



Polymorphic Behavior of Nicotine Metabolism in African American and Caucasian Smokers

Mikayla Brown, Kiariah Muller, Essie Campbell, Srishti Kala, Derrick Swinton, Ph.D.
Clafin University – Department of Chemistry and Biochemistry

Abstract

Nicotine is a major component in tobacco and stimulant. It is addictive and a known carcinogen. The goal of this project is to investigate the disproportionate susceptibility of tobacco related diseases in African American smokers. The prevalence of cancer related effects due to cigarette smoking is higher among African Americans than Caucasian, although they smoke fewer cigarettes per day. Studies have shown that African Americans do not metabolize nicotine as efficiently as Caucasians. Also, it is known that nicotine influences Glycolysis. Genetic and physiological evidence suggests that the activation of serine and glycine biosynthetic pathway is a crucial process in cancer pathogenesis. We use Nuclear Magnetic Resonance and Principal Component Analysis to identify metabolite differences in a population of African American and Caucasian smokers. Our findings conclude that glycine metabolism levels are different in African American and Caucasian Smokers. This is the first research reporting on these findings. The overall significance is that researchers and practitioners will be able to develop personalized treatments for African American undergoing cancer treatment and smoking cessation. We are investigating gene variants that are differentially expressed in the two populations.

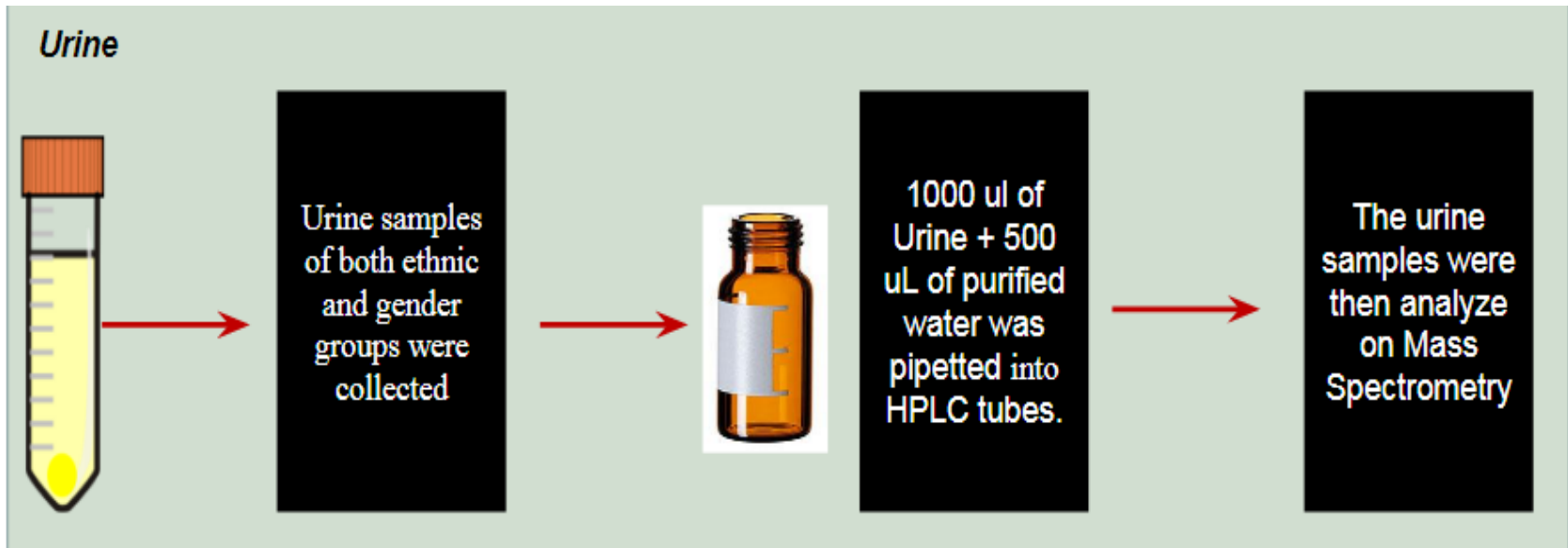
Introduction

- Effects of cigarette smoking impacts groups of all ethnic backgrounds.
- Every year 45,000 African Americans die from smoke-related diseases in the United States.
- Studies have concluded that the cessation rates amongst African Americans are lower than Caucasians despite the fact that this group smokes fewer cigarettes per day relative to Caucasians.
- Researchers believe that the differences between African American smokers and Caucasian smokers are attributable to the rate at which African Americans metabolize and detoxify nicotine and its metabolites.
- African Americans metabolizes nicotine less effectively than Caucasians
- 75% of nicotine is converted to cotinine.
- Nicotine metabolites are subsequently metabolized into their respective glucuronides
- Glucuronides are of interest because the literature concludes that they play a role in cancer.

