楠田　聡（東京女子医科大学母子総合医療センター　所長・教授）

第1回班会議　議事録

日時：2013年1月18日　17時～19時

場所：TKP大宮ビジネスセンターミーティングルーム2

出席者：依藤亨（大阪市立総合医療センター）、横谷進（成育医療センター）、有阪治（獨協医科大学）、西堀弘記（木沢記念病院）、細川悠紀（大阪市立総合医療センター）

議題

１．研究課題について

２．進捗状況について

研究計画の進捗状況を説明（依藤）

科研費承認後、成育医療研究センター中村秀文、佐古まゆみ先生、国立循環器病研究センター山本晴子先生、PMDA、厚労省審査管理課と計画を相談し、GCP治験は極めて困難とそれぞれからアドバイスをうけた。最終的に5例程度の先進医療としての前向き研究と、レジストリ研究としての15例程度の観察研究を同時進行して公知申請の形で承認を目指すこととなりそうである。先進医療で、極力精密な臨床試験を行い、観察研究（レジストリ）を並行して行うことで、介入研究では確認が不十分となる安全性と長期予後の調査を行う予定である。CROとしてファイブリングス社と交渉中である。

臨床試験としては、当初、患者発生後にその施設を参加施設として登録しエントリーする形式を考えていたが、治療開始まで1-2カ月単位でかかるため、患者が不利益をこうむることが予想されるため、あらかじめ数施設で倫理委員会の承認を得ておき、患者発生時にすぐエントリーできるように計画書を変更した。そのため目標症例数を20例から5例に変更した。

３．レジストリ研究（案）について（依藤）

電子的臨床データ収集にすると症例数の割に費用がかかりすぎるので、紙ベースにする予定。疾患HPからリンクするかたちでレジストリHPを考えている。

→患者家族からの直接の相談がくるのでは？（横谷）

４．諸費用について

介入研究の開始が、先進医療の審査期間を考えると平成25年7月以降になるため、今年度の予算が当初想定していたより余る可能性がある。ポンプの発売時期など現時点で不明の点もあり、もう少したたないとはっきりしないが、4月から必要になるのはレジストリ関連費用で、先進医療については遅れる見込みである。

試験薬（オクトレオチド）を一括して事務局（OCGH）で購入する場合、保管する冷蔵庫や保管システムなども準備が必要となるため、そのための費用も予算に組み込む必要がある。（横谷、有阪）

→メーカーの協力が得られるならメーカーから納品してもらうほうがよい。（横谷）
介入試験が終了した時点で治療中の患者（最大5名）の期間以降の薬の供給は？
→メーカーから提供してもらえないか打診してみる（有阪、横谷）
科研費期間終了後にほかのファンドをあたっていく必要がある。（依藤）

５．各施設の倫理委員会の状況確認
→申請から審査に通るまでに各施設とも大体2ヶ月はかかる（横谷、有阪）

現在の計画書がPMDAの対面助言で審査を受けるのが3月25日であり、その計画書が各施設倫理委員会の承認を受けるのは早くて5月以降となるので、先進医療の実施施設は計画書提出時点では大阪市立総合医療センターのみになる。その後小児内分泌学会HPや個人的なつても使用して極力参加施設数を増加する必要がある。評議員を中心に呼びかけては（横谷）。

７．その他協議事項
介入試験の期間について
エントリー期間は先進医療承認後～平成27年2月
研究としての治療期間は1年間。治療期間終了後は継続試験として取り扱う。
（研究期間としては平成28年2月28日or平成28年3月31日）

第2回班会議　議事録

日時：2014年1月24日　17時30分～19時

場所：名古屋国際会議場　2号館(225室)

出席者：緒方勤（浜松医科大学小児科）、西堀弘記（木沢記念病院）、長谷川行洋（都立小児総合医療センター）、細川悠紀（大阪市立総合医療センター）、増江道哉（木沢記念病院、、依藤亨（大阪市立総合医療センター）横谷進（国立成育研究医療センター）

（五十音順、敬称略）

議題

1．研究の概要と進捗状況（依藤）

- CHIに対するオクトレオチド皮下注療法、薬事申請に向けたロードマップについて説明。
- 進捗状況：

  2013年8月5日レジストリ研究開始、現在登録3例、問い合わせ（倫理委員会承認待ち　6例）重篤な有害事象なし。

  2014年1月1日スタディ開始、現在施設登録予定が54施設（大阪市立総合医療センター除く）症例発生0例
- 研究費の報告
- 2014年1月6日に行われた厚生労働省のサイトビジットでの指摘事項
  - ・研究期間延長時の計画変更の必要性
  - ・期間延長時の原資をどうするか（薬剤、消耗品、保険）
  - ・統計解析は必要
  - ・サイトモニタリングを行わないとデータの信頼性が保証できない
  - ・レジストリが容易なので、そちらに症例流れるのではないか
  - ・薬事申請と期間延長時の薬剤提供についてノバルティスと契約を交わしておく必要はないか

レジストリ研究を過去例で募ると「効果のあった症例」のみ登録してしまう選択バイアスがかかる可能性がある。少なくともスタディに参加する施設で規定年数以内に経験した過去例はレジストリに登録してもらうように促す（横谷）

→レジストリとスタディが混乱してしまうのでは？

→全体の枠組み（ロードマップ）を示したうえで、レジストリ、スタディ両方を倫理委員会に提出していただくようにした方が、施設によっては受け入れが良い場合もある。

→スタディ参加を表明している施設に対し、レジストリ対象症例がないか調査する必要がある（緒方）

新生児施設で発症した症例の取り込みをどうするか？
→大きな新生児施設でも内分泌医が全くいないところでこの研究の意義を理解してもらって研究参加してもらうのは容易ではない。
→本症が発症した際に近隣のスタディ参加施設に搬送してもらうストリームを作る。
そのために、現在どの施設が倫理委員会を通っているか、などの進捗がホームページなどで公開するほうがよい。
→疾患 HP の活用を考える（依藤）
→新生児学会への働きかけを考える

