VETERINARY MEDICINE

New Therapeutic Options for Feline Diabetes

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Objectives

Review Feline Diabetes

Understand mechanism of action for new sodium-glucose co-transport-2 inhibitors (SGLT2)

Review the side effects and contraindications of these new drugs.

Feline Diabetes

1:100 to 1:500 cats will be affected by diabetes in their lifetime.

Type 2

- Non-insulin dependent / insulin resistance

Risk Factors

- Obesity
  - 4x more likely to develop diabetes than ideal weight cats
- Age
- Male
- Inactivity
- Steroid Use
- Breed (Burmese)

Clinical Signs

- Weight Loss
- Polyuria / Polydipsia
- Polyphagia
- Muscle Weakness / Hind limb neurologic dysfunction

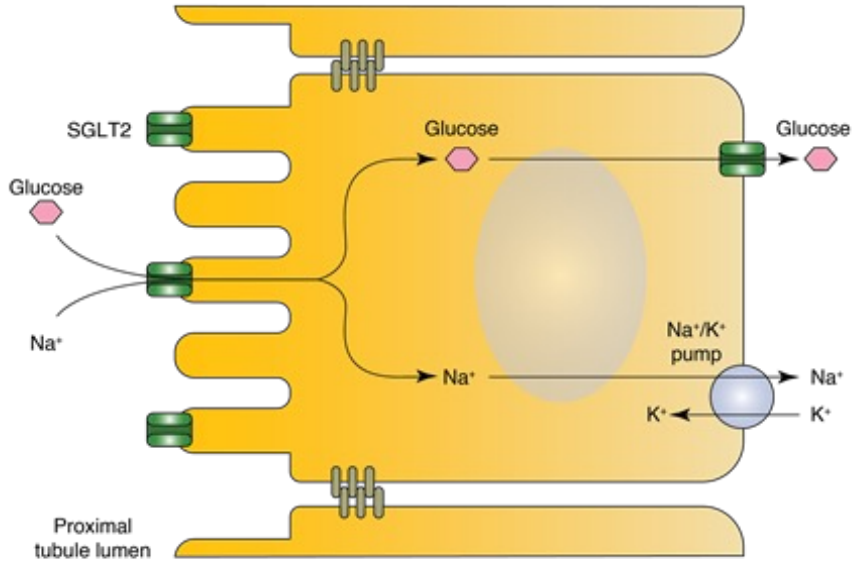
Historical Treatment Options

Exogenous Insulin

- Lente (Vetsulin)
- Protamine Zinc (Prozinc)
- Glargine (Lantus)

Low Carb / High Protein Diet

- Hills (MD)
- Purina (DM)
- Royal Canin (Glycotolerance)