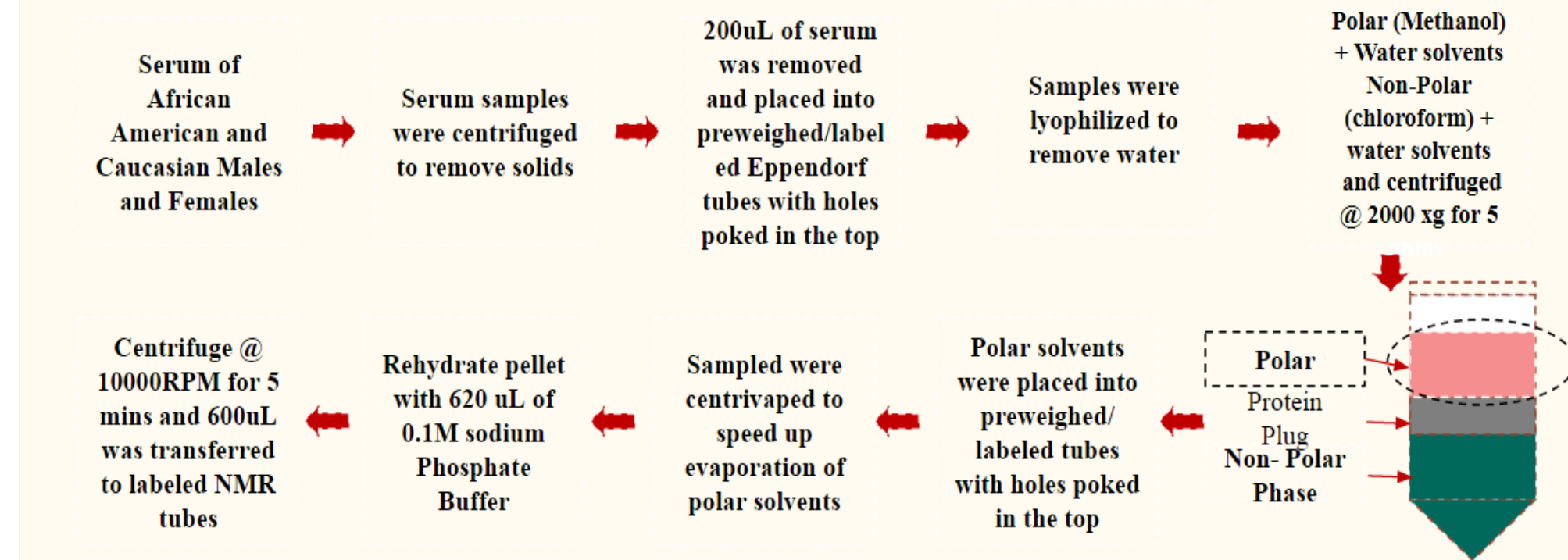
Materials and Methods

Techniques: Serum and Urine extracted samples: African American Male Smokers vs. Caucasian Male Smokers. African American Female Smokers vs. Caucasian Female Smokers.

- Liquid Chromatography/Mass spectrometry (LC/MS) fragments/breaks down molecules where each fragmental pattern of each molecule is unique. It is an analytical technique that measures the mass-to-charge ratio (M/Z) of charged particles/ions.
- Sample Collection: Samples from smokers were collected as part of an Institutional Review Board-approved study (IRB # 2008-09-15ST).



Nuclear Magnetic Resonance (NMR) spectroscopy is used to determine the content and purity of a sample as well as its molecular structure.



- Genotyping is the process of determining differences in the genetic make-up (genotype) of an individual by examining the individual's DNA sequence using biological assays and comparing it to another individual's sequence or a reference sequence.