２．浜松医大　緒方先生より浜松医大における 18F-DOPA　PET 検査準備状況について
浜松ホトニクスと提携し、現在準備中。倫理審査委員会提出予定。

３．木沢記念病院　増江先生より 18FDOPA PET の現在までの 31 症例の検討
各症例の遺伝子検査、ASVS、手術所見との整合性の報告。

第3回班会議　議事録

日時：2014年11月28日　12時20分～13時30分

場所：大宮ソニックシティ7階 707号室

出席者：長谷川行洋（都立小児総合医療センター）、細川悠紀（大阪市立総合医療センター）、依藤亨（大阪市立総合医療センター）横谷進（国立成育研究医療センター）

（五十音順、敬称略）

1．F-DOPA PETのまとめ…依藤先生より（木沢記念病院　増江先生の文献、スライド）

- CHI31例のPETの結果を日児誌にまとめた概要を説明。

2．研究の進捗状況

- 2013年8月レジストリ開始後、登録施設12施設、登録症例14例となっている。
  有害事象延べ21件で嘔吐、白色便、高血糖など予想されたもので、重篤な有害事象なし。
- 2014年1月スタディ開始、先進医療承認に時間を要し、現時点で協力医療機関としての登録数は18施設、承認予定が2施設。
  症例は6月に1例目登録後、現在4例が登録されている。

3．スタディの登録症例について

S-01, S-02は大阪市立総合医療センターで実施。初期治療に反応せず無効例として中止。
S-03,S-04は現在初期治療中で効果は現時点では未報告である。
無効例の問題点としては先行研究で最も多かった父由来片アリル変異の局所型でなかったことが上げられる。（S-01は変異なし、S-02は母由来dominant type）
先行研究とこれらの2例の差を考えると、症例数を増やして検討する必要があるかもしれない。（但し症例数を増やすためには試験期間の延長と研究資金が必要）

4．協議事項

- レジストリについて
  症例数は14/15例で不十分であり、継続が必要。
  レジストリの延長はPMDAへの連絡とUMINの登録変更をする必要がある。
  ＞保険承認の目的のほかにも学術的な意味で本疾患の長期予後を調査する必要があり、その体制を学会主導でサポートしてはどうか。（長谷川）

- スタディについて
  症例数4/5例と不十分である上に、最後の症例が入って最低1年のフォローが必要なので、試験期間延長は必須。

近々先進医療延長届を行うが、費用面の記載は厚労科研費を申請予定と書くことになる。（科研費の結果がわかるのは3月頃）
プロトコル変更は行わず、期間の延長のみ行う予定。（最低1年延長）
費用の面のめどが立つようであれば、症例数も増やす。

- 2014年1月のサイトビジットでの指摘事項
  - ノバルティスに承認申請の確約を取る＞社会的な問題から現在ノバルティスとの接触は避けた方がいいと多方面からアドバイスされているため、この件は保留。
  - 生物統計家をいれる＞成育医療研究センターに採用予定の統計家に依頼する。
  - SDVが必要ではないか？＞費用面の問題があり、厚労科研など延長試験の原資が決まった時点で検討する。

[V] 研究成果の刊行に関する一覧表

学 会 等 発 表 実 績

委託業務題目「先天性高インスリン血症に対するオクトレオチド持続皮下注療法の有効性・安全性に関す

機関名 大阪市立総合医療センターほか

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
先天性高インスリン血症の遺伝子診断：アップデート（口頭）	依藤 亨 川北 理恵 細川 悠紀 玉川 信吉 藤丸 季可	第58回日本人類遺伝学会（仙台）	2013年11月	国内
先天性高インスリン血症に対するオクトレオチド皮下注射療法臨床試験（口頭）	依藤 亨 細川悠紀 川北理恵 増江道哉 西堀弘記 長谷川行洋 有阪 治 緒方 勤 横谷 進	第47回日本小児内分泌学会（東京）	2013年10月	国内
先天性高インスリン血症Update（口頭）	依藤 亨	第23回臨床内分泌代謝アップデート（名古屋	2013年11月	国内
わが国の先天性高インスリン血症の臨床的・分子遺伝学的解析	依藤 亨 細川悠紀 川北理恵 藤丸季可 玉川信吉 中村哲郎	第27回近畿小児科学会（奈良）	2014年2月	国内
小児の低血糖症：update	依藤 亨	第24回臨床内分泌代謝Update（大宮）	2014年11月	国内
小児低血糖の診かた	依藤 亨	第28回近畿小児科学会（大阪）	2015年2月	国内

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Efficacy and safety of long-term continuous subcutaneous octreotide infusion for patients with different subtypes of K(ATP) -channel hyperinsulinism.	Yorifuji T Kawakita R Hosokawa Y Fujimaru R Matsubara K Aizu K Suzuki S Nagasaka H Nishibori H Masue M.	Clin Endocrinol (Oxf). 2013;78:891-7.	2013年6月	国外

Congenital hyperinsulinism: current status and future perspectives.	Yorifuji T.	Annals Pediatr Endocrinol Metab 2014, 19; 57-68.	2014年6月	国外
Congenital hyperinsulinism: Global and Japanese perspectives.	Yorifuji T Masue M Nishibori H.	Pediatr Int. 2014; 56(4):467-76.	2014年8月	国内・国外
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	増江道哉 西堀弘記 高田勲矢 依藤亨	日本小児科学会雑誌 2014, 118; 1342-1349.	2014年9月	国内

[VI] 班員名簿

研究代表者	依藤　亨	大阪市立総合医療センター小児代謝・内分泌内科　部長
研究分担者	横谷　進	国立成育医療研究センター　副院長
	緒方　勤	浜松医科大学小児科　教授
	有阪　治	獨協医科大学小児科　教授
	長谷川行洋	東京都立小児総合医療センター内分泌科　部長
	増江道哉	木沢記念病院小児科　部長
	西堀弘記	木沢記念病院放射線科　部長

[VII] 主要原著論文別冊

Clinical Endocrinology (2013) doi: 10.1111/cen.12075

ORIGINAL ARTICLE

Efficacy and safety of long-term, continuous subcutaneous octreotide infusion for patients with different subtypes of K_{ATP}-channel hyperinsulinism

Tohru Yorifuji*, Rie Kawakita*, Yuki Hosokawa*, Rika Fujimaru*, Kousaku Matsubara†, Katsuya Aizu‡, Shigeru Suzuki§, Hironori Nagasaka¶, Hironori Nishibori** and Michiya Masue††

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Summary

Objective To evaluate the efficacy of long-term, continuous, subcutaneous octreotide infusion for congenital hyperinsulinism caused by mutations in the K_{ATP}-channel genes, *KCNJ11* and *ABCC8*.

Patients Fifteen Japanese patients with diazoxide-unresponsive, K_{ATP}-channel hyperinsulinism.

