molecular diagnosis of a paternally inherited mutation, the development of an imaging modality, 18F-fluoro-L-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET), to localize the focal lesion has changed the management of patients with CHI.[48–53] 18F-DOPA is incorporated into the focal lesion by the action of DOPA decarboxylase, which is abundant in pancreatic β cells. Although an artifact in the head of the pancreas is often caused by the large size of the head and the excretion of 18F-DOPA in the common bile duct, 18F-DOPA PET has generally been reported to be very sensitive and could detect lesions as small as 5 mm.[48]

Other genetic causes of persistent CHI

Glutamate dehydrogenase. An activating mutation in the *GLUD1* gene that codes for glutamate dehydrogenase (GDH) causes a syndrome of CHI associated with hyperammonemia (HIHA syndrome).[54] GDH is an enzyme that catalyzes the conversion of glutamate to α-ketoglutarate and ammonia. Overproduction of α-ketoglutarate, a metabolic intermediate in the Krebs cycle, leads to an increased ATP/ADP ratio and to K_{ATP} channel-mediated oversecretion of insulin, while overproduction of ammonia leads to hyperammonemia. Because GDH receives a positive allosteric activation by leucine and ADP, the syndrome presents with classic leucine-sensitive hypoglycemia and responds well to diazoxide. Hyperammonemia is usually moderate (between 100 and 200 μg/dL) and is unresponsive to dietary protein restriction or other measures to decrease the production of ammonia in the intestines.

L-3-hydroxyacyl-coenzyme A dehydrogenase. The *HADH* gene codes for the enzyme L-3-hydroxyacyl-coenzyme A dehydrogenase (HADH), which was previously known as short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD). The mitochondrial enzyme catalyzes the penultimate step in the β-oxidation of fatty acids to its corresponding 3-ketoacyl CoA. Unlike other enzymes in the β-oxidation pathway, HADH is known to be abundant in pancreatic β cells and interacts directly with GDH to inhibit activity.[55] Therefore, recessively inherited biallelic-inactivating mutations in HADH lead to overactivity of GDH and hyperinsulinism.[55,56] Unlike HIHA syndrome, hyperammonemia is not a feature of HADH deficiency, probably because HADH is not abundant in other cell types that generate ammonia. HADH deficiency is the most common cause of

recessively inherited CHI and could increase urinary 3-hydroxyglutarate and plasma 3-hydroxybutyryl-carnitine levels. However, urinary organic acid analysis and serum carnitine profiles are often normal in these patients. Therefore, molecular analysis should be considered in patients who have diazoxide-responsive CHI and present with recessive inheritance.[57]

Glucokinase. The *GCK* gene codes for glucokinase, which phosphorylates glucose to form glucose-6-phosphate on entry into pancreatic β cells. Because glucokinase serves as a glucose sensor, an activating mutation in this gene causes overproduction of glucose-6-phosphate, which leads to activation of the glucose-induced insulin secretion pathway and oversecretion of insulin.[58–65] The clinical phenotype varies from mild, diazoxide-responsive cases to severe, medically unresponsive cases. Glucokinase could also be a cause of adult hyperinsulinism or postprandial hyperinsulinism.[61] Recently, a novel type of focal CHI presumably caused by a somatic mutation of glucokinase has been reported.[66]

Uncoupling protein 2. The *UCP2* gene codes for mitochondrial uncoupling protein 2 (UCP2), which is ubiquitously expressed in a variety of cell types, including pancreatic β cells, and leaks protons across the inner mitochondrial membrane, thereby uncoupling oxidative phosphorylation from ATP generation. A monoallelic inactivating mutation therefore leads to excess ATP generation and oversecretion of insulin.[67]

Monocarboxylate transporter 1. The *SLC16A1* gene codes for monocarboxylate transporter 1 (MCT1), which mediates the transport of lactate and pyruvate across cell membranes. In patients with exercise-induced hyperinsulinemic hypoglycemia, mutations in the promoter region of this gene have been identified.[68,69] These mutations have been shown to activate the promoter in pancreatic β cells, where MCT1 is normally underexpressed. This leads to the influx of lactate into β cells, when serum levels of lactate are elevated during exercise. Lactate and pyruvate are further metabolized to generate ATP, which leads to oversecretion of insulin through the glucose-induced insulin secretion pathway.

Treatment strategies for CHI

Table 3 shows the current treatment options for patients with CHI. In addition to nutritional support, including continuous intravenous glucose infusion, nasogastric feeding, or gastrostomy, the following medical and surgical treatments have been used.