Results

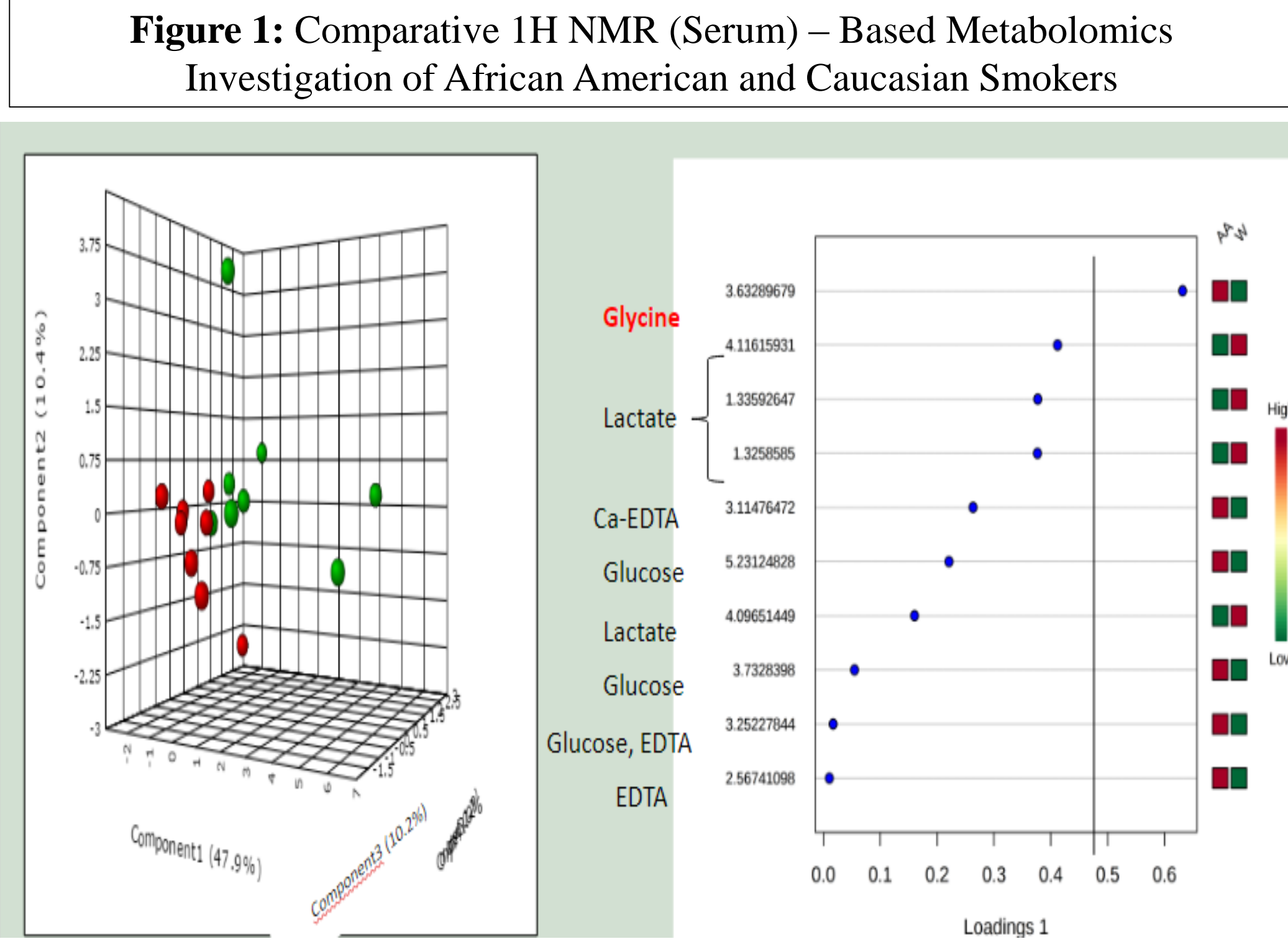
