بنام خدا

هیپوگلیسمی در نوزادان

دکتر انتظاری

Hypoglycemia of infants

Serum glucose< 35 mg/dl 1-3 hr of life
< 40 mg/dl 3-24 hr
< 45 mg/dl after 24 hr

Symptomatic hypoglycemia = 0/1-0/3%

In growth restricted infants = 5-15%

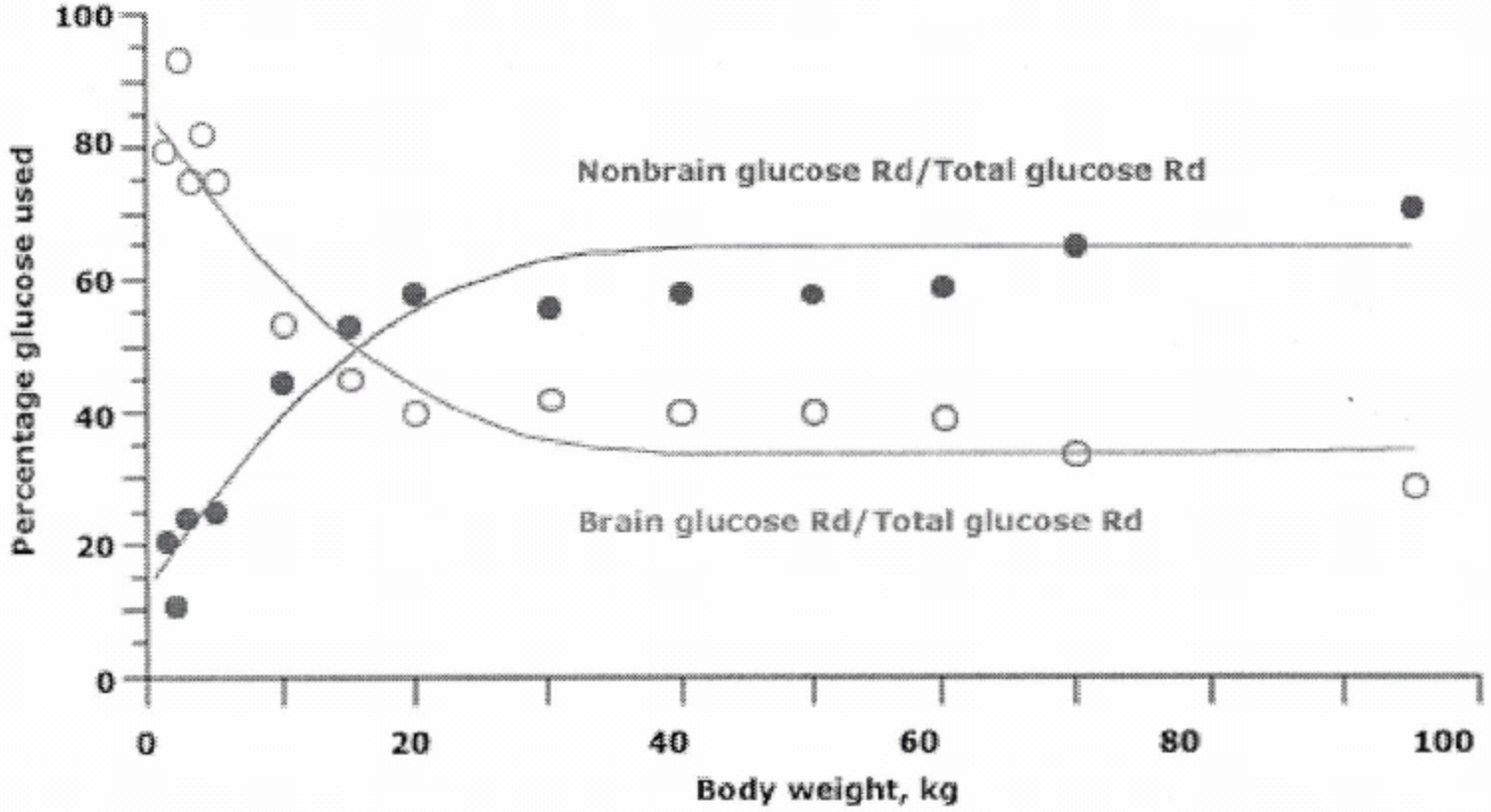
Hypogly develops in about 25-50% infants of DM mother& 15-25% ges.DM mothers

Cont.

