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Hypoglycemia Associated with Type B Insulin Resistance

Hiroyuki Tamemoto, Shin-ichi Tominaga Hideo Toyoshima, San-e' Ishikawa and Masanobu Kawakami
Department of Biochemistry, Jichi Medical University
Department of Comprehensive Medicine, Saitama Medical Center Jichi Medical University
Department of Endocrinology and Metabolism, Saitama Medical Center Jichi Medical University
Japan

1. Introduction

Type B insulin resistance is a rare syndrome caused by anti-insulin receptor antibody. The anti-insulin receptor antibody inhibits binding of insulin to insulin receptor and severe insulin resistance results. Type B insulin resistance usually associates with systemic lupus erythematosus (SLE) or Sjögren syndrome (SjS). In United States, Patients are usually African American women with hyperandorogenism and acanthosis nigricans. To control abnormal autoantibody, predonisolone (PSL), cyclophosphamide, cyclosporine A, azathiopurine, methotrexate, plasmapheresis, mycophenolate mofetil and rituximab are used with various effects. In some cases, hypoglycemia follows after severe hyperglycemia is ameliorated with various therapies. Occasionally, the anti-insulin receptor antibody has partial agonist activity and hypoglycemia is the first symptom. We have experienced a case of hypoglycemia complicated with type B insulin resistance and polymyositis. We reviewed case reports of type B insulin resistance from Japan. The Japanese patients with type B insulin resistance are usually not obese and more men than women were found. Hypoglycemia was observed relatively frequently. Complication with SLE was common, however a rare case complicated with *Helicobacter pyroli* infection was also reported.

2. Case presentation

In Augst 2009, a 54-year-old man admitted to the hospital for muscle pain and weakness. One month before admission, he noticed edema on both feet and swelling of his fingers of both hands. He had no pain however the hotness of the fingers disturbed sleeping. Ten days before admission, he had difficulty in moving his fingers because of the edema and he had pain on the palmar side of his hands. Then, swelling of both thighs and muscle pain of both shoulders had developed. He found weakness of the legs but could still walk on the stairs. His family doctor found elevation of creatin kinase (1580 mU/ml) and thrombocytopenia (79000 /μl) and he was referred to this hospital. On admission, his body height was 167.6 cm, body

weight was 69.6kg and the body mass index (BMI) was 24.0 kg/m². Pitting edema on lower legs and feet was found. His grasping power was difficult to measure because of the swelling of his fingers. However no apparent muscle weakness was observed by manual muscle testing. On his skin, no Gottron's sign or Heliotrope rash was observed. He had muscle pain in the thigh. He had history of left VIIth nerve palsy when he was 40. VIIth nerve palsy recurred on the right side in April and then he was diagnosed as diabetes mellitus. He smoked one pack of cigarette and drinks a can of beer every day. His mother had diabetes and otherwise no particular family history was noticed. The results of the laboratory tests are listed in Table 1.

WBC	6970 /μl	C3	53 mg/dl (65-135)
Hb	12.5 g/dl	C4	11 mg/dl
Ht	38.7%	D-dimer	2.9 μg/ml
Platelet	167000/μl	Anti-Jo-1 antibody	2
AST	163 mU/ml	Anti-RNP antibody	Negative
ALT	91 mU/ml	Anti-nuclear antibody	80 (diffuse, nuclear)
LDH	523 mU/ml	Anti-Scl-70 antibody	Negative
CK	3296 mU/ml	Anti-SSA antibody	16
CK-MM	97%	Anti-SSB antibody	Negative
CK-MB	3%	Anti-mitochondria M2 antibody	12
HbA1c	6.6%	KL-6	331 U/ml
Blood glucose after		SP-D	31.8 ng/ml
75 g oral glucose		SAA	10.8 μg/ml
0 min	54 mg/dl	CRP	0.35 mg/dl
60 min	186 mg/dl	CEA	3.1 ng/ml
120 min	249 mg/dl	CA19-9	3.3 U/ml
Plasma insulin after		Anti-insulin antibody	Negative
75 g oral glucose		Anti-insulin receptor antibody	Inhibition rate 41%
0 min	10 μU/ml	electromyogram	Low & short NMU in
60 min	517μU/ml		biceps, brachioradial,
120 min	981μU/ml		quadriceps femoris
			and tibialis anterior
			muscles

