Hoenig. Pathophysiology of Canine Diabetes. VCNA:SA 1995:25(3)

1. Canine diabetes is divided broadly into IDDM and NIDDM

2. IDDM
   - Etiology: immunologic destruction of beta cells + genetic susceptibility (polygenetic disorder)
   - Autoimmune disease (organ specific) where β-cells are destroyed by T lymphocyte mediated mechanisms
     - Circulating autoantibodies (against β-cell cytoplasm or cell membrane, insulin) are markers of ongoing disease process
   - Little is known about pathogenic mechanisms in the dog
     - Canine DM diagnosed very late in disease process

3. NIDDM
   - Rare in dogs – most cases observed with severe obesity
     - Increasing obesity correlates with degree of deterioration of glucose tolerance
   - Characterized by:
     - Hyperglycemia
     - Insulin resistance
     - Impaired insulin secretion
   - Contributors to development of NIDDM:
     - Beta cell function
     - Hepatic glucose production
     - Insulin mediated glucose uptake

4. Secondary Diabetes
   - Conditions seen in dogs with secondary diabetes
     - Endocrine disorders (hormones oppose action of insulin and cause insulin resistance)
       - Hyperadrenocorticism
       - Progesterone induced growth hormone abnormalities
     - Acute pancreatitis
       - Progressive destruction of pancreatic tissue

<u>General Principles</u>

- Pancreatic islets of Langerhans
  - Beta cells: produce insulin
  - Alpha cells: produce glucagon
  - Delta cells: produce somatostatin
  - PP or F cells: pancreatic polypeptide
- Beta cells compromise 60-80% of the islet
  - Form central core surrounded by 3 other cell types
  - Endocrine cells arranged in non-random distribution in dogs

IDDM

- Etiology: immunologic destruction of beta cells + genetic susceptibility (polygenetic disorder)
- Most common lesion: destruction in number and size of islets; hydropic ballooning degeneration of β-cells
- 75% of β-cells must be destroyed before hyperglycemia is observed
    - Decrease in cell mass associated with decreased insulin secretion
- Beta cells have little regenerative capacity
- Autoimmune disease (organ specific) where β-cells are destroyed by T lymphocyte mediated mechanisms
    - Circulating autoantibodies (against β-cell cytoplasm or cell membrane, insulin) are markers of ongoing disease process
    - Presence of more than 1 antibody greatly increases risk of developing DM
    - Prediabetics (humans and some animal models): may be non-lymphocyte dependent phase proceeding beta cell destruction by cytotoxic T lymphocytes
- Destruction mediated through release of beta cell proteins that are taken up by Ag presenting dendritic cells in islets
    - leads to secretion of cytokines which are toxic to beta cells through induction of free radicals
- Canine diabetes is diagnosed very late in disease process
    - As little is known about pathogenic mechanisms in the dog that lead to destruction of beta cells

NIDDM

- Heterogeneous disorder
- Rare in dogs – most cases observed with severe obesity
    - Increasing obesity correlates with degree of deterioration of glucose tolerance
- Characterized by:
    - Hyperglycemia
    - Insulin resistance
    - Impaired insulin secretion
- Contributors to development of NIDDM:
    - Beta cell function
    - Hepatic glucose production
    - Insulin mediated glucose uptake
- *Beta cell function*
    - Insulin processing and the beta cell glucose sensing device is altered
        - Altered beta cell glucose metabolism:
            - Site specific defects in transport of glucose across plasma membrane of beta cell
            - Defective phosphorylation of glucose by glucokinase
            - Increase in dephosphorylation of glucose
            - Deficiency of mitochondrial enzymes
            - Glycogen accumulation in response to high glucose concentrations
- *Hepatic glucose production*
    - Impaired insulin release, hepatic insulin resistance, hyperglucagonemia and increase in free fatty acids all act on the liver to promote gluconeogenesis → increase in hepatic glucose production
- *Insulin mediated glucose uptake*
    - Impairment of insulin secretion + insulin resistance at target tissues (liver and muscle) causes reduced clearance of glucose and reduced suppression of glucose production

Secondary Diabetes

- Conditions seen in dogs with secondary diabetes
    - Endocrine disorders:
        - Hyperadrenocorticism
        - Progesterone induced growth hormone abnormalities
        - These hormones oppose action of insulin and cause insulin resistance
    - Acute pancreatitis
        - Progressive destruction of pancreatic tissue

Questions

1. Name the 4 types of cells that make up pancreatic islet of Langerhans and their products.

2. _____% of β-cells must be destroyed before hyperglycemia is observed.
    a. 25%
    b. 50%
    c. 75%
    d. 80%

3. Name 3 conditions seen in dogs with secondary diabetes.

4. Briefly describe the proposed etiology of IDDM.

Answers

1. Name the 4 types of cells that make up pancreatic islet of Langerhans and their products
   Pancreatic islets of Langerhans
   a. Beta cells: produce insulin
   b. Alpha cells: produce glucagon
   c. Delta cells: produce somatostatin
   d. PP or F cells: pancreatic polypeptide

2. _____% of β-cells must be destroyed before hyperglycemia is observed
   a. 25%
   b. 50%
   c. 75%
   d. 80%

3. Name 3 conditions seen in dogs with secondary diabetes: acute pancreatitis, hyperadrenocorticism, progesterone induced growth hormone abnormalities

4. Describe the proposed etiology of IDDM
   Etiology: immunologic destruction of beta cells + genetic susceptibility (polygenetic disorder)
   Autoimmune disease (organ specific) where β-cells are destroyed by T lymphocyte mediated mechanisms