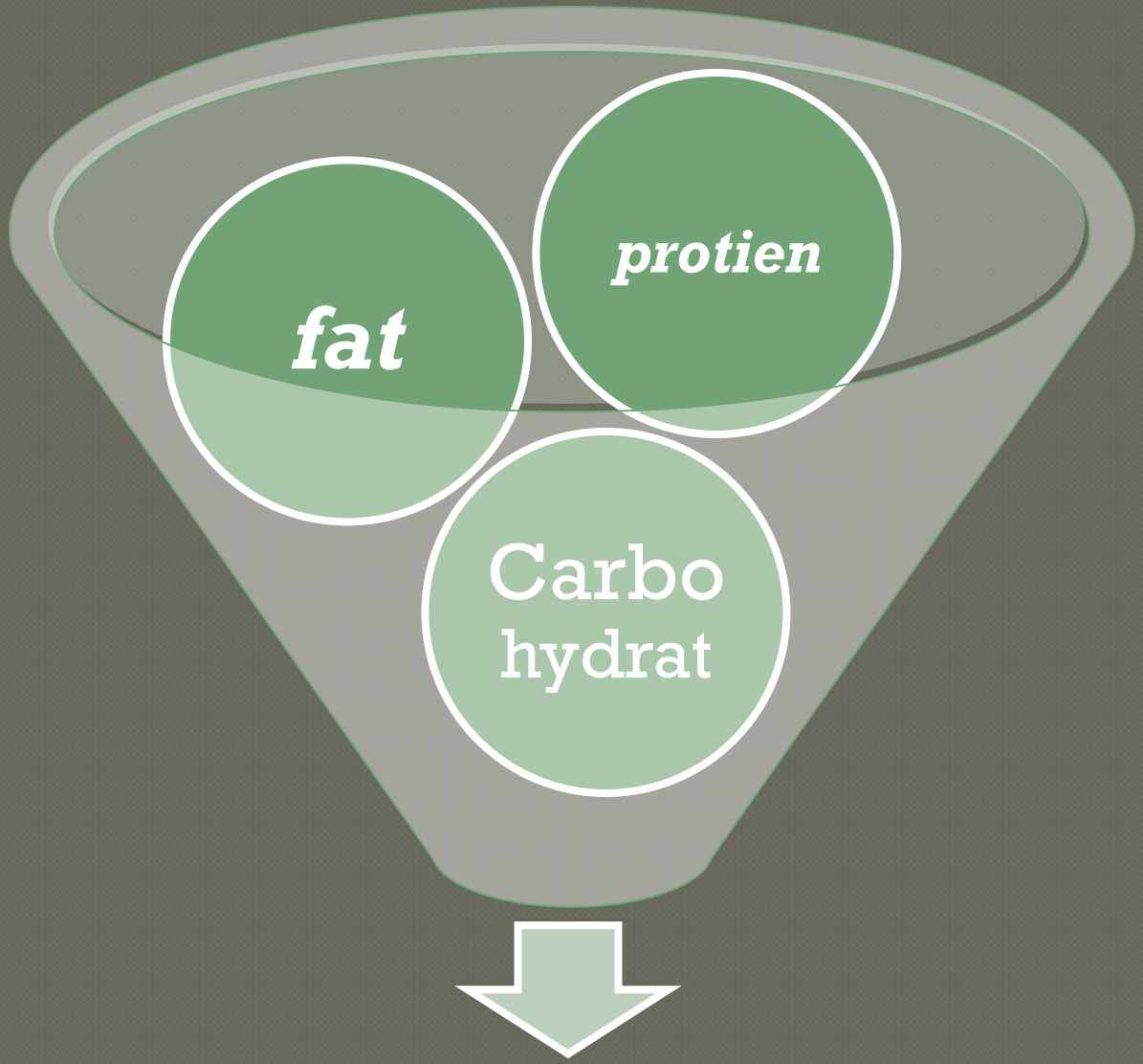
- Small percentage of hypoglycemic infant become symptomatic
- Major sequel: (about 25-50% specificly in < 6 mo infants) :
  MR , recurrent seizure activity , fall in IQ , learning disability ,
  atrophic gyri , reduced myelination ,
  atrophy in cerebral cortex