Methods Molecular diagnoses were made by sequencing and multiple ligation-dependent probe amplification analysis. In patients with paternally inherited, monoallelic mutations, 18F-DOPA PET scans were performed to determine the location of the lesion. The patients were treated with continuous, subcutaneous octreotide infusion at a dosage of up to 25 μg/kg/day, using an insulin pump to maintain blood glucose levels higher than 3·33 mmol/l. Additional treatments (IV glucose, glucagon or enteral feeding) were administered as needed. The efficacy of the treatment was assessed in patients who received octreotide for 4 months to 5·9 years.

Results Three patients had biallelic mutations, and 12 had monoallelic, paternally inherited mutations. Four patients with monoallelic mutations showed diffuse 18F-DOPA uptake, whereas seven patients showed focal uptake. Octreotide was effective in all the patients. The patients with biallelic mutations required a higher dosage (17–25 μg/kg/day), and two patients required additional treatments. By contrast, the patients with monoallelic mutations required a lower dosage (0·5–21 μg/kg/day) irrespective of the PET results and mostly without additional treatments. Treatment was discontinued in three patients at 2·5, 3·3 and 5·9 years of age, without psychomotor delay. Except for growth deceleration at a higher dosage, no significant adverse effects were noted.

Conclusions Long-term, continuous, subcutaneous octreotide infusion is a feasible alternative to surgery especially for patients with monoallelic K_{ATP}-channel mutations.

(Received 10 July 2012; returned for revision 31 July 2101; finally revised 10 October 2012; accepted 10 October 2012)

Introduction

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycaemia in the neonatal and infantile periods with an incidence of approximately 1 in 40 000 births in Japan.

Although a variety of causative genes have been identified for this disorder,[1] when restricted to diazoxide-unresponsive cases, defects in the ATP-sensitive potassium channel (K_{ATP}-channel) are by far the most commonly associated alterations, accounting for 92% in our series of 48 Japanese cases of diazoxide-unresponsive persistent CHI (our unpublished results).

K_{ATP} CHI is caused by loss-of-function mutations in 1 of 2 genes, *ABCC8* or *KCNJ11*, encoding the two subunits of the pancreatic K_{ATP}-channel, SUR1 and Kir6·2, respectively. Two major histological forms of K_{ATP} CHI are known: the diffuse and focal forms. In the diffuse form, insulin-oversecreting abnormal β cells are distributed throughout the pancreas, whereas in the focal form, abnormal β cells occupy a restricted area in the pancreas. The diffuse forms are caused either by biallelic, recessively inherited K_{ATP}-channel mutations, or by monoallelic, dominantly inherited mutations.[2] On the contrary, the focal forms are found in individuals with a paternally inherited, monoallelic K_{ATP}-channel mutation.[1,3–5] Subsequent somatic loss of the maternal allele caused by paternal isodisomy leads to a loss of the activities of the K_{ATP}-channel and the

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adjacent tumour suppressors (*H19* and *CDKN1C*) normally expressed by the maternal allele. These cells gain a growth advantage, eventually forming a focal lesion of insulin-overproducing β cells.[1,3–5]

Traditionally, patients with CHI showing a poor response to medical treatment have been treated by subtotal pancreatectomy, removing > 95% of the pancreas to prevent serious neurological sequelae of hypoglycaemia.[6] The results of the procedure, however, were rarely satisfactory. Some were left with residual hypoglycaemia, and even when hypoglycaemia was controlled, most of the patients developed diabetes mellitus postoperatively.[7]

This situation has changed recently. When a focal lesion is identified preoperatively, the patient can be cured by partial resection of the pancreas, without postoperative complications.[1,8] With the recent development of diagnostic modalities for the identification and localisation of focal lesions, surgical treatment by a multidisciplinary approach has become the mainstay of treatment for focal diazoxide-unresponsive CHI.[1]

Even today, however, patients with the diffuse form of K_{ATP} CHI often require subtotal pancreatectomy with frequent postoperative complications.[9] In addition, when a focal lesion is identified, surgical resection is not always easy if the lesion is in the head of the pancreas and potentially adjacent to the main pancreatic duct or the common bile duct.[10] Total removal of the head of the pancreas and drainage of the distal pancreas into the Roux-en-Y jejunal loop has been advocated for such cases.[10,11] The procedure, however, can be difficult for paediatric surgeons who do not routinely perform surgery for the correction of this rare disorder, and the frequency of long-term postoperative complication is not known. Because approximately two-thirds of the focal lesions arise in the head or the uncus of the pancreas (our unpublished results in Japan), this problem occurs frequently.

Octreotide, a synthetic somatostatin analogue, is currently used for treatment of CHI.[12–14] Although long-term treatment with octreotide has been reported,[15–18] the treatment regimen differs from centre to centre, and few reports have correlated its efficacy and safety with subtypes of hyperinsulinism. In this study, we evaluated the efficacy and safety of long-term octreotide treatment in Japanese patients with genetically proven K_{ATP} CHI. The amount of octreotide to control hypoglycaemia was then correlated with the genotype and 18F-DOPA PET findings.

Subjects and methods

Subjects

Fifteen Japanese patients with diazoxide-unresponsive K_{ATP} CHI who were treated with continuous subcutaneous octreotide infusion for 4 months to 5·9 years were included in the study. At presentation, all patients showed blood glucose below 2·5 mmol/l (45·05 mg/dl) and insulin level greater than 25 pmol/l (3·6 μU/ml). The patients first underwent molecular diagnosis at Osaka City General Hospital while blood glucose levels were maintained by continuous glucose infusion. Then, the patients who were suspected with a possible focal K_{ATP} CHI, because a paternally inherited monoallelic mutation was found in either *ABCC8* or *KCNJ11*, were further assessed by 18F-DOPA PET scan at Kizawa Memorial Hospital. The patients showing diffuse uptake or focal uptake in the head of the pancreas, which could be difficult to enucleate, were preferentially enrolled into the long-term octreotide treatment.

Methods

Mutational analysis. Mutational analysis of the K_{ATP}-channel genes, *KCNJ11* and *ABCC8*, was performed as described previously.[19] All exons and exon–intron boundaries were amplified from genomic DNA and directly sequenced. Deletion mutations that might not have been detected by the PCR-sequencing strategy were analysed by multiple ligation-dependent probe amplification (MLPA) of all 39 exons of the *ABCC8* gene. The analyses were performed using SALSA MLPA kit P117 (MRC Holland, Amsterdam) as recommended by the manufacturer.

