The Path From Hormone Abnormality to Hypoglycemia

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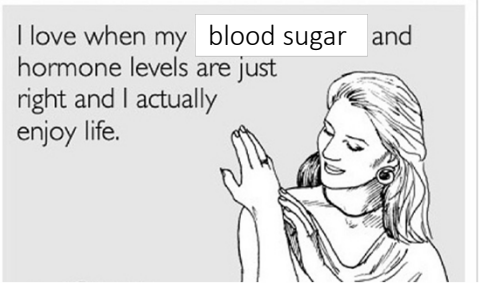
Conflicts of Interest

- None

Objectives

- Discuss the human body systems required for normal fasting adaptation.
- Describe how hormone abnormalities can lead to hypoglycemia.
- Discuss case studies of infants and children with hypoglycemia and determine which hormone excess or deficiency could be implicated as a cause of hypoglycemia.



Body and Brain need a constant source of fuel

Glucose

Glucose and the Adult Brain

- Glucose = main fuel for the body and brain
  - At rest, 60% of glucose is used by the brain
  - Glucose Utilization Rate = ~2mg/kg/min
- Glucose from food = 3 hours
- Then, fasting adaptation is required
- Fasting time to hypoglycemia = ~48 hours

Berg, JM, Tymoczko, JL, & Stryer, L. (2002). Biochemistry, 5th Ed, Section 30.2.
Bier, DM, et al. (1977). Measurement of "true" glucose production rates in infancy and childhood with 6,6- dideuteroglucose. Diabetes, 26, 1016-23.

Glucose and the Infant Brain

- Infant brain
  - ⇧Brain:body mass
  - ⇧Glucose utilization
  - ⇩Fuel stores
- Comparison with Adults (10kg infant)
  - Fuel stores = 15% of adult
  - Caloric needs = 60% of adult
  - Glucose utilization = 2-3X faster
  - Glucose Utilization Rate = 4-6mg/kg/min
- Fasting time to hypoglycemia = 24+ hours

Sperling, M.A. (2008). *Pediatric endocrinology 3rd edition.* Philadelphia, PA: Sauders Elsevier.

Older/Bigger = Fast Longer

Fasting Metabolites by Age – 20 hour fast

Age in Years	0-1	2-6	7-18
Glucose (mg/dL)	59	72	76
Beta-hydroxybutyrate (mmol/L)	2.23	1.19	0.62

Adapted from van Veen (2011). Metabolic profiles in children during fasting. *Pediatrics.* 127:e1021.

Guideline for Fasting Time to Hypoglycemia

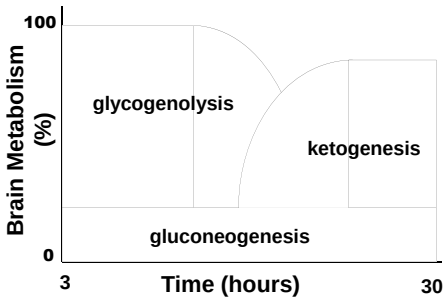
Age	Hours Fasting
Neonate	12
Infant	24
Child	36
Adult	48

Normal Fasting Adaptation

Fasting Fuel Production

- Gluconeogenesis
- Glycogenolysis
- Lipolysis/Fatty Acid Oxidation/Ketogenesis

Fasting Systems in Normal Child



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Hepatocytes

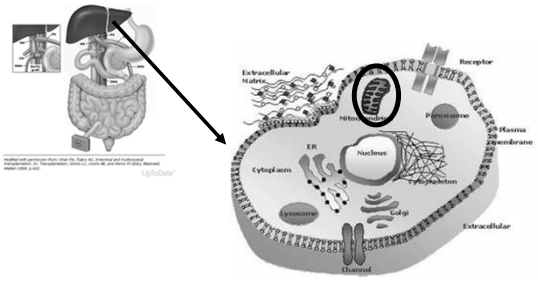
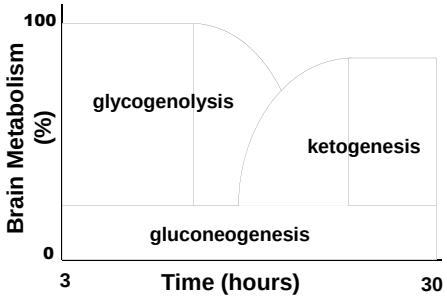


Image courtesy of National Institute of General Medical Sciences.