Diazoxide

Diazoxide binds to the SUR1 subunit of the K_{ATP} channel and keeps the channel in an open state, thereby inhibiting glucose-induced insulin secretion. This medication has been used extensively in patients with CHI and is considered to be the first choice for treatment of all types of CHI.[70] It is effective for a variety of subtypes of CHI; however, unfortunately, it is usually ineffective for the most severe forms of neonatal-onset, K_{ATP} channel hyperinsulinism.[9,71] Except for water retention and hypertrichosis, diazoxide has relatively few adverse effects. However, it should be used in smaller infants with caution because water retention could lead to reopening of the ductus arteriosus or heart failure, especially when given without diuretics.[72]

Table 3 Current treatment modalities for congenital hyperinsulinism

Nutritional	Hypertonic intravenous glucose infusion
	Cornstarch, frequent feeding, nasogastric tube feeding, gastrostomy
Medications	Diazoxide
	5–20 mg/kg/day oral
	Nifedipine
	0.25–2.5 mg/kg/day oral
	Octreotide
	5–25 μg/kg/day subcutaneous
	Glucagon
	1–20 μg/kg/h subcutaneous, intravenous
Surgery	Pancreatectomy (partial, subtotal, near total)

Octreotide and other somatostatin analogues

Octreotide

Octreotide is a long-acting somatostatin analogue that binds to the somatostatin receptors SSTR2 and SSTR5 and inhibits secretion of a variety of hormones, including gastrin, cholecystokinin, glucagon, growth hormone, secretin, pancreatic polypeptide, thyroid-stimulating hormone, vasoactive intestinal peptide, and insulin. The use of octreotide for the treatment of patients with CHI was first reported nearly 20 years ago.[73,74] Octreotide has been widely used and is effective for the treatment of patients with diazoxide-unresponsive CHI at least to some extent, and often patients can discontinue intravenous administration of glucose. In addition to short-term use before pancreatectomy, long-term subcutaneous administration of octreotide often leads to spontaneous remission of K_{ATP} channel CHI without surgery.[75] Common adverse events include gastrointestinal disturbances, especially at the initiation of treatment, and a dilated gallbladder with or without gallstones, biliary sludge, or white stool. In addition, rare but more serious adverse events, such as necrotizing enterocolitis[76] and hepatitis,[77–79] have been reported. Despite its usefulness, the use of octreotide for the treatment of patients with CHI is not licensed in any country, including Japan. A government-funded clinical trial to prove the efficacy and safety of octreotide is currently underway in Japan (UMIN Clinical Trials Registry, UMIN000012620, SCORCH study).

Other somatostatin analogues

On the basis of the same treatment strategy, successful use of other somatostatin analogues for the treatment of patients with hyperinsulinemic hypoglycemia has been reported, including long-acting octreotide,[80] lanreotide,[81,82] and pasireotide.[83] These medications have the advantages of a longer duration of activity (long-acting analogues) or activities for a broader range of somatostatin receptors (pasireotide). However, because of limited experiences, their efficacy and adverse event profiles are not currently clear.

Glucagon

Glucagon is a 29-amino acid peptide that is produced by the α cells of the islets. It is one of the counterregulatory hormones and acts by stimulating glycogenolysis and gluconeogenesis from the liver. Although it can be administered by subcutaneous or intramuscular injection, continuous intravenous administration is the most frequent route for patients with CHI who do not respond to treatment with diazoxide or octreotide. Traditionally, the use of glucagon for CHI has been limited to preoperative short-term use because of frequent crystallization within the route of administration. Recently, however, successful long-term subcutaneous use has been reported.[84,85]

Pancreatectomy

Decades ago, before the identification of the focal form of CHI, subtotal or near-total pancreatectomy was the treatment of choice for medically unresponsive patients with CHI. The consequences were often unsatisfactory, with many patients experiencing residual hypoglycemia or frequent occurrence of postoperative insulin dependent diabetes mellitus.[9,10] Currently, however, when we identify a focal form of CHI preoperatively by 18F-DOPA PET scan, the patient can potentially be cured by partial pancreatectomy without developing postoperative diabetes. However, there are several difficulties with this approach. First, even if we could identify the localization of the lesion by PET scan, the lesion is not always visible or palpable. Intraoperative ultrasonography sometimes helps to identify the lesion,[86] but extensive intraoperative biopsies are usually needed to identify the lesion and determine the extent of pancreatectomy.[40] Second, the localization of the focal lesion often poses surgical problems. When the lesion is in the tail or body of the pancreas, the surgery is straightforward. The patient could be cured by either enucleation of the lesion or distal pancreatectomy without developing postoperative diabetes. However, if the lesion is in the head of the pancreas and close to other structures, such as the main pancreatic duct or the common bile duct, damage to those structures must be avoided. When the lesion cannot be safely enucleated, pancreatic head resection and Roux-en-Y pancreaticojejunostomy is the proposed procedure of choice[87,88] but is a major operation and not without postoperative complications.[89] When the patient's condition could be maintained without intravenous administration of glucose, long-term medical treatment with octreotide or glucagon appears to be an alternative approach worth considering.[75,84]