Glucose use brain v nonbrain

Glucose use by the brain versus other tissues



Estimated percentage of glucose rate of disappearance (Rd) used by brain and tissue from infancy to adulthood (n=141). The tissue data points represent the m values for subjects with body weights, in kg, of 0.5-1.0, 1.1-2.0, 2.1-3.0, 3.1-4.0



Glu homostasis

Glu Homeostasis

- Role of fuel & source energy storage (38mol ATP/mol glu)
- Energy – usable intermediates (lac.- pyru.- ala.- keton body)
- Up capacity newborn to take up keton body(5 fold)
- Changes in autonomic, nervous & hormones by hypoglycemia
- Glycogenolysis, lypolysis, ketogenesis

Glu homeostasis

- Placental transfer in 1-1/5hr first life
- Acute interruption of M.glu impose changes in H, R, E
- Catecholamine(B-adrenergic activity) mobilize fetal Glu & FFA
- Fall in fetal insulin
- Increase in fetal glucagon(3-5 fold)
- GH secretion (a-adrenergic of EN)
- Cortisol secretion

NL plasma Glu balance

- Nl endocrine system
- Intact enzyme system
- An adequate supply of endogenous fat , glycogen & potential gluconeogenic substrates(AA, glycerol, lactate)

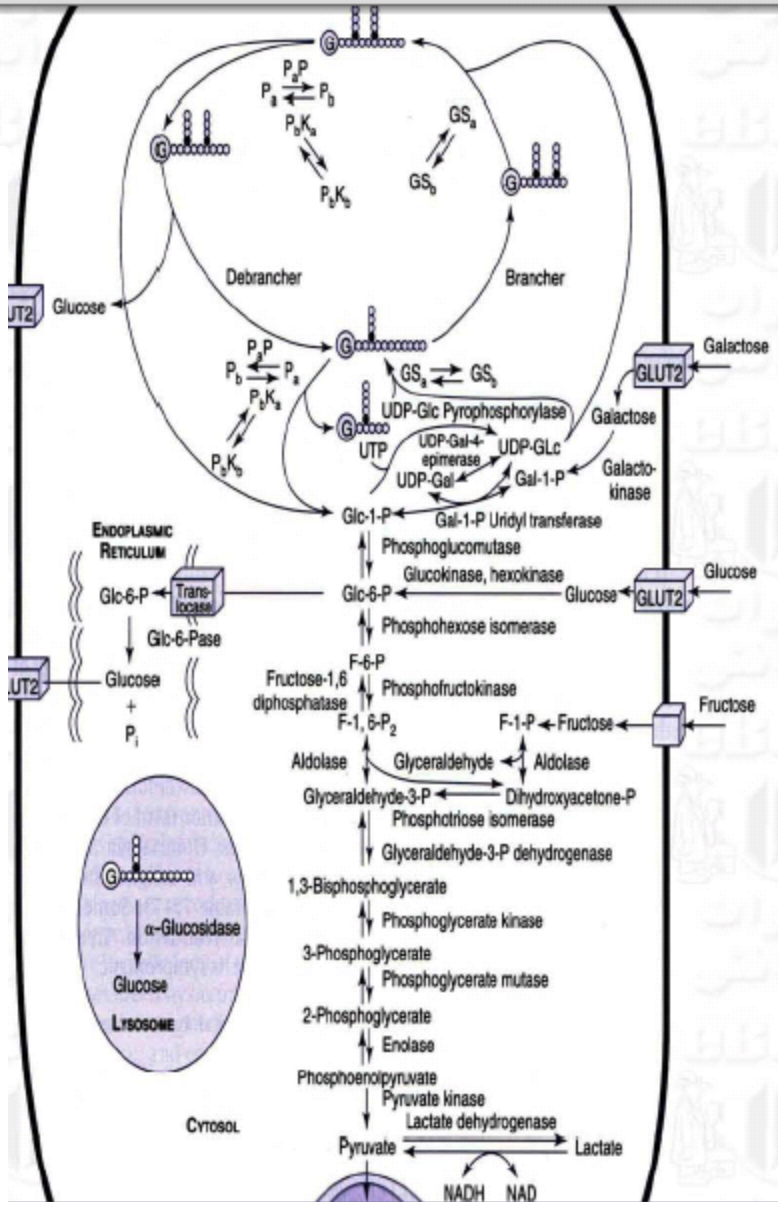
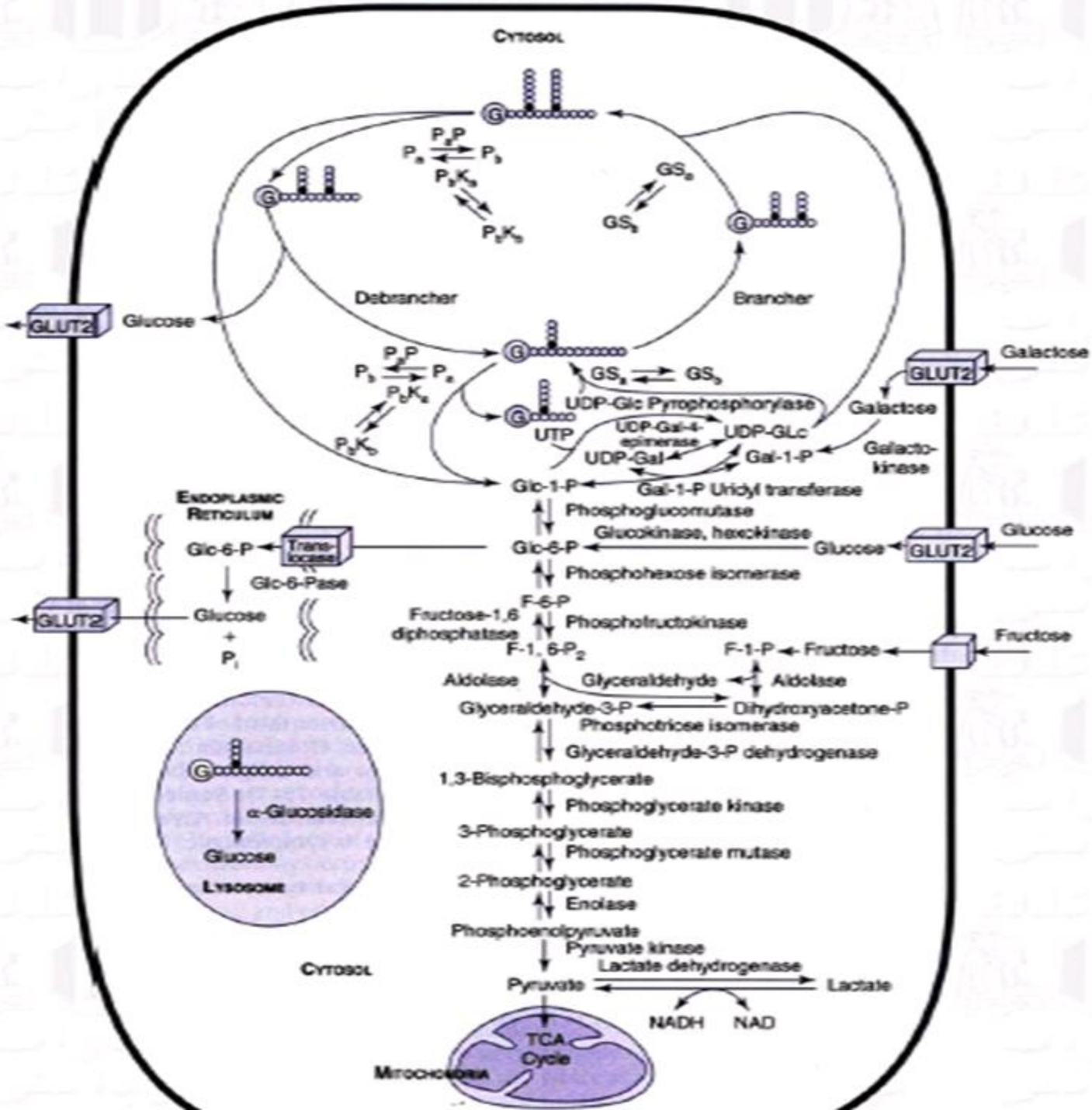