Table 1. Laboratory data of the case NMU: neuromuscular unit

He presented symptoms of fasting hypoglycemia and his fasting plasma glucose showed values between 50 and 70mg/dl repeatedly. His fasting plasma immunoreactive insulin (IRI) level was 21.2 μU/ml and was inappropriately high when the plasma glucose was 62mg/dl. At two hours after breakfast, his plasma glucose was 139mg/dl and the IRI at this time point was 379 μU/ml. The HbA1c at admission was 6.6%. To confirm diagnosis, 75 g oral glucose tolerance test was performed. The blood glucose level after 2 hours was 249 mg/dl. The IRI and C-peptide levels 2 hours after load were 981 μU/ml and 12.5 ng/ml respectively. Anti-insulin antibody was negative. Anti-insulin receptor antibody was present and the inhibition rate was 41%. During the course, serum creatine kinase level increased to over 7000 mU/ml and AST and ALT also moderately increased over 300

mU/ml. The antinuclear antibody, anti-SSA antibody and the Jo-1 antibody were positive, but not for anti-Scl70 or anti-SSB antibodies. Anti-mitochondria M2 antibody was also positive. The electromyogram was compatible with myopathy. A diagnosis of polymyositis complicated with type B insulin resistance was given. After that he was re-evaluated by a dermatologist for the presence of acanthosis nigricans and mild lesions were found in the axilla and the periumbilical region. Predonisolone therapy was started from 60 mg/day. The fasting plasma glucose increased to 198mg/dl and the plasma insulin level was 1399 μU/ml. To control the hyperglycemia, insulin therapy was started from 2 units of ultra-rapid insulin before each meal, then increased to 15 U/day. Severe hyperglycemia was ameliorated within one week and insulin therapy was stopped because fasting hypoglycemia recurred. Fasting hypoglycemia occurred repeatedly after discontinuation of insulin therapy but was manageable by oral glucose intake. The clinical course is presented in Figure 1.

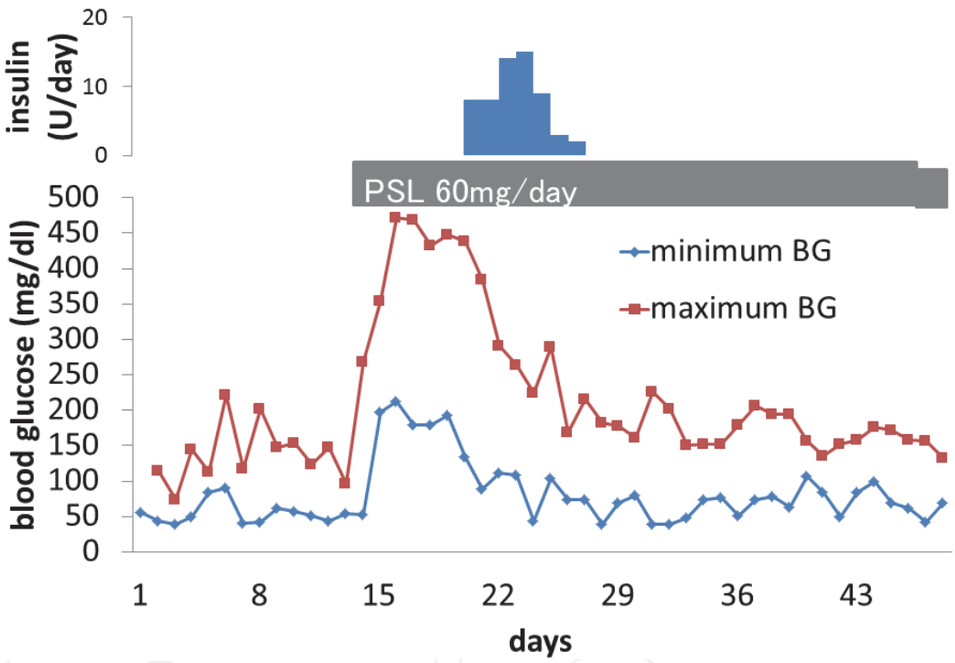

Fig. 1. Clinical course of the case

The creatine kinase and AST responded gradually, however the response was slow and methotrexate 10 mg/week was added to prednisolone therapy. After one month predonisolone was tapered to 50mg/day then 40mg/dl three weeks later. Thereafter tapering schedule was slowed to 2.5mg/day every two weeks. The creatine kinase level decreased to upper normal limit at two months after admission. The HbA1c at this time point was 6.0%.