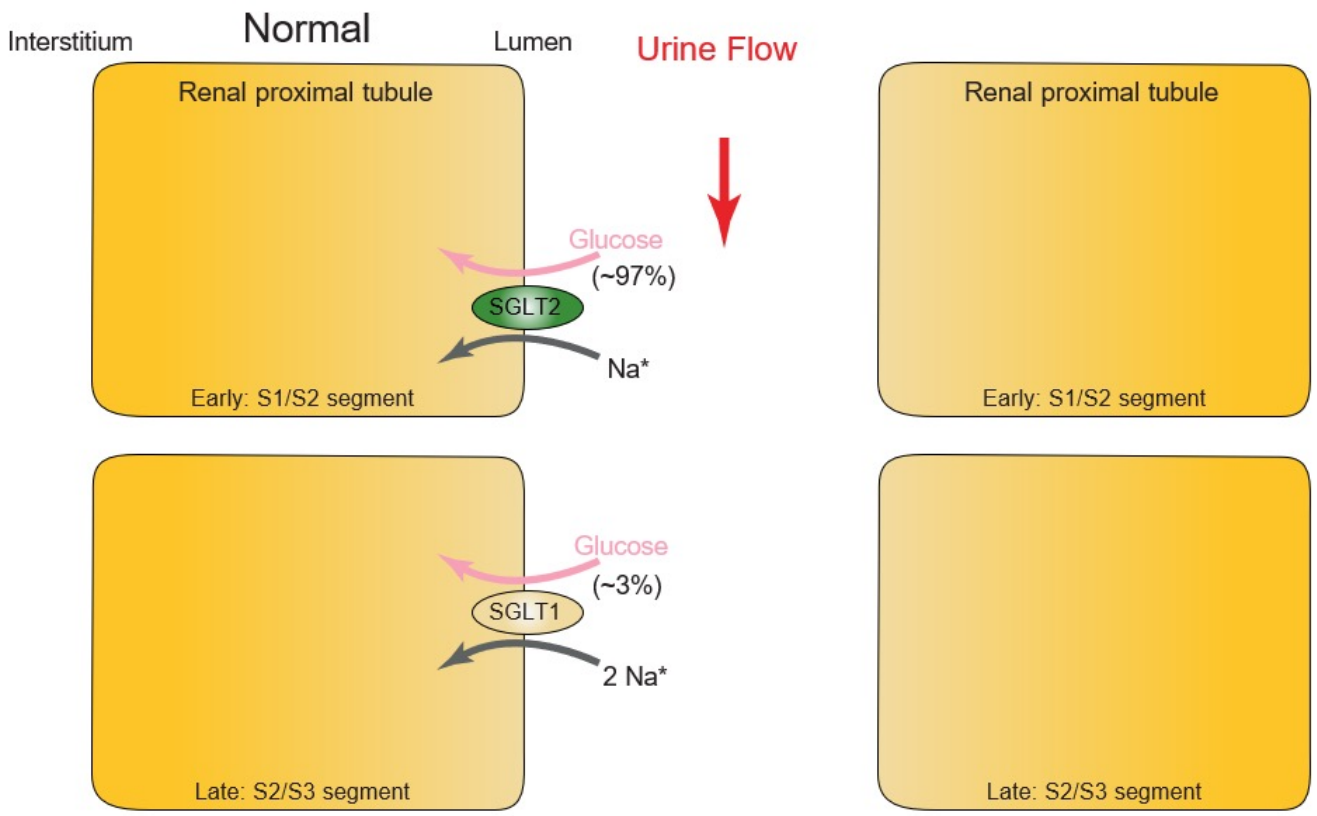


Sodium-Glucose Co-Transporters

- Membrane pumps that exchange
  - Glucose
  - Amino Acids
  - Vitamins
  - Osmolytes & Ions