Gluconeogenesis

- **The creation of glucose in the body from non-carbohydrate substrates**
- **Not a significant source of glucose production**

Fasting Systems in Normal Child



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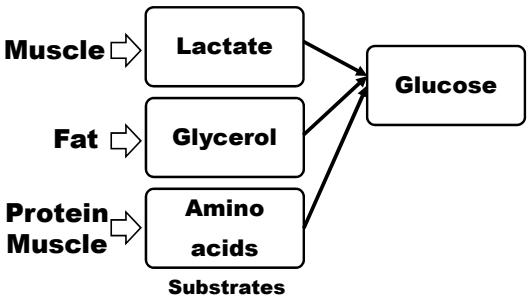
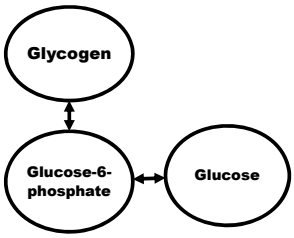
Gluconeogenesis



http://www.ncbi.nlm.nih.gov/books/NBK22591/

Glycogenolysis

- Breakdown of glycogen to glucose in the liver
- Main source of fuel in the early hours of fasting

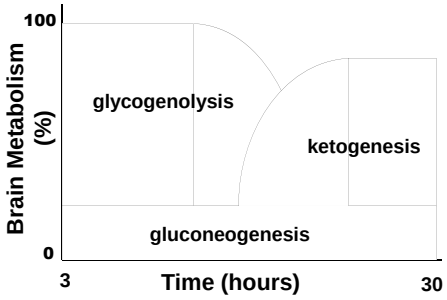


Sperling, M.A. (2008). *Pediatric endocrinology 3rd edition.* Philadelphia, PA: Sauders Elsevier.

Lipolysis, Fatty Acid Oxidation, and Ketogenesis

- Fat breakdown and ketone production
- Ketones = alternate fuel
- Main source of fuel later in fasting
- Ketogenic diet
- Atkins diet

Fasting Systems in Normal Child



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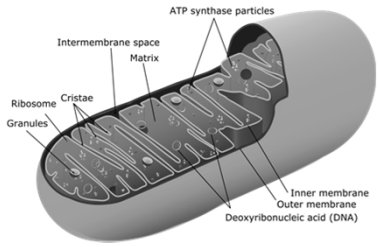
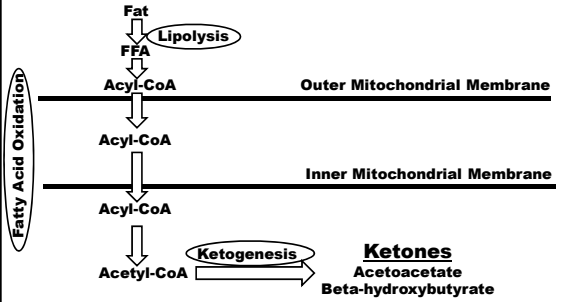
Mitochondria



Used with permission from Mariana Ruiz Villarreal.

Ketogenesis Pathway



http://lipidlibrary.aocs.org/Biochemistry/content.cfm?ItemNumber=39187

Summary

- **Three main mechanisms the body has for producing fuel in the fasting state:**
  - **Gluconeogenesis**
  - **Glycogenolysis**
  - **Lipolysis/Fatty Acid Oxidation/Ketogenesis**

Hormones and Hypoglycemia

What hormones (in excess or deficient amounts) cause hypoglycemia?

- **Insulin**
- **Glucagon**
- **Epinephrine**
- **Cortisol**
- **Growth Hormone**

Hormonal Control of Fasting Systems

	Glyco-genolysis	Gluconeo-genesis	Lipolysis	Fatty Acid Oxidation/ Ketogenesis
Insulin	-	-	-	-
Glucagon	+	+		
Epinephrine	+	+	+	+
Cortisol		+		
Growth Hormone			+	

Adapted from Sperling, M.A. (2008). *Pediatric endocrinology 3rd edition.* Philadelphia, PA: Saunders Elsevier.

Insulin

- Insulin ⇩BG levels by transporting glucose molecules into the cells and out of the blood stream
- Insulin inhibits all parts of fasting adaptation
- Eat food = ⇧Glucose = ⇧Insulin = inhibition of fasting systems

Cryer, P.E. (2013). Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *NEJM*, 369:362-72.