FIGURE 76–1. Pathway related to glycogen storage diseases and galactose and fructose disorders. Nonstandard abbreviations are as follows: GS_a, active glycogen synthetase; GS_b, inactive glycogen synthetase; P_a, active phosphorylase; P_b, inactive phosphorylase; P_aP, phosphorylase a phosphatase; P_bK_a, active phosphorylase b kinase; P_bK_b, inactive phosphorylase b kinase; G, glycogenin, the primer protein for glycogen synthesis. (Modified from AR Beaudet: Glycogen storage



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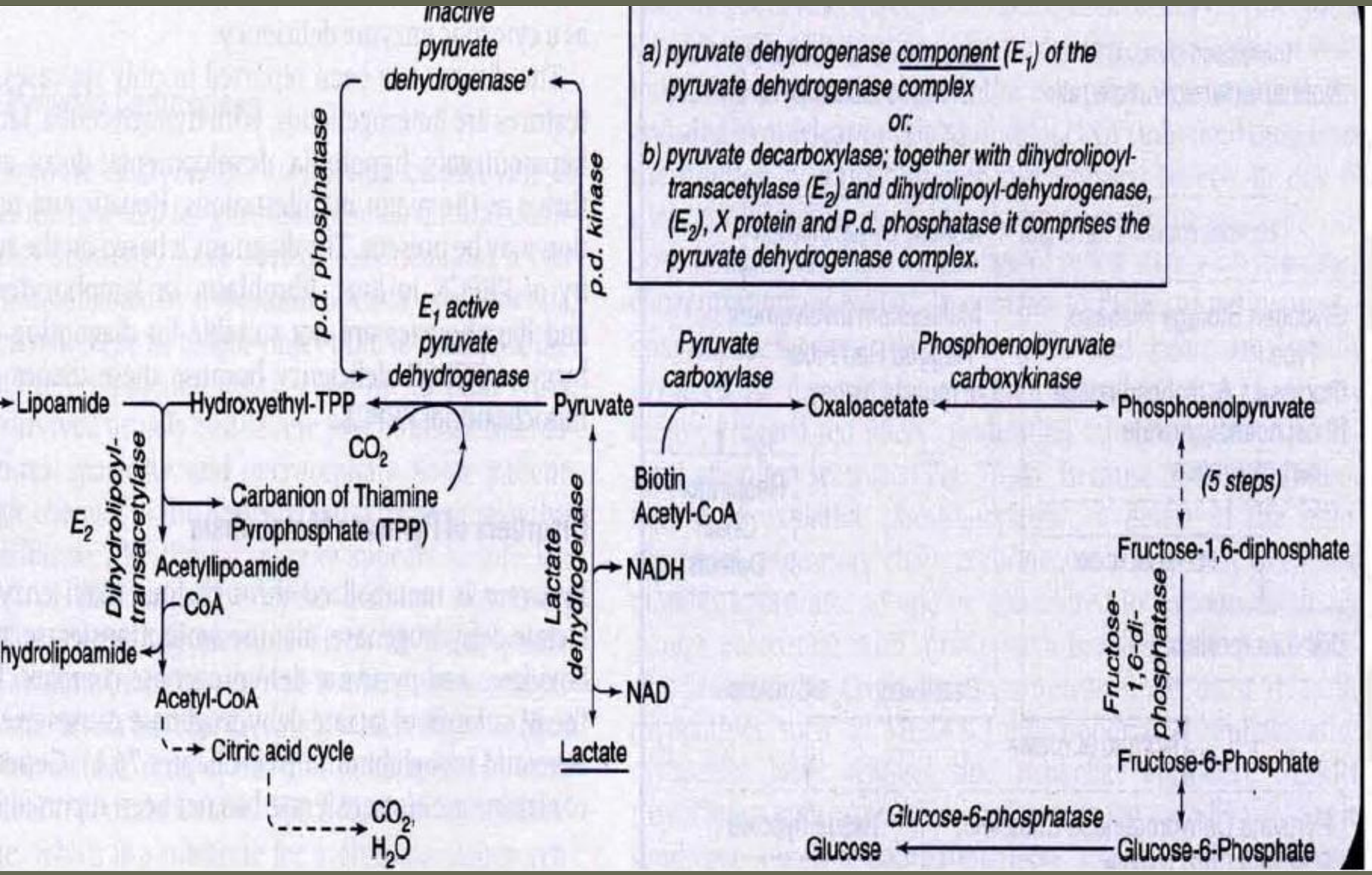
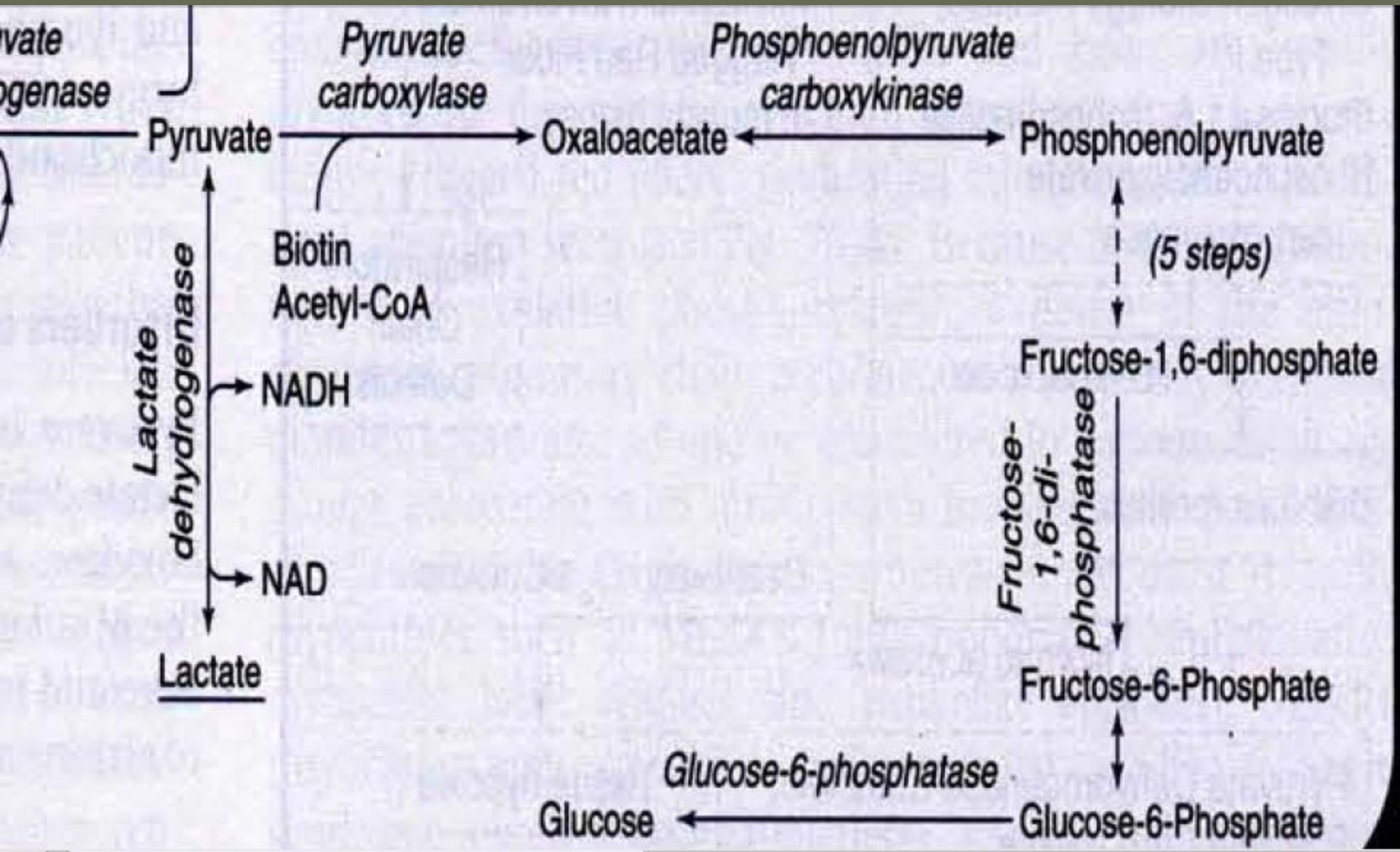