Type B insulin resistance syndrome in Japan compared with that in the United States (US) have some differences.

Our case was positive for anti-insulin receptor antibody however his insulin resistance was weak and hyperglycemia after PSL therapy was easily controlled by short term insulin therapy. Relatively low inhibition rate of insulin binding (41%) may be the cause of this observation. The difference of clinical course compared with the typical case in US may be related to ethnicity. Therefore we screened case reports on type B insulin resistance in Japan (Table 2).

No	Age	sex	AN	BMI	Underlying disease	Hypoglycemia	OHA or insulin usage before hypoglycemia	Reference
1	54	M	Yes	24	polymyositis	Yes	No	This case
2	47	F	NR	NR	SLE	No		Takeda
3	48	F	NR	NR	SLE, depression	No		Sakai[1]
4	50	F	Yes	NR	SLE	Yes	Yes (IGF-1)	Yamasaki
5	59	M	NR	16	SLE	Yes	No	Kawashiri
6	55	M	NR	NR	SLE(possible)	Yes	No	Gojo
7	57	M	NR	NR	SLE	Yes	Yes	Ogata
8	56	M	No	22.7	SLE	Yes	No	Sato, Shigihara
9	23	F	Yes	20.4	SLE	Yes	No	Nagayama
10	61	F	NR	NR	SjS	No		Ito
11	72	F	No	21.2	SjS	No		Furukawa
12	44	F	Yes	Not obese	SjS, Hashimoto	No		Hirano
13	60	M	NR	NR	RA	Yes	No	Tokumori
14	67	M	NR	NR	UCTD	Yes	No	Yamagata
15	59	M	NR	NR	CH(C), PEG-IFN+ ribavirin	No		Miyamoto
16	74	M	Yes	18.4	IPMT	No		Uehara
17	48	F	Yes	19	T2DM only	Yes	Yes	Sakai[2]
18	68	M	NR	22.6	AP	No		Tashiro
19	84	M	No	23	ITP,	Yes	No	Imai
	86		NR	NR	ITP	Yes	No	Yamamiya

AN: acanthosis nigricans, BMI: body mass inex (kg/m^2), SLE: systemic lupus erythematosus, SjS: Sjögren's syndrome, RA: rheumatoid arthritis, UCTD: undifferentiated collagen tissue disease, CH(C): chronic hepatitis virus C infection, PEG-IFN: pegylated interferon, IPMT: intrapancreatic duct mucinous tumor, AP: angina pectoris, ITP: idiopathic thrombocytopenic purpura, IGF-1: insulin-like growth factor-1, NR: not reported

Table 2. Patients' profiles of type B insulin resistance in Japan

No	HbA1c (%)	Insulin dose (U/day)	FPG (mg/dl)	IRI (U/ml)	CPR (ng/ml)	PSL dose (mg/day)	Other treatments
1	6.0	15	62	21.2		60	MTX
2	13.4	80	NR	NR	NR	50	IGF-1, CyA, rituximab
3	NR	340		NR	NR	25	CyA 200mg/day, rituximab 500mg x2
4	NR	610	220	821	3.7 nM	30	IGF-1
5	9.5	68	67	316	3.08	30	Plasma exchange immunoadsorption CPA, CyA, IGF-1
6	NR	-	NR	NR	NR	NR	Bed time snack
7	NR	>300	NR	NR	# >450	Pulse	Plasma exchange
8	9.1	-	38	697.7	14.2	60	-
9	NR	-	116	2313	55	mPSL 0.5g x2 PSL 30	-
10	NR	NR	NR	NR	NR	50	IGF-1
11	11.1	160	NR	462	5.1	-	IGF-1
12	NR	300	131	699.5	NR	40	IGF-1
13	6.3	-	48	581	0.42	40	-
14	NR	NR	NR	NR	NR	50	*H.p.* eradication
15	NR	NR	NR	NR	NR	NR	-
16	13.8	138	NR	NR	#138.4		
17	11.2	>200	180	490	6.52	-	-
			111	NR	6.52		
			66	15.9	0.7		
18	8.5	-(OHA)	NR	>1000	NR	2.5	-
19	5.0	-	56	NR	NR	-	*H.p.* eradication
		-	NR	NR	NR	20	