Hyperinsulinized State

- Excess exogenous insulin – diabetes
- Excess endogenous insulin – congenital hyperinsulinism (HI)
- Fasting systems are inhibited by insulin when they are really needed
- Treatment
  - Diabetes – administer carbohyrdate, glucagon
  - Congenital HI – medication, surgery, continuous dextrose, glucagon

Glucagon

- Hormone released by alpha cells in the pancreas
- Stimulates glycogenolysis and gluconeogenesis
- ⇩Glucose = ⇧Glucagon

Glucagon Deficiency

- Leads to hypoglycemia
- Isolated glucagon deficiency is very rare
- Other causes:
  - Pancreatectomy
  - T1DM
  - Advanced T2DM
- Treatment?

Vidnes, J. & Oyaster, S. (1977). Glucagon deficiency causing severe neonatal hypoglycemia in a patient with normal insulin secretion. *Pediatric Research*, 11:943-949.
Cryer, P.E. (2013). Mechanisms of hypoglycemia-associated autonomic failure in diabetes. ***NEJM***, 369:362-72.

Epinephrine

- Hormone secreted from adrenal medulla
- Released during stress 

- Epinephrine actions:
  - ⇧HR
  - Vasodilation of vessels to muscle and liver
  - Vasoconstriction of most other blood vessels
- Stimulates all fasting systems

Cryer, P.E. (2013). Mechanisms of hypoglycemia-associated autonomic failure in diabetes. ***NEJM***, 369:362-72.
http://www.cvphysiology.com/Blood%20Pressure/PB018.htm

Epinephrine

During stress or fasting:

⇧Epinephrine = Stimulation of Fasting Systems

Result = ⇧Fuel

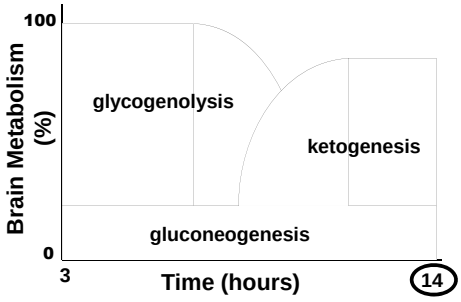
Epinephrine Deficiency

- **Leads to hypoglycemia**
- **Deficiency is rare**
- **More common = Epinephrine is blocked**
- **What medications block Epinephrine?**
  - **Beta-blockers**
    - **atenolol**
    - **propranolol**
    - **nadolol**
    - **metoprolol**
    - **labetalol**
    - **timolol**

Epinephrine Blocked

- **Child on beta blocker**
- **Develops fasting ketotic hypoglycemia**
- **Treatment = decrease fasting time**

Fasting Systems in Normal Child



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Cortisol

- Produced by adrenal cortex
- Maintains homeostasis
  - Immune response
  - Anti-inflammatory action
  - BP
  - HR
  - CNS activation
- Another stress hormone
- Stimulates gluconeogenesis

Cortisol

During stress or fasting:

⇧Cortisol = Stimulation of Gluconeogenesis

Result = ⇧Fuel

Cortisol Deficiency

- Many causes
- Results in:
  - Inability to stimulate gluconeogenesis during fasting and stress
  - Fasting and stress-induced hypoglycemia
- Presentation
  - Neonates = hypoketotic hypoglycemia
  - Children = ketotic hypoglycemia
- Treatment
  - Replace cortisol
  - Shortened fasting time

Sperling, M.A. (2008). *Pediatric endocrinology 3rd edition.* Philadelphia, PA: Saunders Elsevier.

Growth Hormone

- Pituitary hormone
  - ⇨ growth factor release
    - ⇨ long bone growth
- Various additional functions
- Stimulates lipolysis
- Levels ⇧ with fasting
  - ⇨ lipolysis
    - ⇨ ketogenesis

Sperling, M.A. (2008). *Pediatric endocrinology 3rd edition.* Philadelphia, PA: Saunders Elsevier.

Growth Hormone Deficiency

- Leads to impaired lipolysis and ketogenesis and hypoglycemia
- Presentation
  - Neonates = hypoketotic hypoglycemia
  - Children = ketotic hypoglycemia
- Treatment – replace growth hormone

Case Studies

Case Study 1

- 6 year old male with 2 recent episodes of fasting hypoglycemia
  - Episode 1:
    - Normal overnight fast – 12 hours
    - Difficult to arouse in the morning
    - Floppy, crying
    - No illness
    - Parents called 911
    - Glucose in ED was 42mg/dL (2.3mmol/L)
    - Large ketonuria
    - BG rose with juice and child discharged