Inactive pyruvate dehydrogenase*
p.d. phosphatase
p.d. kinase
E1 active pyruvate dehydrogenase
a) pyruvate dehydrogenase component (E1) of the pyruvate dehydrogenase complex
or:
b) pyruvate decarboxylase; together with dihydrolipoyl-transacetylase (E2) and dihydrolipoyl-dehydrogenase, (E2), X protein and P.d. phosphatase it comprises the pyruvate dehydrogenase complex.
Pyruvate carboxylase
Phosphoenolpyruvate carboxykinase
Lipoamide
Hydroxyethyl-TPP
Pyruvate
Oxaloacetate
Phosphoenolpyruvate
CO2
Carbanion of Thiamine Pyrophosphate (TPP)
E2
Dihydrolipoyl-transacetylase
Biotin
Acetyl-CoA
(5 steps)
Acetyllipoamide
CoA
Lactate dehydrogenase
NADH
Fructose-1,6-diphosphate
hydrolipoamide
NAD
Fructose-1,6-di-phosphatase
Acetyl-CoA
Citric acid cycle
Lactate
Fructose-6-Phosphate
CO2, H2O
Glucose-6-phosphatase
Glucose
Glucose-6-Phosphate


vate
ogenase
Pyruvate
carboxylase
Phosphoenolpyruvate
carboxykinase
Pyruvate
Oxaloacetate
Phosphoenolpyruvate
Biotin
Acetyl-CoA
(5 steps)
Lactate
dehydrogenase
NADH
Fructose-1,6-diphosphate
Fructose-
1,6-di-
phosphatase
NAD
Lactate
Fructose-6-Phosphate
Glucose-6-phosphatase
Glucose
Glucose-6-Phosphate

Neonatal transient hypoglycemia

- Inadequate substrate or immature enzym (prematurity, LBW, IUGR,macrosomia ,delayed feeding)
- Transient neonatal hyperinsulinism (infant of diabetic or toxemic mother, E.fetalis, SGA, macrosomia,twin, birth asphyxia)

Neonatal persistent hypoglycemi

- Hyperinsulinism
- Counter-regulatory H. deficiency
- Glycogenolysis & gluconeogenesis Dis (GSD0-9, pyruvate carboxylase dif. fructose intolerance, Galactosemia)
- Lipolysis disorders
- Fatty acid oxidation disorders
- AA & organic acid disorders

Other etiology of hypoglycemia

- Systemic disorders
  (sepsis – neonatal hyperviscosity – burn – shock – factitious – malaria – dumping)
- Liver disease
  (Reye – cirrhosis – hepatitis)
- Substrate-limited
  (insulin – oral agents – propranolol – alcohol – salicylates – bactrim – poisons)

BOX 81-4. Criteria for Diagnosing Hyperinsulinism Based on "Critical" Samples (Drawn at a Time of Fasting Hypoglycemia: Plasma Glucose <50 mg/dL)

1. Hyperinsulinemia (plasma insulin > 2 μU/mL)*
2. Hypofattyacidemia (plasma free fatty acids < 1.5 mmol/L)
3. Hypoketonemia (plasma β-hydroxybutyrate: < 2.0 mmol/L)
4. Inappropriate glycemic response to glucagon, 1 mg IV (delta glucose > 40 mg/dL)

*Depends on sensitivity of insulin assay.

From: Stanley CA, Thomson PS, Fingold DN, et al: *Hypoglycemia in Neonates and Infants in Pediatric Endocrinology*. 2nd ed, Sperlims M (editor) WB Saunders 2002, pp 135–159.

BOX 81–3. Analysis of Critical Blood Sample during Hypoglycemia and 30 Minutes After Glucagon*

SUBSTRATES

Glucose
Free fatty acids
Ketones
Lactate
Uric acid
Ammonia

HORMONES

Insulin
Cortisol
Growth hormone
Thyroxine, thyroid-stimulating hormone†

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*Glucagon 1 mg IV or IM.

†Measure once only before or after glucagon administration. Rise in glucose of ≥ 40 mg/dL after glucagon given at the time of hypoglycemia strongly suggests a hyperinsulinemic state with adequate hepatic glycogen stores and intact glycogenolytic enzymes. If ammonia is elevated to 100–200 μM, consider activating mutation of glutamate dehydrogenase.