Global and Japanese perspectives on CHI

Global trends in the management of CHI

Focal CHI

Identification and localization of focal CHI using 18F-DOPA PET and subsequent partial pancreatectomy appear to be the global standard, but this multidisciplinary approach is possible only where the medical resources are available.[90]

Diffuse CHI

Even today, the management of diazoxide-unresponsive diffuse CHI is not straightforward. The global trend is to avoid near-total pancreatectomy as much as possible because the incidence of postsurgical diabetes is high[9,10] and the outcome is unpredictable.[89,91] Fewer patients are undergoing near-total pancreatectomy than before,[9] and even when pancreatectomy is necessary, often the goal is to make medical treatment easier by reducing the mass of abnormal β cells.

Japanese perspectives

Although the established global standard for the management of CHI basically holds true for Japanese patients, there are several important disparities from both medical and social standpoints.

Different molecular background of CHI

Previous reports from Israel and France showed that approximately 40% of patients with surgically treated CHI had focal lesions.[92,93] However, according to recent molecular analyses of patients with K_{ATP} channel CHI, there appears to be racial disparity in the molecular background. For example, reports from a German registry showed that 38% of patients with K_{ATP} channel CHI had paternally inherited monoallelic mutations, thus suggesting the presence of a focal lesion.[94] Similar studies from other countries have reported different figures; in the UK,[29] Italy,[95] and China,[96] paternal monoallelic mutations were found in 25%, 54%, and 58% of patients with K_{ATP} channel CHI, respectively. We previously reported that 84.2% of Japanese patients with K_{ATP} channel CHI had paternal monoallelic mutations;[97] at the time of this writing, we have completed molecular analyses on 130 Japanese patients with CHI and found that 80.4% of patients with K_{ATP} channel CHI had paternal mutations. It is known that not all patients with a paternal mutation have a focal lesion,[98,99] but it appears that identification of focal CHI is even more important for Japanese patients.

Different accuracy of 18F-DOPA PET

Previous reports have repeatedly shown the efficacy of 18F-DOPA PET in localizing focal CHI.[48–53] Our experiences in Japan have demonstrated that the procedure is also useful for localization of the lesions. However, in Japanese patients, the interpretation of the results is often difficult because a focal lesion may resemble a diffuse lesion or a multifocal lesion.[100] The reason for this discrepancy is not known currently. Our impression is that the symptoms of patients with focal lesions often appear to be milder compared with previously reported clinical scenarios in Caucasian patients, which might be reflected by the lower uptake of 18F-DOPA in Japanese patients. In fact, in our experiences with 18F-DOPA PET imaging in Caucasian patients, most of these patients had greater uptake in terms of standardized uptake value compared with Japanese patients.

Different management strategy for focal CHI in the head of the pancreas

As described previously, focal lesions in the head of the pancreas are not easy to enucleate. The proposed treatment strategy for those lesions is pancreatic head resection and Roux-en-Y pancreaticojejunostomy.[87,88] Because this is major surgery with possible postoperative complications, pediatric surgeons and

caregivers are not always enthusiastic about performing this procedure. Combined with the fact that focal lesions in Japanese patients appear to be less aggressive and could be relatively easily controlled by continuous subcutaneous infusion of octreotide, when we cannot safely enucleate the lesions in the head of the pancreas, we often choose to continue medical treatment without pursuing the instant cure of the disease.[75] Many of these patients could later be weaned off treatment with spontaneous remission of the disease.

Resources to achieve optimal multidisciplinary treatment

For state-of-the-art treatment of CHI, a team consisting of experienced pediatric endocrinologists, radiologists, pathologists, and surgeons is necessary. In addition, 18F-DOPA PET and a molecular diagnostic laboratory must be available. It is not easy to fulfill these requirements, especially in developing countries. In Japan, the authors' facilities are virtually the only ones to currently offer molecular diagnostic services and 18F-DOPA PET scans. Surgical and medical treatment is often performed at regional centers with advice from the staff at our facilities. As a result, the surgeons and pathologists at the regional centers do not have sufficient experience in the treatment of this disorder.

Because only 10–20 cases of diazoxide-unresponsive severe CHI are expected to arise in Japan each year,[20] one or two facilities dedicated to CHI would be sufficient to care for all patients with CHI in Japan and possibly in the entire region of East Asia. Domestic and international collaboration is necessary for better outcomes of patients with this disorder.

Future perspectives

There are several unanswered questions and unmet needs in regards to CHI that should be addressed in the near future. Some of the answers to these questions are on the horizon but are incomplete. Finding the answers to these questions is the responsibility of the current and future investigators in this field.