Case Study 1

- Episode 2
  - Slightly longer overnight fast - ~15 hours
  - Very irritable, sleepy, lethargic in the morning
  - Parents tried to give juice and brought to ED
  - Glucose = 55mg/dL (3.05mmol/L)
  - Large Ketonuria
  - CO_2 = 15 mmol/L (18-28)
  - GH = 11 mg/mL (>10)
  - Cortisol = 25 mcg/dL (>18)
  - BG rose with IV dextrose and child discharged and referred to Endocrinology

Case Study 1

- Remembering he is 6, what do you think of his fasting duration? (12-15 hours)
  Short
- What do you think about his:
  - Ketonuria? (Large)
  - GH? (11 mg/mL)
  - Cortisol? (25 mcg/dL)

  Hypoglycemia not from excess insulin or GH/Cortisol deficiency

Case Study 1

- Endocrinology Clinic
  - No previous symptoms of hypoglycemia
  - Growth and development normal
  - FH: No hypoglycemia
    Father with prolonged QT syndrome
  - ROS: Child recently diagnosed with prolonged QT syndrome and started on atenolol
  - PE: Unremarkable

Case Study 1

- Why did he have low glucose levels?
  - Beta blocker = blocked epinephrine = impaired fasting adaptation = ketotic hypoglycemia
- How do we treat him?
  - Shorten fasting time
    - 10 hours when well
    - 5 hours when ill
- How long should he be able to fast at 6 years?
  - 36 hours

Case Study 2

- 3 week old male
  - Hyperbilirubinemia
  - Hypoglycemia
- Transferred to NICU from another hospital for evaluation and management of hypoglycemia
- Birth History: 38 weeks, 3047grams - AGA, maternal PIH, Apgars 6^1 and 8^5, hypoglycemia measured shortly after birth

Case Study 2

- Hypoglycemia
  - Persistent since birth - 3 weeks
  - GIR = 10mg/kg/min
  - Lowest glucose = 38mg/dL on DOL 11
- What do you think about his GIR?
  - Too high – normal max is ~6mg/kg/min
  - Indicates organic hypoglycemia disorder

Case Study 2

Critical sample

	Result	Expected
Glucose	37 mg/dL	
Insulin	<1 uIU/mL	<1
BOHB	0.32 mmol/L	>2.5
FFA	0.39 mmol/L	>2
Lactate	1.3 mmol/L	0.5-1.6
Ammonia	24 umol/L	9-33
GH	5.26 ng/mL	>10
Cortisol	0.3 mcg/dL	>15
ACP	Normal	Normal
Urine OA	Normal	Normal
Glucagon Stim	Δ 40	Δ < 25

Thoughts?

Case Study 2

Differential Diagnosis

- Congenital Hyperinsulinism
- Cortisol Deficiency
- GH Deficiency

- What should we do next?

Case Study 2

Pituitary Stimulation Testing

Time (min)	GH (ng/mL)	Cortisol (mcg/dL)
0	4.01	0.4
30	4.41	0.4
60	5.66	0.4
180	5.0	0.3

Free T4 (0.8-11.8mg/dL)	0.6
Total T4 (5-13 ug/dL)	3.3
Total T3 (0.9-2.6 ng/mL)	1.1
TSH (0.57-19.5 mcU/mL)	6.18

Case Study 2

Brain MRI:

Septo Optic Dysplasia:

- Absent septum pellucidum
- Optic nerve hypoplasia
- Ectopic posterior pituitary
- Hypoplastic pituitary stalk

Case Study 2

- Diagnosis:
  - Anterior Hypopituitarism
    - TSH
    - ACTH
    - GH
- Treatment
  - Thyroxine 44mcg daily
  - Hydrocortisone 12mg/m^2/day – tid
  - Growth hormone 0.3mg/kg/week – daily

Case Study 2

- Outcome
  - Able to fast 8 hours with BGs all >80mg/dL
  - Discharged to home

Case Study 3

- 3 year old with SOD and Anterior Hypopituitarism
- Treated with thyroxine, hydrocortisone, and growth hormone

Case Study 3

- One night he started vomiting
- Parents gave oral stress hydrocortisone
- Continued with intermittent vomiting for several hours
- He became more lethargic
- Parents called Endocrinology doctor and were told to give him IM Solucortef and come to the ED
- Parents did not give Solucortef but came right to the ED

Case Study 3

- ED
  - Arrived with hypotension and tachycardia
  - Serum glucose 17mg/dL
  - Treated with IV glucose and hydrocortisone
  - Crisis resolved
  - Residual seizure disorder, learning disability, and food aversion that were not previously present

Questions?

That's All, Folks

Thank you