BOX 81–5. Diagnosis of Acute Hypoglycemia in Infants and Children

ACUTE SYMPTOMS PRESENT

1. Obtain blood sample before and 30 min after glucagon administration.
2. Obtain urine as soon as possible. Examine for ketones; if not present and hypoglycemia confirmed, suspect hyperinsulinemia o fatty acid oxidation defect; if present, suspect ketotic, hormone deficiency, inborn error of glycogen metabolism, or defective gluconeogenesis.
3. Measure glucose in the original blood sample. If hypoglycemia is confirmed, proceed with substrate-hormone measurement as in Box 81–3.
4. If glycemic increment after glucagon exceeds 40 mg/dL above basal, suspect hyperinsulinemia.
5. If insulin level at time of confirmed hypoglycemia is greater than 5 μU/mL, suspect endogenous hyperinsulinemia; if greater than 100 μU/mL, suspect factitious hyperinsulinemia (exogenous insuli injection). Admit to hospital for supervised fast.
6. If cortisol is less than 10 μg/dL or growth hormone is less than 5 ng/mL, or both, suspect adrenal insufficiency or pituitary disease or both. Admit to hospital for hormonal testing and neuroimaging.

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HISTORY SUGGESTIVE: ACUTE SYMPTOMS NOT PRESENT

1. Careful history for relation of symptoms to time and type of food intake, bearing in mind age of patient. Exclude possibility of alcohol or drug ingestion. Assess possibility of insulin injection, salt craving, growth velocity, intracranial pathology.
2. Careful examination for hepatomegaly (glycogen storage disease; defect in gluconeogenesis); pigmentation (adrenal failure); stature and neurologic status (pituitary disease)
3. Admit to hospital for provocative testing:
   a. 24-hr fast under careful observation; when symptoms provoked proceed with steps 1–4 as when acute symptoms present
   b. Pituitary-adrenal function using arginine-insulin stimulation test if indicated
4. Liver biopsy for histologic and enzyme determinations if indicated
5. Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected (dumping syndrome, etc.)

TABLE 81–1. Hypoglycemia in Infants and Children: Clinical and Laboratory Features

Group	Age at Diagnosis (mo)	Glucose (mg/dL)	Insulin (μU/mL)	Fasting Time to Hypoglycemia (hr)
Hyperinsulinemia (n = 12)				
Mean	7.4	23.1	22.4	2.1
SEM	2.0	2.7	3.2	0.6
Nonhyperinsulinemia (n = 16)				
Mean	41.8	36.1	5.8	18.2
SEM	7.3	2.4	0.9	2.9

Adapted from Antunes JD, Geffner ME, Lippe BM, et al: Childhood hypoglycemia: Differentia hyperinsulinemic from nonhyperinsulinemic causes. J Pediatr *1990; 116:105–8.*

Clinical manifestation

- Activation of autonomic N.S. & EN release (apnea & cyanosis, pallor, hypothermia, sweating, weak or high-pitch cry, tachycardia &tachypnea, hyperexcitable)
- Cerebral glucopenia (hypotonia, convulsion, difficulty feeding, eye rolling, jitteriness, lethargy, staring)

Critical samples of blood

- Measurement of key substrates
  (plasma Glu, FFA, B-hydroxybutyrate, lactate, total & free carnitine, acylcar.)
- Measurement of glucoregulatory H.
  (plasma insuline, c-peptide, cortisol, GH)

Other tests of blood

- Serum electrolyte(for calculation AG)
- LFT
- Serum Ammonia
- Metabolic screening
- Toxicology(salicylate, ethanol, drug, sulfonylurea)

Other tests of urine

- Urine ketons
- Reducing substance of urine
  (for gala & fruc)
- Toxicology studies of frozen urine
  (for organic acid, dicarboxylic acid, acylglycine)

Treatment of hypoglycemia

- 4 ml/kg of D/W 10% bolus when seizure
- 2 ml/kg bolus when other than seizure
- 8 mg/kg/min glu infusion with increase 15-20% glu used
- Glucagon in acute phase
- Octreotide & glucocorticoid
- Diazoxide in hyperinsulinisem
- Subtotal pancreatectomy

Supervision of hyperglycemia

- BS every 2 hr after therapy when < 40
- BS every 4-6 hr when NL range(24-48hr)
- Infants at HR for hypoglycemia BS Q1-2hr(6-8hr) & Q4-6hr(24-48hr) should be checked
- NL inf rate of glu 4-8 mg/kg/min

Cont.

- Glu in whole blood 15% lower than that in plasma(specificly in high Hct)
- BS is monitored at least weekly in TPN
- BS values decrease 15-20 mg/dl/hr in samples at room temperature


THE END