FPG: fasting plasma glucose, IRI: immunoreactive insulin, CPR: C-peptide reactivity, PSL: predonisolone, mPSL: methyl predonisolone, MTX: methotrexate, IGF-1: insulin-like growth factor-1, CyA: cyclosporine A, CPA: cyclophosphamide, #: urinary excretion of C-peptide (μg/day), H.p.: Helicobactor pyroli, OHA: oral hypoglycemic agent

Table 3. Treatments of type B insulin resistance in Japan

In US, the majority of patients with type B insulin resistance are African American woman. Hyperandorogenism and acanthosis nigricans are common. Severe insulin resistance is the predominant symptoms and fasting or reactive hypoglycemia may follow after hyperglycemia is ameliorated by various treatments. Among reports on Japanese patients with type B insulin resistance, we found more men (11) than women (8). The description of acanthosis nigricans was not common. Among 9 cases with available report, 6 had acanthosis nigricans and 3 had not. Severe obesity was also rare. In the 24 cases of type B insulin resistance reported by Arioglu et al. three cases presented hypoglycemia after prolonged hyperglycemia (Arioglu 2002). Among the 19 cases in Japan, 11 cases had hypoglycemia somewhere during the course. Eight of these 11 cases were not using oral hypoglycemic agent or insulin when hypoglycemia was first noticed. Examples are briefly introduced below.

A 23-year-old Japanese woman with SLE and on hemodialysis developed severe general fatigue (Nagayama et al. 2008). Her fasting blood glucose was between 25 to 45mg/dl. Her serum insulin level was 2313.8 μU/ml and anti-insulin receptor antibody was positive by ^{125}I –insulin binding inhibition assay. She also presented with acanthosis nigricans. Her hypoglycemia was restored after steroid pulse followed by high dose steroid therapy.

A 56-year-old Japanese man was admitted to the hospital because of unconsciousness and hypoglycemia (Sato 2010). Anti-insulin antibody was positive. Episodes of hypoglycemia and hyperglycemia repeated despite predonisolone therapy (5-10 mg/day) Laboratory test revealed pancytopenia, positive antinuclear antibody and mild proteinuria. He also presented persistent discoid lesion of the skin. Renal biopsy was consistent with lupus nephritis. He was diagnosed as SLE and the dose of predonisolone was increased to 60 mg/day. After that his blood glucose improved along with proteinuria. The dose of predonisolone could be successfully tapered to 30 mg/day.

3. Underlying disease

Type B insulin resistance associates most frequently with SLE and related connective tissue diseases. Sjögren's syndrome and rheumatoid arthritis were also found. On the other hand, what is the prevalence of anti-insulin receptor antibody in SLE patients? Rosenstein et al. analyzed consecutive 38 patients with SLE or undifferentiated connective tissue disease (UCTD) for anti-insulin receptor antibody (Rosenstein et al. 2001). Within 26 SLE patients one was positive for anti-insulin receptor antibody and none in the 12 UCTD patients. None of their patients presented insulin resistance syndrome. In our case, polymyositis was the underlying disease. We searched PubMed for "polymyositis" and "insulin resistance" and found several reports on juvenile dermatomyositis (JDA) associated with lipodystrophy. In a report from Canada, 4 of 20 patients with JDA had lipodystrophy and severe insulin resistance (Huemer 2001). However anti-insulin receptor antibody was not detected by radioimmunoassay in these cases. Their pathophysiology was explained in the context of lipodystrophy. Lipodystrophy associated with dermatomyositis is not confined to pediatric patients. A case of 55-year-old woman with dermatomyositis complicated with lipodystrophy is reported (Lee and Hobbs). She developed hypertriglyceridemia 3 years after diagnosis of dermatomyositis and then lipodystrophy in the thigh appeared. Severe insulin resistance was not reported in this case. Our case did not have typical skin lesions