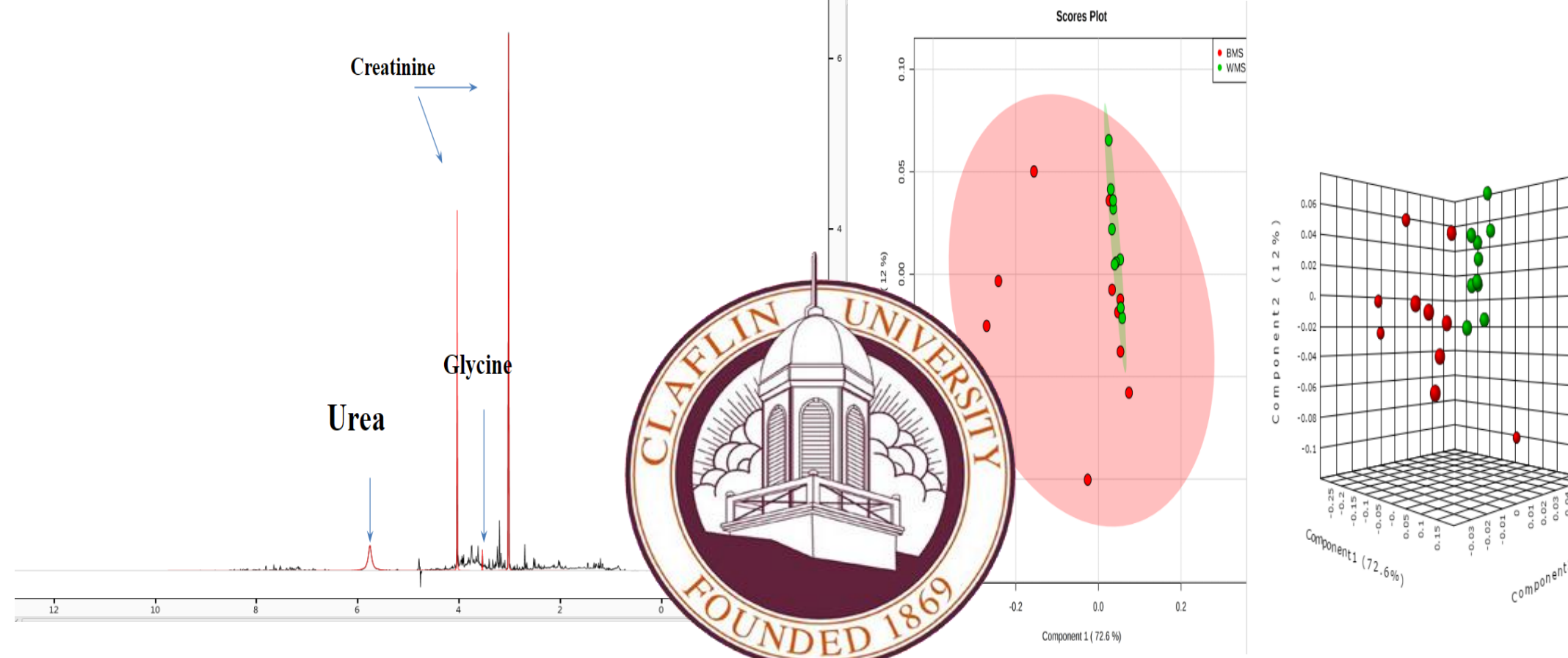