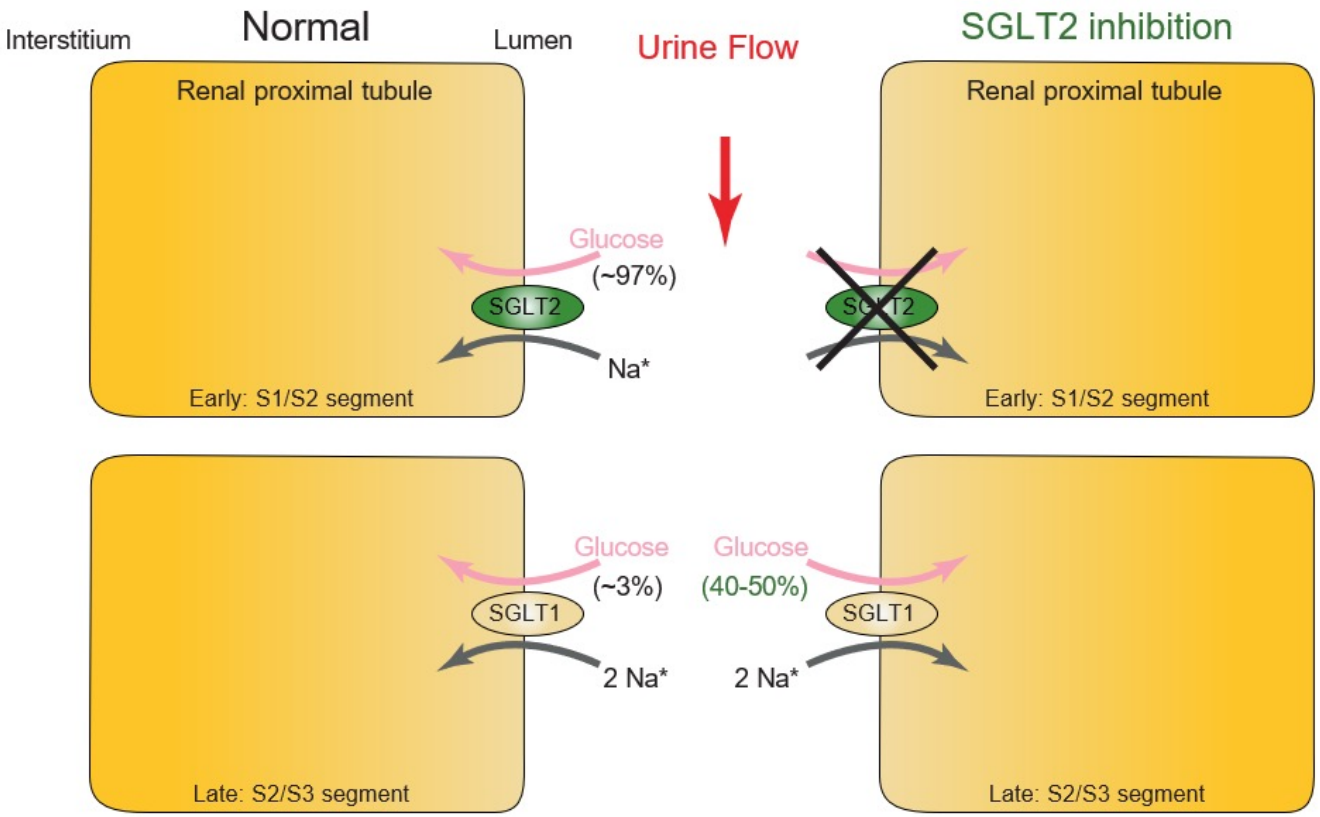
SGLT-1 and SGLT-2

- SGLT-1
  - Low capacity, High affinity
  - Mostly in the GI tract
- SGLT-2
  - High capacity, Low affinity
  - Mostly in the Proximal tubule
- Kidneys passively filter glucose through glomerulus
  - SGLT2 reabsorbs >90%
  - SGLT1 reabsorbs ~10%



SGLT-2 Inhibition

- "-flozins" highly specific to SGLT2
  - Only 40-50% of glucose reabsorbed if SGLT2 is inhibited
  - SGLT1 uptake of glucose increases
- Increase urinary glucose excretion
- Lower plasma glucose



Human Drugs

FDA approval for Type 2 DM in humans

- Canagliflozin (Invokana®) in March 2013
- Dapagliflozin (Farxiga®) January 2014
- Empagliflozin (Jardiance®) August 2014
- Ertugliflozin (Steglatro®) December 2017
- Bexagliflozin (Brenzavvy™) January 2023

Veterinary Drugs

Side Effects: Bexagliflozin(Plumbs)

- In 30% to 40% of cats, vomiting, diarrhea/loose stool, hyporexia/anorexia, and elevated BUN, USG, and serum fPL
- In 10% to 20% of cats, lethargy, dehydration, weight loss, UTIs, elevated liver enzymes (eg, AST, ALT), and elevated SDMA
- In 1% to 10% of cats, behavioral changes; inappropriate urination; hypercalcemia (total or ionized); proteinuria; elevations in creatinine, creatine kinase, and total bilirubin; ketosis/ketonuria; DKA; euglycemic DKA; pancreatitis/pancreatic necrosis; hepatopathy hepatic lipidosis, anemia/hemolytic anemia, peritonitis, urothelial carcinoma, and death
- Hypoglycemic blood glucose measurements (65 mg/dL or less) were noted during 8-hour glucose curves in 22% of cats; however, no clinical signs of hypoglycemia were observed.