suggestive of dermatomyositis nor lipodystrophy. Therefore our case is not categorized in these insulin resistance associated with dermatomyositis. There are also reports of type B insulin resistance associated with interferon-alpha treatment (Miyamoto). Unfortunately, the detail of this case was not described in the literature. A similar case is reported by Daniel et al. A 55-year-old African American man with hepatitis C developed severe hyperglycemia eight months after treatment with interferon-alpha and ribavirin. He needed up to 125 U/hr of insulin and anti-insulin receptor antibody was detected in his serum. After discontinuation of interferon-alpha and ribavirin, his insulin resistance resolved spontaneously. Type B insulin resistance associated with idiopathic thrombocytopenic purpura (ITP) is also reported. *Helicobactor pyroli* infection is one of the causes of ITP and eradication of *H. pyroli* by proton pump inhibitor and antibiotics may relieve the thrombocytopenia. In Japan a case of type B insulin resistance that was ameliorated after eradication of *H. pyroli* has been reported (Imai). Interestingly, three years after the first episode, hypoglycemia recurred in this patient (Yamamiya). This time his plasma insulin was below detection limit when he was hypoglycemic. Anti-insulin receptor antibody was not proved by ^{125}I-insulin binding inhibition assay. Unfortunately, other method to detect anti-insulin receptor antibody has not been performed. Imunoprecipitation of insulin receptor by the patient's serum may probe anti-insulin receptor antibody. The change of the epitope of the anti-insulin receptor antibody may result in agonistic activity without inhibiting insulin binding.

4. Treatment of abnormal glucose metabolism

The dose of insulin utilized to control hyperglycemia was substantially small compared with that in the US (Arioglu, Lupsa, Malek). The Japanese patients with type B insulin resistance were treated no more than several hundred units a day. In the cases reported by Arioglu, on average 5100 U/day was used. A case with type B insulin resistance and SLE reported by Bao et al. required up to 4500 U/day insulin to control hyperglycemia. She was treated with azathiopurine for 3 months. Another severe insulin resistance case reported by Ostwal et al. required up to 2800 U/day. She had SLE and anti-insulin receptor antibody was probed by immunoprecipitation assay. A steroid pulse therapy with mehylpredonisolone 1 g for 3 days was performed followed by maintenance dose of steroid and azathiopurine. Her insulin requirement decreased gradually and stopped. After that she required 3-hourly meals to avoid hypoglycemia. In the treatment of hyperglycemia, insulin like growth factor-I (IGF-I, Astellas Pharmaceutical Co. Ltd. Tokyo) injection was tried in several Japanese patients with varying effectiveness. The anti-insulin receptor antibody does not necessarily affect insulin-like growth factor receptor. Therefore IGF-1 injection is worth trying if there are no contraindications such as proliferative retinopathy or malignancy. Type B insulin resistance is potentially a self-limited disease. However to treat severe hyperglycemia in a certain time frame may require immunosuppressive medications and/or plasma exchange. In our patient, severe hyperglycemia developed only after initiation of predonisolone therapy. His hyperglycemia was controlled with relatively small dose of insulin in a short time and hypoglycemia repeated after discontinuation of insulin therapy. This may reflect the agonistic character of anti-insulin receptor antibody in his case. Because predonisolone is frequently used to treat underlying disease, hypoglycemia is relatively easy to control although timed snack may be required to avoid fasting hypoglycemia.

5. Treatment of autoimmunity

Attempt to control abnormal autoantibody is mainly through control over underlying disease. Because SLE is the most predominant underlying disease, predonisolone therapy with or without pulse therapy is most commonly attempted. Methotrexate, azathiopurine, cyclophosphamide and mycophenolate mofetil are also used in resistant cases. Plasmapheresis or immunoadsorption is used in some cases to remove anti-insulin receptor antibody in a short time. Recently rituximab is another choice to reduce B-cells producing autoantibodies. Because the case of type B insulin resistance is rare, randomized control study is difficult to perform. Therefore the comparison of effectiveness of these various therapies is difficult. The choice of treatment seems to be determined by the familiarity of the doctors to each treatment. Also the anti-insulin receptor antibody may disappear spontaneously at least in some cases. This complicates the analysis of result. Therefore it seems to be prudent to choose treatment based on the effectiveness to control the underlying disease.