Figure 5: Glycine: Urine African American Male Smokers vs. Caucasian Male Smokers

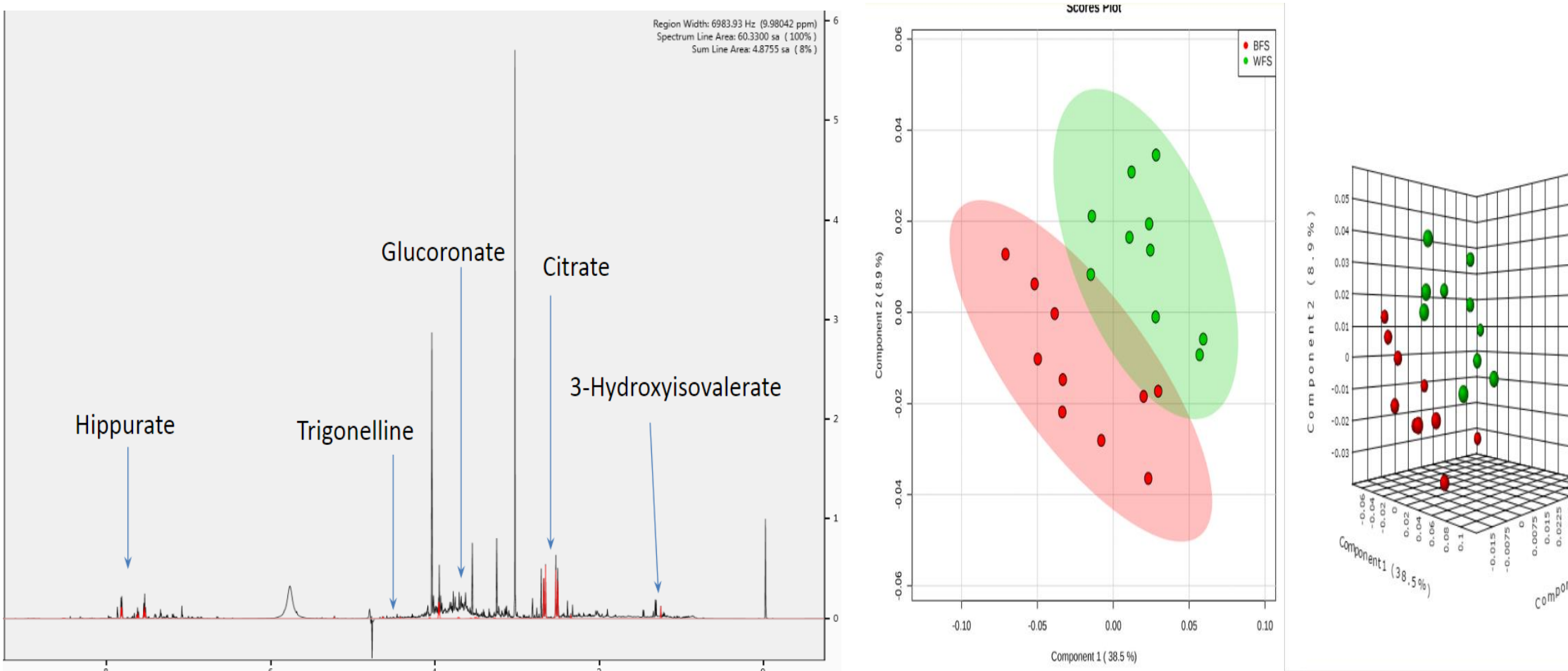
Figure 6: Glycine: Urine Samples of African Africans Males vs. Caucasians Male



There is a difference in Glycine excretion in African American Males and Caucasian Male Smokers