18F-DOPA PET. 18F-DOPA PET studies were performed at the PET facility of Kizawa Memorial Hospital, as described previously.[20] The scan results were fused with those of a CT scan performed at the same time to localise the focal lesion more accurately.

Octreotide treatment. The patients were treated with continuous, subcutaneous octreotide infusion using an insulin pump to maintain blood glucose levels higher than 3·33 mmol/l (60 mg/dl).[21] Starting at a lower dose, the amount of octreotide was titrated up to 25 μg/kg/day to minimize the amount of IV glucose. Blood glucose was measured at least eight times a day at the initiation of the treatment by using a portable glucometer, and 1–4 times a day at home after the patient was discharged. The age of the patients at the initiation of octreotide was 11 day to 12 month. In four patients (patients 4, 11, 13, 14), octreotide was first initiated by multiple daily injections to confirm its effectiveness and then switched to continuous infusion within 4 weeks. Other treatments immediately before and after the initiation of octreotide are shown in Table 1. After the initial stabilization of blood glucose and after the age of 4 months, most infants who did not undergo pancreatectomy were fed cornstarch up to 2 g/kg at bedtime to help reduce the required dosage of octreotide. Additional treatments (IV glucose, glucagon or enteral feeding) were administered as needed to maintain normoglycaemia. The study was conducted in accordance with the Declaration of Helsinki (British Medical Journal, 1964, ii, 177) after obtaining informed consent from the guardians, and the protocols for molecular diagnosis, 18F-DOPA PET and octreotide treatment were approved by the institutional review boards of each participating hospital.

Clinical and laboratory data collection. Clinical and laboratory data, which were collected from the medical record of each patient, included gestational age; birth weight; blood glucose and insulin at diagnosis; details of octreotide treatment and any

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Table 1. Characteristics of the patients enrolled in the study

No	Gene	Mutation (amino acid change)	Localisation by 18F-DOPA PET	Gender	Age at onset	Octreotide			Changes in clinical status before and after octreotide infusion		Current clinical status
						Initial dose (μg/kg/day)	Age at start	Duration of octreotide	Before	After	
1	ABCC8	c.1773delC (p.F591Ffs*14) c.2992C>T (p.R998*)	ND	M	0 day	25	11 day	2·2 years	IVG (4), GCG,	IVG (1·1), GCG	90% pancreatectomy followed by octreotide
2	ABCC8	c.2506C>T (p.R836*) c.4575_4587del13 (p.T1525Tfs*15)	ND	M	2 days	17	27 days	2·7 years	IVG (8·3)	EF	Continued on octreotide
3	ABCC8	c.2506C>T (p.R836*) c.4412-13G>A (p.?)	ND	F	0 day	17	5 months	5·9 years	IVG (16)	None	Continued on octreotide
4	ABCC8	c.2992C>T (p.R998*)	body	M	0 days	4	28 days	4 months	IVG (15), DZX	None	Cured by partial resection (0 years 4 months)
5	ABCC8	c.2992C>T (p.R998*)	body	M	5 months	0·5	12 months	1·5 years	IVG (3)	None	Spontaneous remission (2 years 6 months)
6	ABCC8	c.2506C>T (p.R836*)	uncus	F	1 months	10·95	10 months	1·5 years	IVG (6·86)	None	Cured by partial resection (1 years 6 months)
7	ABCC8	c.2506C>T (p.R836*)	diffuse	M	0 days	12·5	17 days	3·3 years	IVG (8), GCG	None	Spontaneous remission (3 years 3 months)
8	ABCC8	c.62 insG (p.V21Gfs*67)	diffuse	F	2 months	3·2	4 months	5·6 years	IVG (9·6)	None	Spontaneous remission (5 years 11 months)
9	ABCC8	c.2506C>T (p.R836*)	diffuse	F	7 months	2·3	8 months	4·6 years	IVG (5·95)	None	Continued on octreotide
10	ABCC8	c.4307G>A (p.R1436Q)	diffuse	M	7 months	5	7 months	5 months	IVG (3·1)	None	Continued on octreotide
11	ABCC8	c.4608 + 1G>C (p.?)	head	F	1 days	12	21 days	7 months	IVG (13)	None	Partial resection followed by octreotide
12	KCNJ11	c.350_352del TCT (p.F117_S118delinsS)	head	F	6 months	3	8 months	1·8 years	IVG (2·4)	None	Continued on octreotide
13	ABCC8	c.68delA (p.N23Tfs*55)	head	M	6 months	9	7 months	4 months	IVG (5)	None	Continued on octreotide
14	ABCC8	c.62T>A (p.V21D)	head	M	1 days	6·4	2 months	5 months	IVG (4)	None	Continued on octreotide
15	KCNJ11	c.405_406insG (p.L136Afs*136)	ND	F	5 m	21	8 months	1·6 years	IVG (6·5)	None	Continued on octreotide

*GCG, glucagon; IVG, intravenous glucose (glucose infusion rate, mg/kg/min); EF, enteral feeding, DZX, diazoxide.
The demographic features of each patient are summarised together with the results of the molecular analyses, 18F-DOPA PET and other parameters related to the octreotide treatment. ND, not done.

additional treatment required to achieve euglycaemia; laboratory results including complete blood counts, blood chemicals (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, total protein, albumin, urea nitrogen, creatinine, total cholesterol, triglyceride), electrolytes, thyroid function tests and abdominal ultrasound; reports of short-term adverse effects such as abdominal symptoms; and long-term neurological and growth outcomes when applicable.

Results

Table 1 provides a summary of the demographic features of the patients, as well as the genotype, 18F-DOPA PET findings, details of the octreotide treatment and clinical outcomes. All identified mutations were point mutations, and no exonic deletions were found by MLPA. As reported previously,[19] monoallelic paternal K_{ATP}-channel mutations are predominant in Japan and the molecular breakdown also reflected this trend. Three patients had biallelic mutations of the K_{ATP}-channel genes, and the remaining 12 had monoallelic paternal mutations suggestive of the possible focal form. 18F-DOPA PET scans were performed in 11 of the patients with monoallelic mutations. Four of them showed apparently diffuse uptake, and the remaining seven showed focal uptake: five in the head or the uncus and two in the body of the pancreas.