6. Prognosis

Arioglu reported that the prognosis of type B insulin resistance may be poor especially in those with hypoglycemia. Among the 19 cases at least two was reported as deceased. One of the two, a 23 year-old woman was on hemodialysis complicated with SLE when her hypoglycemia developed. She had intractable lung infection during the treatment of exacerbated SLE. Another case, a 56 year-old man with severe SLE died of sepsis. Hypoglycemia was not the direct cause of death for these cases. We have no data for other cases.

7. Characterization of anti-insulin receptor antibody

The presence of anti-insulin receptor antibody is probed with various methods. Inhibition of binding of ^{125}I-labelled insulin to insulin receptor is the method commonly used by commercial laboratory in Japan. The result is reported as inhibition rate. One problem of binding inhibition is that we cannot know whether the anti-insulin receptor antibody has agonist activity to insulin receptor. Another problem is that insulin binding is interfered by anti-insulin antibody if it coexists. This is a rare occasion however there are several cases in whom both anti-insulin antibody and anti-insulin receptor antibody were probed. The anti-insulin receptor is polyclonal and the character of the antibody may change during the course. Yamasaki et al. analyzed the insulin-like activity of the patient's serum during the course from severe hyperglycemia to fasting hypoglycemia. At first, her hyperglycemia was resistant to insulin at maximum 610 μU/day. After treatment with PSL, fasting hypoglycemia occurred. The activity to stimulate 2-deoxyglucose uptake was most prominent in the serum during the hyperglycemic phase and the serum during the hypoglycemic phase showed weaker activity. The activity to stimulate insulin receptor autophosphorylation was also most strong in the serum during the hyperglycemic phase. Their data suggest that antibody with agonistic activity may also present in patients who show no hypoglycemia. Receptor down regulation caused by autoantibody may modify the patient's response.

8. Epitopes of the autoantibodies

The extracellular part of the insulin receptor is composed of leucine rich domain 1, cysteine rich domain, leucine rich domain 2 and three fibronectin type III domains (McKern). Analysis using chimeric receptor has provided clue to the epitope of the anti-insulin receptor antibodies. Chimeric IGF-I receptor containing residues 450-601 of the insulin receptor was recognized by 12 of 15 sera from type B insulin resistance (Zhang & Roth). Residues 471-593 is the first fibronectin type III domain and monoclonal antibody to this region can inhibit high affinity insulin binding (Surinya). The epitopes of anti-insulin receptor antibody were analyzed by recognition of peptides from human insulin receptor expressed in bacteria (Pritgent 1990). A monoclonal antibody (83-14) mimics insulin action and inhibits insulin binding. This antibody recognizes amino acids 469-592. Another monoclonal antibody (18-44) also mimics insulin action but does not inhibit insulin binding. This antibody recognizes amino acids 765-770 within the third fibronectin type III domain in the N-terminus of the beta subunit. Chrystallographic study of the ectodomain of human insulin receptor revealed that the insulin binding pocket is made of N-terminal leucine rich repeat and the first fibronectin type III domain (McKern). The third fibronectin type III domain is outside the insulin binding pocket. Therefore if antibody to amino acids 765-770 is predominant, hypoglycemia without insulin resistance will result. In such a case, anti-insulin receptor antibody cannot be proved by binding inhibition assay. In the case reported by Yamamiya, anti-insulin receptor antibody was not detected by insulin binding inhibition when hypoglycemia recurred. This may result from change in the epitopes of the autoantibody. We should recall the possibility of anti-insulin receptor antibody when we see hypoglycemia associated with very low insulin level.

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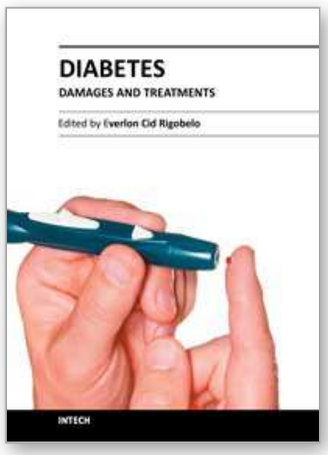

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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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