Figure 3: Urine African American Female Smokers vs. Caucasian Female Smokers

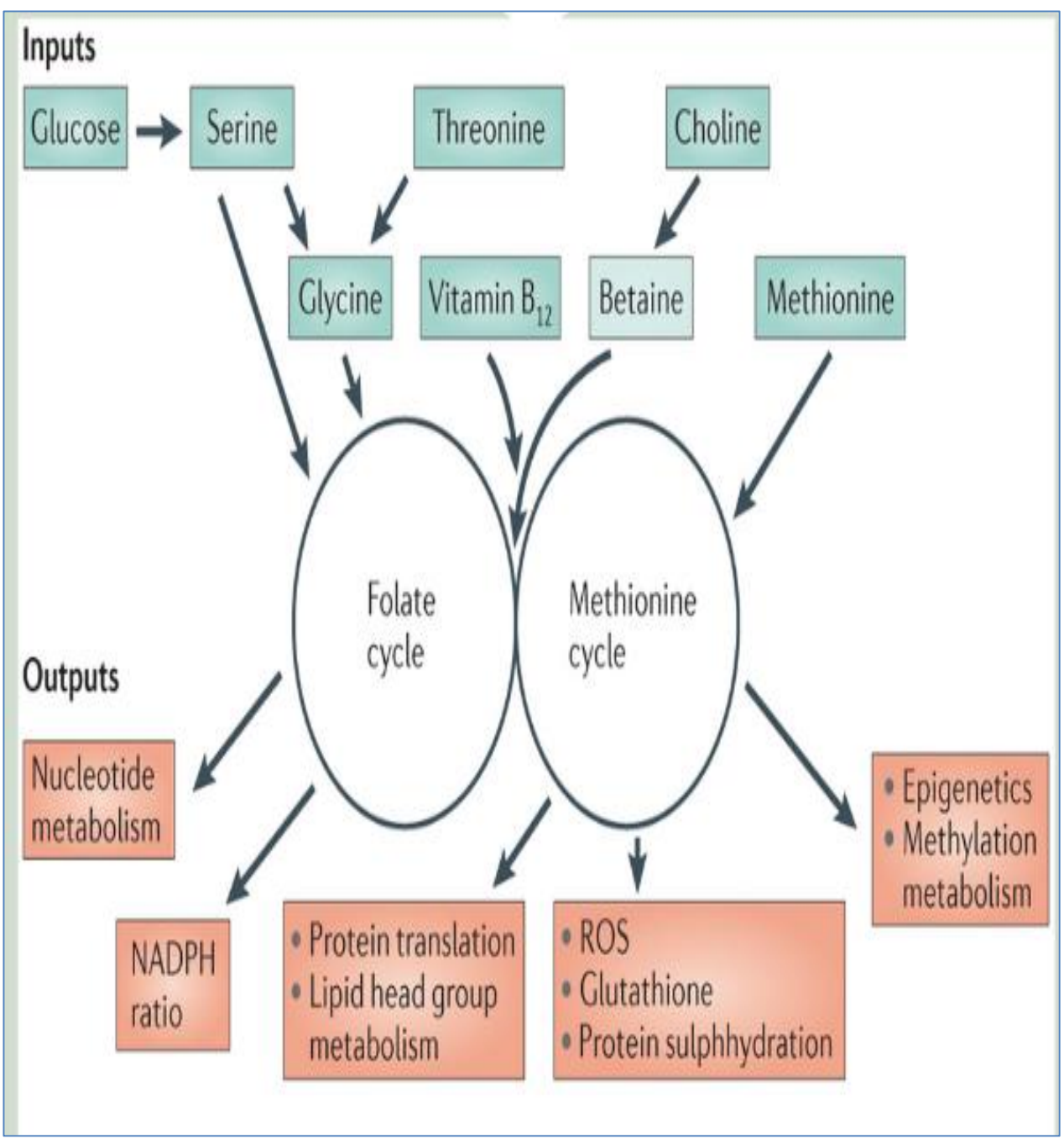
Figure 4: Urine African American Female Smokers vs. Caucasian Female Smokers