The octreotide treatment was effective, at least partially, in all the patients (Table 1). For the patients with biallelic mutations (patients 1–3), octreotide was less effective requiring a higher dosage than for the patients with monoallelic mutations (17–25 μg/kg/day); mean, 19·7 μg/kg/day; $P = 0{\cdot}02$ by the Welch *t*-test), and two of them required additional treatment with hypertonic intravenous glucose infusion (patient 1) or enteral feeding (patient 2) to maintain normoglycaemia. As IV glucose could not be completely stopped, patient 1 underwent 90% pancreatectomy at the age of 4 months. After surgery, the patient continued to experience hypoglycaemia, which could be controlled with a lower octreotide dosage (12 μg/kg/day) without additional IV glucose. These patients with biallelic mutations were still being treated with octreotide at the time of the study at 2, 2 and 6 years of age, respectively. However, the required octreotide dosage was decreased to 6·5, 15 and 7·6 μg/kg/day, respectively.

By contrast, the patients with monoallelic mutations required a lower dosage (0·5–21 μg/kg/day; mean, 6·25 μg/kg/day), mostly without additional treatments. There were no significant differences in dosage requirements between the different PET signal patterns, with a dosage of 2·3–12·5 μg/kg/day (mean, 5·8 μg/kg/day) administered to the patients with diffuse uptake and paternal monoallelic mutations as compared with the 0·5–21 μg/kg/day (mean, 6·5 μg/kg/day) administered to the patients with focal uptake ($P = 0{\cdot}78$ by the Welch *t*-test).

Three patients with a focal 18F-DOPA uptake (patients 4, 6, 11) underwent partial pancreatectomy. Two of them (patient 4, 6) were cured, and octreotide treatment was discontinued at the time of the surgery. One (patient 11) remained hypoglycaemic after surgery due to incomplete resection of the focal lesion, and octreotide treatment was therefore continued at the same dosage.

Nine other patients with monoallelic mutations (four diffuse, four focal and one unknown uptake of 18F-DOPA) chose to continue the octreotide treatment without surgery. Three of them (patients 5, 7, 8) actually achieved remission at the age of 2·5, 3·3 and 5·9 years, respectively, requiring no additional treatment. These patients were subjected to continuous glucose monitoring for 3 days without any treatment, and no episodes of hypoglycaemia were reported. The remaining six patients with monoallelic mutations were still receiving octreotide. The dosage of octreotide, however, was gradually decreasing with age. In patient 9, after 4·6 years of treatment, the dosage could be decreased to 0·6 μg/kg/day as she was prepared for treatment discontinuation.

None of the 15 patients showed obvious psychomotor retardation. Patients 2, 3, 7, 8, 9, who underwent extended octreotide treatment, showed normal results in the formal assessment of the developmental quotients at 112, 82, 94, 102 and 107 (normal range >70), respectively (Table 1).

With regard to the route of administration, continuous infusion of octreotide seemed to be superior to multiple daily injections. Of the four patients who were converted to continuous subcutaneous infusion from multiple daily injections, two were able to tolerate a decrease in the required octreotide dosage from 18 to 9 μg/kg/day (patient 13) and from 8 to 6·4 μg/kg/day (patient 14). In the remaining two patients (patients 4 and 11), there were no changes in the octreotide dosage. However, in patient 4, continuous nocturnal nasogastric tube feeding could be discontinued after conversion to continuous infusion at the same dosage as that used for multiple injections.

Overall, except for the transient gastrointestinal symptoms (poor appetite, constipation, or change in stool colour) observed in three patients (patients 11, 13, 14), the treatment was well tolerated. Laboratory test results revealed no significant changes in the blood count, blood chemicals, serum electrolyte concentration and thyroid function during the course of the treatment, and gallstones did not develop in any of the patients. However, at the higher dosages (>17 μg/kg/day), growth deceleration was observed in two patients (patients 2 and 3) with biallelic mutations (Fig. 1). The deceleration appeared to be caused by the suppression of growth hormone secretion due to the octreotide treatment. In patient 3, serum IGF1 measurements were 16·3 nmol/l at 2·0 years of age, 16·5 nmol/l at 3·0 years and 11·4 nmol/l at 4·0 years. Growth hormone provocation tests performed at the age of 4·0 years showed reduced peak growth hormone values of 1·43 μg/l by the levodopa loading test and 3·33 μg/l by the clonidine loading tests (cut-off, 6 μg/l). Because the growth deceleration was more significant in patient 3, the octreotide dosage was gradually decreased from 17 μg/kg/day to 8 μg/kg/day during the age of 4 years, which resulted in the recovery of the growth rate accompanied by an increase in the serum IGF1 to 24·5 nmol/l at the age of 6 years, indicating that the suppression of growth and growth hormone secretion were dose dependent. Growth deceleration was negligible in the

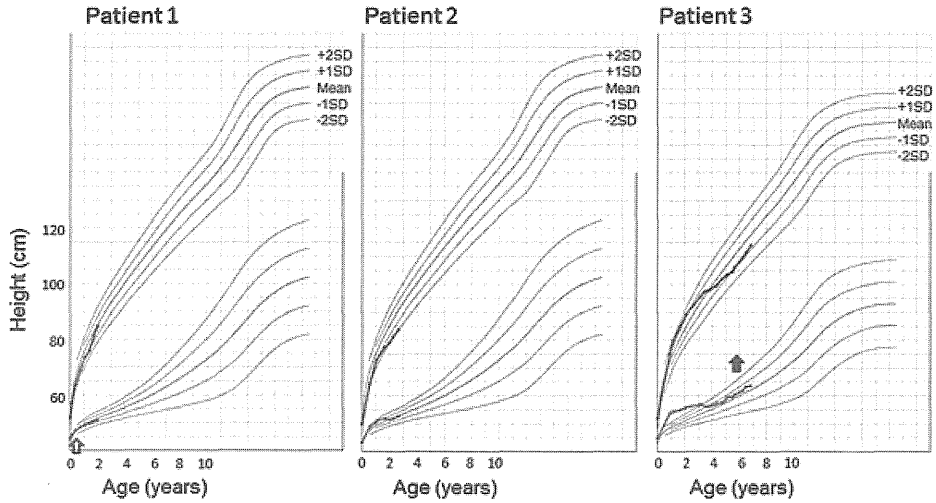

Fig. 1 Growth curve of patients with biallelic K_{ATP}-channel mutations treated by long-term, subcutaneous octreotide infusion (patients 1–3). A tendency towards growth deceleration was observed in patients 2 and 3 after 2 years of age, loss of approximately 1 and 2 SD of height, respectively. Growth deceleration was not observed in patient 1, who underwent 90% pancreatectomy and continued on octreotide at a lower dosage. The open arrow in the left panel shows when patient 1 underwent surgery, and the closed arrow in the right panel shows when the octreotide dosage was reduced from 17 to 8 μg/kg/day in patient 3, indicating the dose dependency of growth deceleration.