Questions

1 What are the genetic causes of the remaining 50% of cases of persistent CHI?
2 What are the causes of transient CHI?
3 What are the causes of so-called "adult nesidioblastosis"?
4 What would be the safe threshold of blood glucose to avoid neurological sequelae?
5 What is the mechanism of spontaneous remission of CHI?
6 How can we explain the dominance of paternal mutation in patients with diffuse CHI on 18F-DOPA PET?
7 Which type of CHI evolves into diabetes later in life?
8 Which novel diagnostic imaging modality is superior to 18F-DOPA PET?
9 How can we surgically manage diffuse, diazoxide-unresponsive CHI?
10 What novel medications could be used for diazoxide-unresponsive CHI?
11 How we can establish international collaborations so that all infants born with CHI will equally benefit from the current standard of care?

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原　著

先天性高インスリン血症の18F-DOPA PETによる局在診断と治療予後

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要　旨

先天性高インスリン血症の膵臓病変局在診断に18F-fluoro-L-DOPA positron emission tomography（18F-DOPA PET）検査は最も簡便で有用と考えられている．今回我々はK_{ATP}チャネル遺伝子異常のある先天性高インスリン血症の31症例に18F-DOPA PET検査を実施した．遺伝子局在型のPET検査で局在型は61%，局在型の71%は頭部型であった．遺伝子診断は局在部位の同定はできないが，局在型かびまん型かの型判定に誤りはなく，PET検査の適応のスクリーニングとして有用であった．PET検査で同定された局在は病変とすべて一致した．しかし，病変の広がりまでは反映しない場合があった．選択的膵流入動脈カルシウム注入法はPET結果が遺伝子診断と一致しない場合やPETで病変が検出不能の場合に有用だが，侵襲的検査のため相補的に用いるのが良いと考えられた．日本人の先天性高インスリン血症は比較的軽症型が多く遺伝子局在型では2～6歳頃に自然治癒する傾向にあり神経学的後遺症も両側後頭葉白質萎縮とてんかんの2例のみであった．内科的治療による合併症・後遺症も少ないため，PETびまん型や手術の難しいPET頭部型は内科的治療を継続して自然治癒を待つのがよい選択であると考えられた．

キーワード：先天性高インスリン血症，K_{ATP}チャネル遺伝子異常，
18F-fluoro-L-DOPA positron emission tomography（18F-DOPA PET），
選択的膵流入動脈カルシウム注入法（arterial stimulation and venous sampling），
オクトレオチド

はじめに

先天性高インスリン血症は新生児・乳児期の持続性低血糖症の最も多い原因で，迅速・適切な治療をしないと，重篤な神経学的後遺症をきたす可能性がある．わが国における発症頻度は，出生3.5万人に1人であるとされている[1]．内科的治療に抵抗性のある先天性高インスリン血症は神経学的後遺症を回避するために外科的治療の適応となる．本症の膵臓病変はインスリノーマと異なり，CT・MRI・血管造影など一般の画像診断で病変の局在を同定することが困難であり，従来は盲目的に膵亜全摘が行われてきた．しかしながら，その結果は必ずしも満足できるものではなく，多くの症例で術後も低血糖が残存する一方，低血糖がコントロールされた症例の多くに術後糖尿病が発症した．18F-fluoro-L-DOPA（18F-DOPA）は膵β細胞に豊富に存在するDOPAデカルボキシラーゼによりβ細胞内に取り込まれるので，膵病変の局在は18F-DOPAを用いたpositron emission tomography（PET）検査により同定することが可能であると考えられている[2][3]．欧米では18F-DOPA PET検査により膵病変の局在を同定し，局所切除で後遺症なく治癒したとの報告が多くなされている[3]～[5]．国内では木沢記念病院が唯一の18F-DOPA PET検査施設であるため，全国の症例を検査解析してきた[6][7]．18F-DOPA PET検査は有用な検査であるが，感度や特異度において限界があるといわれている[4][5]．そこで今回我々は，木沢記念病院で18F-DOPA PET検査を実施した31症例を解析し，局在型診断のための他の検査との比較，内科的・外科的治療予後，合併症，神経学的後遺症を検討した．

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対象と方法

K_{ATP}チャネル遺伝子異常のある先天性高インスリン血症の31症例（両親由来遺伝子異常3例，父親由来遺伝子異常28例；男児18例，女児13例；PET検査時年齢1か月～19歳）を対象として，2005年7月より2013年3月までに木沢記念病院で18F-DOPA PET検査を実施した．18F-DOPA PET検査の依頼元・症例治療中の施設一覧を表1に示す．

我々が，過去に報告したように[6]～[8]，局在型の診断方法には，1）遺伝子診断でK_{ATP}チャネル遺伝子異常が父由来の変異のヘテロ接合体である，2）画像診断として