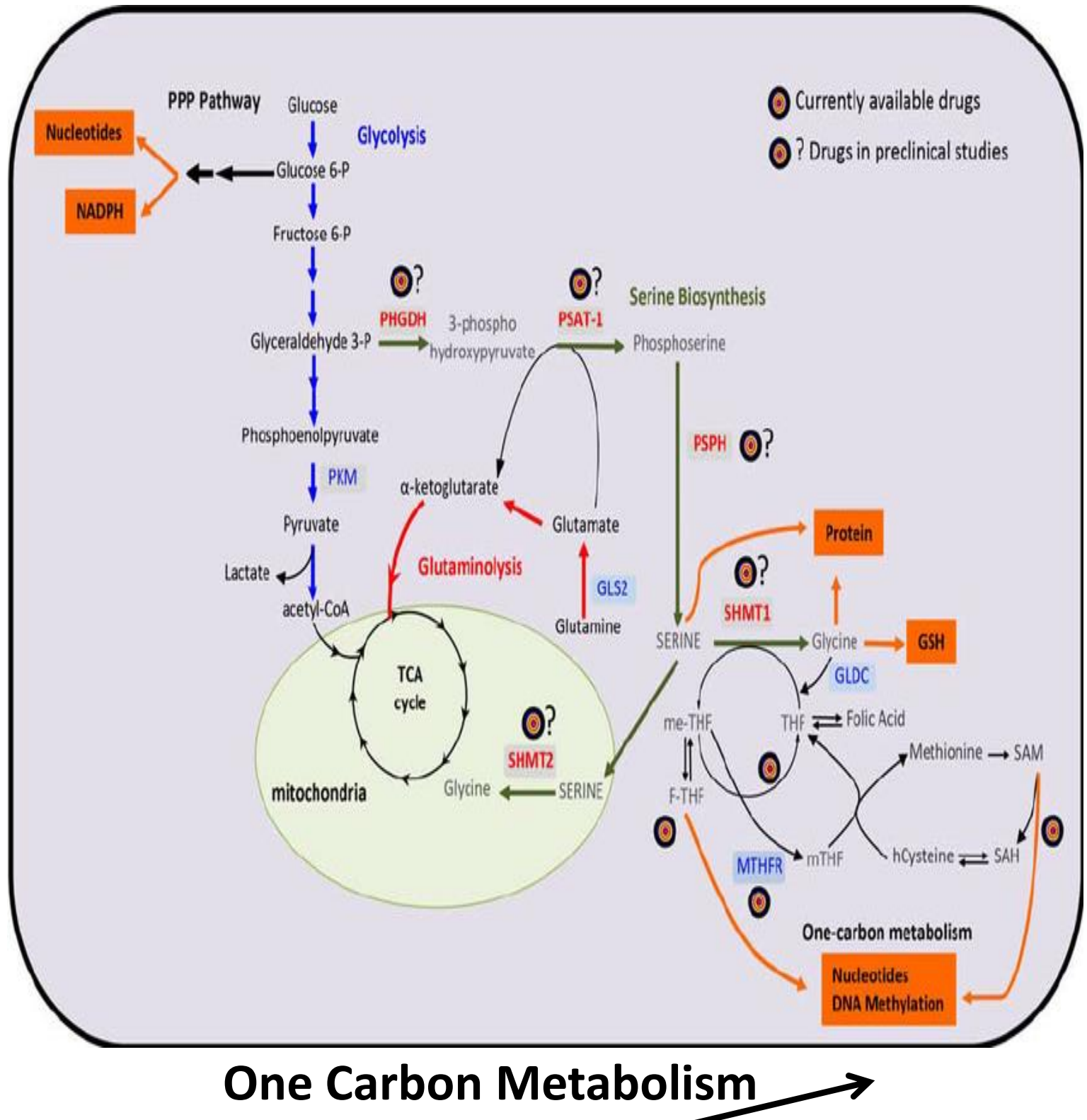
There is no disparity in Glycine's excretion in African American Female Smokers and Caucasian Female Smokers.

One-Carbon Mechanism in Cancer

- Glycine is the most basic amino acid in the aliphatic group.
- Serine is an amino acid which contains an alcohol in the R group.
- Biosynthetically linked together they provide precursors for the synthesis of nucleic acids, proteins, and lipids.



A schematic overview of the metabolic pathways involved in cancer biology



Cancer cells show an increased flux through to the glycolysis, pentose phosphate pathway and high glutamine consumption. Moreover, they also show an increased uptake of glycine and serine. In particular, the serine synthesis pathway utilizes the glycolytic intermediate glyceraldehyde-3-phosphate, which is converted by PHGDH, PSAT-1 and PSPH into serine.

In red are the cancer-associated genes. PHGDH, phosphoglycerate dehydrogenase; PSAT-1, phosphoserine aminotransferase 1; PSPH, phosphoserine phosphatase; SHMT, Serine hydroxymethyltransferase; GLS-2, glutaminase 2; GLDC, glycine decarboxylase; GSH, glutathione; MTHFR, methylenetetrahydrofolate reductase; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; THF, tetrahydrofolate; me-THF, 5,10-methylenetetrahydrofolate; F-THF, 10-formyltetrahydrofolate; mTHF, 5-methyltetrahydrofolate; PKM, pyruvate kinase; PPP, pentose phosphate pathway.

Conclusion

Glycine and serine are biosynthetically linked together they provide precursors for the synthesis of nucleic acids, proteins, and lipids. Our results conclude that there are racial and gender differences in glycine metabolism. African American Males show higher levels of glycine relative to White Male Smokers. Currently, African American Females and Caucasian Females smokers are not showing differences in glycine metabolism.

Future Plans

- We plan to perform genotyping studies to investigate hormonal regulation of Glycine synthesis and metabolism.
- We plan to explore expression of mitochondrial glycine synthesis enzymes SHMT2 and its cytosolic prelog, SHMT1, in different breast cancer types and ethnicities.

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