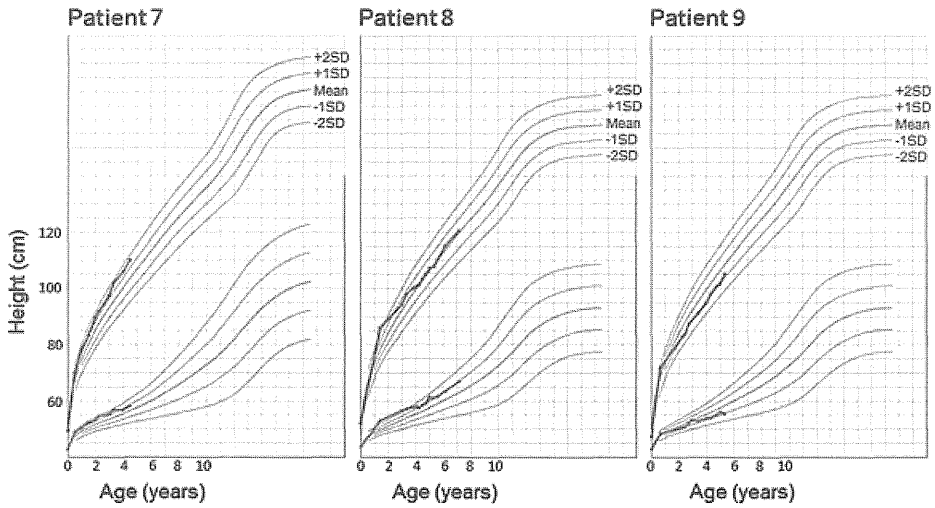

Fig. 2 Growth curve of the patients with monoallelic K_{ATP}-channel mutations treated with long-term, subcutaneous octreotide infusion. No obvious growth deceleration was observed.

patients with monoallelic mutations who were treated with a lower octreotide dosage (Fig. 2).

Discussion

The results of our study indicate that primary long-term, continuous, subcutaneous octreotide infusion with the purpose of achieving spontaneous remission could be an alternative treatment, especially in patients with monoallelic paternal mutations and in those showing diffuse or focal uptake in the head or uncus of the pancreas on 18F-DOPA PET scan. Without additional treatment such as continuous IV glucose infusion or enteral feeding, the burden of the long-term treatment was similar to that of the insulin pump therapy for infantile diabetes, which was acceptable at least to the guardians included in our study.

For patients with biallelic mutations, the situation is somewhat different. The required octreotide dosage is large, which may lead to growth deceleration after infancy. The treatment periods tend to be longer, and very often, additional treatments are required, making the long-term management of these patients more difficult. One possible strategy for such patients could be elective partial resection of the pancreas for mass reduction, as performed for patient 1, and postoperative continuous octreotide treatment until spontaneous remission is achieved. The assessment of a larger number of cases is necessary to establish the best strategy for these patients.

In our series, the octreotide dosage required to achieve euglycaemia did not differ between the patients with diffuse and focal uptakes on the 18F-DOPA PET scan, as long as they had paternally inherited monoallelic mutations. Most monoallelic K_{ATP}-channel mutations are paternal,[19,22] suggesting the presence of a focal lesion. However, PET scan results show that a proportion of these patients actually present with a diffuse uptake.[19,22] Whether this represents the presence of an undetectable second mutation or unusually scattered focal lesions remains unknown. From a statistical standpoint, selectively missing the maternal mutation is highly unlikely, supporting the latter hypothesis. Our results with regard to the therapeutic response support the hypothesis that diffuse K_{ATP} CHI with monoallelic mutations is more similar to focal K_{ATP} CHI than to recessively inherited K_{ATP} CHI with only a limited number of abnormal β cells scattering widely in the pancreas.

Transient gastrointestinal problems and growth deceleration at higher dose of octreotide were the only adverse events encountered in this study. With regard to the height outcome of the patients, contradictory results have been published previously.[15,17,23] If the observed deceleration in height velocity is caused by suppression of growth hormone secretion, the patient should catch up in growth, at least to some extent, once the octreotide therapy could be stopped before puberty. The discrepancy of our results and those of previously reported height outcome might reflect this difference in the timing of observation. As surgically treated patients were also reported to lose height SDS for unknown reasons,[23] long-term follow-up of a larger cohort is necessary to assess the height outcome according to different treatment modalities.

Although no serious adverse events were noticed during the study period, this could be only due to the small number of the patients enrolled in this study. Presently, the most serious known side effect of octreotide treatment for congenital hyperinsulinism is the development of necrotising enterocolitis.[24] This association could develop in full-term infants and should be given full attention during the octreotide treatment.

As the treatment is not entirely free from serious side effects, the dosage of octreotide should be minimized. In our study, it appeared that, by changing to continuous infusion, the dosage of octreotide could be reduced compared with multiple injections. The serum half-life of octreotide following single subcutaneous injection is known to be 1·5–2 h. Assuming that we need certain serum concentration of octreotide to keep euglycaemia and we inject octreotide three times a day, theoretically, we need much higher dose of octreotide to achieve the same glycaemic goal. This needs to be tested systematically in a larger number of patients, and, in this regard, longer-acting somatostatin analogue such as lanreotide or long-acting release octreotide could also be useful alternatives to continuous octreotide infusion.[25,26]

As the focal form of K_{ATP} CHI is known to be caused by paternal uniparental disomy which, if occurred at the earlier stage of development, leads to Beckwith-Wiedemann syndrome, a theoretical concern common to the long-term treatment of focal K_{ATP} CHI is the possibility of future development of β-cell neoplasm. The patients, therefore, should be followed up for a long time even if they reach spontaneous remission.

In summary, we believe that long-term, continuous, subcutaneous octreotide infusion is a useful alternative to surgery especially for patients with monoallelic K_{ATP}-channel mutations. Because the disorder is relatively rare, the systematic accumulation of a larger number of cases is necessary to establish an optimal treatment regimen as an evidence-based therapeutic strategy.