Side Effects: Velagliflozin (Plumbs)

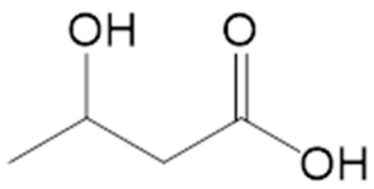
- Velagliflozin is contraindicated in cats that are hypersensitive to it, cats that were previously (or are currently) treated with insulin, and cats that have insulin-dependent diabetes mellitus. Use velagliflozin with caution in cats with a baseline serum creatinine of 1.6 to 2 mg/dL; these cats should be monitored closely for weight loss or signs of volume depletion or dehydration.
- In pre-approval field studies,[1,8] reported adverse reactions included:
  - Most frequent: diarrhea/loose stool (53%), weight loss (44%), vomiting (37%)
  - In 10% to 20% of cats (in decreasing frequency), polyuria, polydipsia, hyporexia/anorexia, hypersalivation and/or gagging, dehydration, and elevated BUN (typically less than 1.5 time the upper limit of normal)
  - In 1% to 10% of cats (in decreasing frequency), lethargy, polyphagia, UTIs, DKA or euglycemic DKA, hypercalcemia, inappropriate urination or incontinence, ketonuria, death, elevated liver enzymes (1/3 of which were greater than 2 times the upper limit of normal), hypertriglyceridemia, hyperphosphatemia, elevated fPL, pancreatitis, elevated creatinine, and hepatic lipidosis

Euglycemic Diabetic Ketoacidosis (eu-DKA)

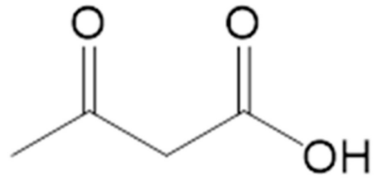
- What is euglycemic DKA?
  - DKA that occurs despite normal serum glucose
    - Occurs almost exclusively in patients on SGLT2i
    - Unlikely to have been seen in practice previously
  - Insulin administration is critical to these patients, despite normoglycemia
  - Administer dextrose along with insulin to support glucose levels
  - Get them eating
  - Treatment is very similar to “regular” DKA

Beta-hydroxybutyrate (BHBA) monitoring

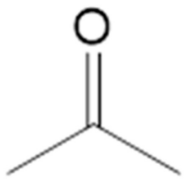
- Serum BHBA is the predominant ketoacid in DKA
  - Serum ketone levels ↑ before urine ketone levels
  - Urine dipsticks only detect acetoacetate (acetoacetic acid)
- Portable ketone monitors can measure serum BHBA
  - Abbott™ Precision Xtra© is one example
- Send out testing available through IDEXX™ and other laboratories



Beta-hydroxybutyrate



Acetoacetate



Acetone

Clinical Plan

- Physical Exam/History
  - Not “sick” – good appetite, not lethargic, otherwise healthy on PE
  - Newly diagnosed, never been on insulin
- Bloodwork
  - No evidence of significant renal or hepatic disease
  - BHBA <37 mg/dL (3.6 mmol/L) or less than <25 mg/dL (2.4 mmol/L) if Hx of renal disease or metabolic acidosis
  - No other lab values consistent with DKA including metabolic acidosis
  - Spec fPL <5.3 mcg/L

Recheck Plan

- 3-5 days later
  - BHBA
  - Weight
- 2 weeks
  - BHBA
  - Fructosamine
- 4 weeks
  - BHBA
  - Fructosamine
- 8 weeks
  - BHBA
  - Fructosamine
- Every 3 months
  - BHBA
  - Fructosamine

Use with Insulin?

- From Plumbs:
  - Bexagliflozin is contraindicated in cats that are hypersensitive to it, cats that were previously (or currently) treated with insulin, and cats that have insulin-dependent diabetes mellitus. Do not use bexagliflozin in cats with (or that have evidence of) hepatic disease or reduced renal function.
  - Velagliflozin is contraindicated in cats that are hypersensitive to it, cats that were previously (or are currently) treated with insulin, and cats that have insulin-dependent diabetes mellitus. Use velagliflozin with caution in cats with a baseline serum creatinine of 1.6 to 2 mg/dL; these cats should be monitored closely for weight loss or signs of volume depletion or dehydration.
- Issue is if the cat is insulin dependent, DKA will develop over time.
- This arose as an issue in human medicine where patients would present with signs of DKA but had normal blood glucose due to SGLT-2 use.