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Review article

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Congenital hyperinsulinism: current status and future perspectives

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The diagnosis and treatment of congenital hyperinsulinism (CHI) have made a remarkable progress over the past 20 years and, currently, it is relatively rare to see patients who are left with severe psychomotor delay. The improvement was made possible by the recent developments in the understanding of the molecular and pathological basis of CHI. Known etiologies include inactivating mutations of the K_{ATP} channel genes (*ABCC8* and *KCNJ11*) and *HNF4A*, *HNF1A*, *HADH*, and *UCP2* or activating mutations of *GLUD1*, *GCK*, and *SLC16A1*. The understanding of the focal form of K_{ATP} channel CHI and its detection by ^{18}F-fluoro-L-DOPA positron emission tomography have revolutionized the management of CHI, and many patients can be cured without postoperative diabetes mellitus. The incidence of the focal form appears to be higher in Asian countries; therefore, the establishment of treatment systems is even more important in this population. In addition to diazoxide or long-term subcutaneous infusion of octreotide or glucagon, long-acting octreotide or lanreotide have also been used successfully until spontaneous remission. Because of these medications, near-total pancreatectomy is less often performed even for the diazoxide-unresponsive diffuse form of CHI. Other promising medications include pasireotide, small-molecule correctors such as sulfonylurea or carbamazepine, GLP1 receptor antagonists, or mammalian target of rapamycin inhibitors. Unsolved questions in this field include the identification of the remaining genes responsible for CHI, the mechanisms leading to transient CHI, and the mechanisms responsible for the spontaneous remission of CHI. This article reviews recent developments and hypothesis regarding these questions.

Keywords: Hyperinsulinism, Congenital, Hypoglycemia

Introduction

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infancy, and severe hypoglycemia in infancy can cause permanent brain damage[1-4]; therefore, optimal management is extremely important. In the past, our armamentarium against severe CHI was very limited. With only diazoxide and near-total pancreatectomy as available options, many patients were left with psychomotor delay or epilepsy. Even worse, a number of patients developed postoperative insulin-dependent diabetes mellitus[3,5,6].

Over the past 20 years, however, remarkable progress has been made in the diagnosis and management of CHI, which has directly translated into improved neurological outcomes for patients[3,7]. This improvement in the understanding of the pathogenesis of CHI and the development of diagnostic modalities have helped in deciding the optimal management strategy for each patient[8-10]. However, the situation is still far from ideal. Several unsolved questions and unmet needs remain.

In this review, I first discuss the diagnostic criteria and the practical treatment goals for CHI, which are the prerequisites for all subsequent management. Then, after a brief introduction of

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the mechanism of glucose-induced insulin secretion, I review the current status of the understanding and management of CHI. Finally, I list some of the unsolved questions in this field and introduce key findings that may guide us in the future.

Diagnostic criteria and treatment goals for CHI

1. Diagnosis of CHI (Table 1)

To diagnose hyperinsulinemic hypoglycemia (HI), physicians rely both on clinical clues to identify hyperinsulinism and on laboratory tests to prove hyperinsulinemia.

1) Clinical clues to suspect HI

The presence of HI may be suspected even when the patient is still in an emergency room by asking three questions: When did hypoglycemia develop after the last meal? Does the patient respond to glucagon injection? What is the amount of glucose infusion needed to keep the patient euglycemic?

(1) When did hypoglycemia develop after the last meal?

Euglycemia is maintained by a balance between hepatic glucose output and peripheral uptake induced by insulin. Hepatic glucose output is determined by three factors: food absorption, glycogenolysis, and gluconeogenesis. Fig. 1 shows the duration of glucose production by each of these mechanisms. In disorders of glycogenolysis, the patient typically becomes hypoglycemic after 4–5 hours of fasting. Similarly, in disorders of gluconeogenesis, the patient typically develops hypoglycemia after an overnight fast. When the patient has hyperinsulinemia, hypoglycemic episodes can occur at any time point, sometimes even at 2 hours after the last meal.

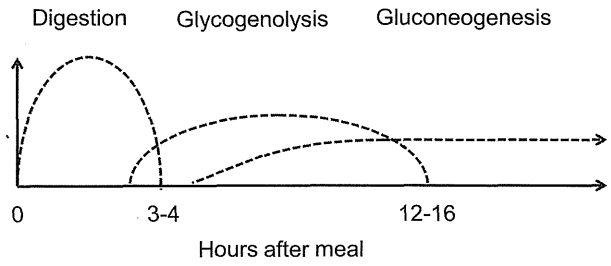

Fig. 1. Glucose source during fasting.

(2) Does the patient respond to glucagon injection?

When hypoglycemia is caused by a defect in glycogenolysis, the patient does not respond to intramuscular/intravenous injection of glucagon, which stimulates glycogenolysis. Similarly, when a patient has a defect in gluconeogenesis, by the time the patient becomes hypoglycemic, the glycogen storage in the liver should have been exhausted; therefore the patient does not respond to glucagon either. Only when the patient has hyperinsulinemia can hepatic glycogen be mobilized by glucagon, and glycemic response (>1.7–2.0 mmol/L) is seen.

(3) What is the amount of glucose infusion needed to keep the patient euglycemic?

When hypoglycemia is caused by etiologies other than hyperinsulinism, euglycemia should be maintained by providing the amount of intravenous glucose that corresponds to the normal hepatic (or possibly renal) glucose output: 4–6 mg/kg/min in neonates, 1–2 mg/kg/min in adults, and intermediate values in older children. When euglycemia cannot be maintained by these amounts of continuous glucose infusion, clinicians may suspect the presence of hyperinsulinemia.

2) Laboratory evidence of hyperinsulinism

(1) Insulin at hypoglycemia

HI is diagnosed by demonstrating inappropriately elevated insulin in the presence of hypoglycemia (<2.5 mmol/L, 45 mg/dL). However, it is often difficult to prove hyperinsulinemia by a critical sample taken during a hypoglycemic event[11,12]. In addition, the term "inappropriately elevated" insulin level is not precisely defined: some authors suggest that any detectable level of insulin is abnormal[8,9], whereas others propose different cutoffs[13]. With regard to the insulin levels during hypoglycemia, "any detectable level" is probably an overstatement because it may suggest but not prove HI. The cutoffs depend on the sensitivity of the particular assay as well as on the insulin sensitivity of each patient. In our own series of 94 confirmed Asian patients with CHI, the insulin at hypoglycemia ranged

Table 1. Diagnosis of hyperinsulinemic hypoglycemia

	Serum insulin at hypoglycemia, pmol/L (μU/mL)	Glucose infusion rate to maintain euglycemia (mg/kg/min)	Glycemic response to glucagon, mmol/L (mg/dL)	Free fatty acid/ketone bodies	Ref.
1	ND	>8	>1.5 (27)	ND	10
2	Any detectable level	>10 (neonate) >7 (5 years old), >4 (adults)	>1.7 (30)	Inappropriately low fatty acids and ketones	9
3	>6.95 (1)	ND	>2–3 (36–54)	Negative ketone bodies in urine/plasma	13
4	Any detectable level	>8	ND	ND	8
Proposed criteria	>20.84 (3)	>8 (neonates), >3 (adults), in-betweens (children)	>2 (36)	3-hydroxybutylate < 1.3 mmol/L, FFA < 1 mmol/L	

ND, not described; FFA, free fatty acid.

8.75–1,250 pmol/L (1.26–180 μU/mL) with a median of 73.3 pmol/L (10.55 μU/mL; unpublished data). In contrast, insulin levels during hypoglycemic events in patients without HI ranged from undetectable to 43.1 pmol/L (6.2 μU/mL) while the detection limit was >2.1 pmol/L (0.3 μU/mL). Clearly, these values overlap.

(2) Relatively low free fatty acid and ketone bodies at hypoglycemia

Insulin inhibits lipolysis; therefore, low free fatty acid and ketone bodies during hypoglycemia are also used as diagnostic adjuncts. In normal infants (0–24 months of age), blood 3-hydroxybutylate and free fatty acid levels after a 20-hour fast are 3.11 mmol/L (range, 1.29–4.34 mmol/L) and 2.15 mmol/L (range, 1.03–3.24 mmol/L), respectively[14]. These values can be used to set cutoffs for HI. In our series of 207 cases with confirmed CHI, the highest 3-hydroxybutylate at hypoglycemia was 0.44 mmol/L (unpublished data).

3) Proposed diagnostic criteria to suspect HI

It is difficult to set definitive diagnostic criteria for HI. Several authors propose different cutoff values to diagnose HI (Table 1), but these criteria should be regarded as suggestive and not necessarily diagnostic. The bottom of Table 1 includes proposed criteria that strongly suggest the presence of HI in children.

2. Treatment goals of CHI

The goals of HI treatment are to prevent neurological sequelae of hypoglycemia. Factors that could affect neurological outcomes include age, comorbid conditions, severity of the initial episode, and duration and frequency of subsequent hypoglycemic episodes[15-18]. Therefore, the treatment goals should be individualized. Currently, blood glucose >3.33–3.89 mmol/L (60–70 mg/dL) is the most commonly recommended target for HI treatment[10,11,13].

Insulin secretion and the ATP-sensitive potassium channel

1. Glucose induced insulin secretion (the GSIS pathway) (Fig. 2)

In pancreatic β-cells, extracellular glucose is transported into the cytoplasm by the action of glucose transporter (GLUT2). The glucose is then phosphorylated by glucokinase. Glucokinase is not easily saturated by the physiological range of intracellular glucose, and is not inhibited by its end product glucose-6-phosphate. Therefore, it serves as the fuel gauge of the β-cells. Glucose-6-phosphate is then metabolized via glycolysis, the Krebs cycle, and oxidative phosphorylation to generate ATP. An increased ATP/ADP ratio within β-cells leads to the closure of the ATP-sensitive potassium channel (K_{ATP} channel), which causes depolarization of the cell membrane and opening of the voltage-gated calcium channel. The resulting influx of calcium ions then causes fusion of the insulin secretory granules with the cell membrane and secretion of insulin[19].

2. The K_{ATP} channel

The K_{ATP} channel is an octameric structure composed of four molecules of pore-forming Kir6.2 and four molecules of SUR1 that surround the pore and regulate the channel activity.

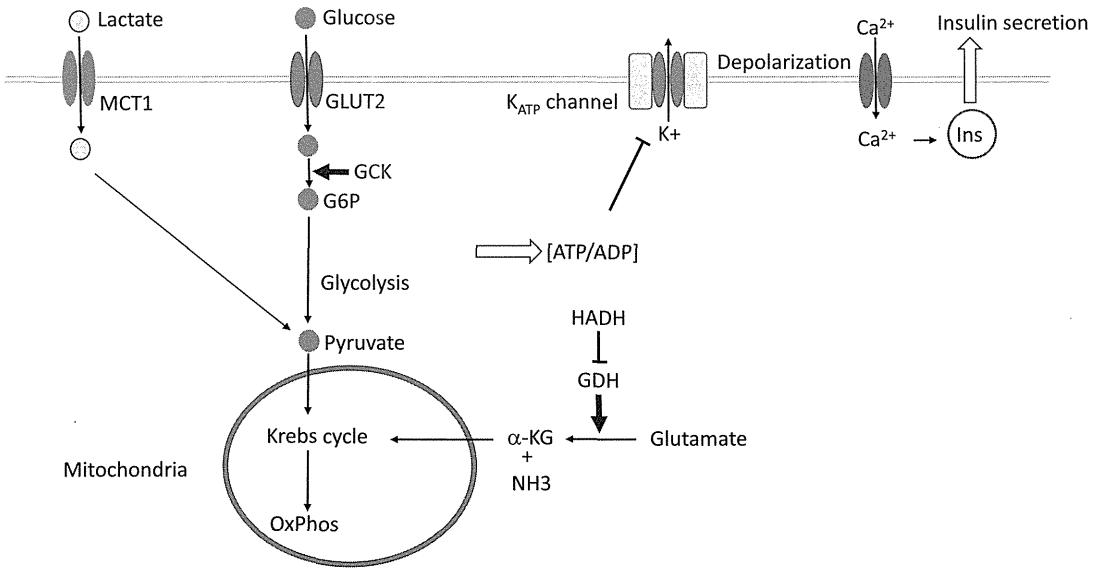

Fig. 2. The glucose-induced insulin secretion pathway. GLUT2, glucose transporter 2; GCK, glucokinase; G6P, glucose 6-phosphate; MCT1, monocarboxylate transporter 1; GDH, glutamate dehydrogenase; HADH, L-3-hydroxyacyl-coenzyme A dehydrogenase; α-KG, α-ketoglutarate; Ins, insulin.