**Neuro-Biogenic Amines; urine  first morning void**

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>RESULT/UNIT per g creatinine</th>
<th>REFERENCE INTERVAL</th>
<th>PERCENTILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine, free</td>
<td>182 µg</td>
<td>65–400</td>
<td></td>
</tr>
<tr>
<td>Epinephrine, free</td>
<td>1.6 µg</td>
<td>1.5–20</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine, free</td>
<td>14.5 µg</td>
<td>15–80</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>94 µg</td>
<td>50–250</td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>34 µg</td>
<td>6–60</td>
<td></td>
</tr>
<tr>
<td>Gamma-aminobutyrate (GABA)</td>
<td>2.9 µmol</td>
<td>1–8</td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td>120 µmol</td>
<td>6–52</td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>5491 µmol</td>
<td>350–3500</td>
<td></td>
</tr>
<tr>
<td>Phenethylamine (PEA)</td>
<td>61 nmol</td>
<td>16–160</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>109 mg</td>
<td>35–225</td>
<td></td>
</tr>
</tbody>
</table>

**SPECIMEN DATA**

- **Comments:**
  - **Date Collected:** 03/07/2015
  - **Time Collected:** <dl: less than detection limit
  - **Date Received:** 03/16/2015
  - **Collection Period:** first morning void
  - **Date Completed:** 02/09/2015
  - **Volume:**
  - **Body Surface Area:** 0–63
  - **Methodology:** LCMS QQQ, Creatinine by Jaffe Method

©DOCTOR’S DATA, INC. • ADDRESS: 3755 Illinois Avenue, St. Charles, IL 60174-2420 • CLIA ID NO: 14D0646470 • MEDICARE PROVIDER NO: 148453

0001921
Introduction

For the analysis of neuro-biogenic amines excreted in urine, the method employed by Doctor’s Data is designed to detect and measure the free, unconjugated forms of these components. The exception is made for Metanephrine and Normetanephrine, for which the standard of care is based upon reference intervals established for the total metanephrines, which includes both the free and sulfur-conjugated forms of these components. Analysis is performed using tandem LC-MS, using calibrators prepared from certified sources.

"A Comprehensive Guide to Functional Assessment of Urinary Neuro-Biogenic Amines" is available online at www.doctorsdata.com to assist in the interpretation of neurotransmitter test results. The Guide covers neurotransmitter biochemistry, nutritional therapy options, and physiological and environmental conditions that may contribute to neurological and behavioral symptoms. Please refer to the Guide for additional information not included in these abridged interpretive paragraphs.

Urinary neuro-biogenic amines provide an overall assessment of a patient’s ability to synthesize and metabolize neurotransmitters, both in the periphery and, for some enzymes, behind the blood brain barrier as well. Alterations in urinary neurotransmitter status may be associated with a variety of conditions including metabolic disorders, mood/behavioral disorders, and in rare occasions the presence of certain tumors. Associations between urinary neurotransmitter levels and health conditions have been documented in scientific literature and may provide valuable insights as part of a comprehensive health assessment.

The activities of many enzymes are expressed differently in specific cells and organs, therefore circulating levels of their metabolites may have distinctive sources. For example, dopamine and serotonin synthesis in the body occurs primarily in the gastrointestinal tract (GIT). Urinary levels of neurotransmitters primarily reflect the activity of the peripheral and GIT enteric nervous systems. Up to 20% of urinary neurotransmitters are estimated as originating in the CNS.

Enzymes and receptors involved in neurotransmitter metabolism may be subject to mutations and single nucleotide polymorphisms (SNPs). A lack of nutritional cofactors (vitamins, minerals) required for normal enzyme function may also decrease enzymatic activity and neurotransmitter levels. Enzymatic defects in synthesis or metabolism may affect levels of neurotransmitters, and normal neurotransmitter receptor function is necessary for normal neurotransmitter activity. Neurotransmitter levels may also be influenced by diet, lifestyle and other health conditions such as high sodium diet, age, gender, body mass index, kidney function, environmental exposures, infection and tobacco use.

References:


Kaidanovich-Beilin, O; Cha, DS; McIntyre RS. (2012) Crosstalk between metabolic and neuropsychiatric disorders, F1000 Biology Reports vol. 4 p. 14.

Norepinephrine LOW

The level of norepinephrine is lower than expected in this sample. Norepinephrine is a catecholamine hormone and neurotransmitter secreted by the adrenal gland. It is the principal neurotransmitter in sympathetic nerve endings. Norepinephrine may help regulate vigilant attention, cognition and sleep. Studies indicate that the brain contributes at most 20% of circulating norepinephrine levels.

Low levels of norepinephrine may be associated with conditions such as orthostatic hypotension, dopamine beta-hydroxylase (DBH) enzyme deficiency and Menke's disease. Alpha-2 agonistic pharmaceuticals decrease sympathetic nerve outflow and norepinephrine levels. Metirosine therapy may decrease norepinephrine levels. Surgical sympathectomy or medical conditions that disrupt autonomic nerve functions may also decrease norepinephrine levels. Low levels of precursor amino acids phenylalanine or tyrosine, or low levels of the precursor neurotransmitter dopamine may result in low norepinephrine levels.

The synthesis of norepinephrine from dopamine requires Vitamin C and copper. About half of all norepinephrine is produced in the gastrointestinal tract, pancreas and spleen. Most of the norepinephrine produced by these mesenteric organs is removed from portal vein blood by the liver and converted to vanillylmandelic acid (VMA) for excretion.

References:


Glutamate HIGH

Glutamate is a non-essential amino acid that acts as an excitatory neurotransmitter for metabolic signaling pathways. Glutamate signaling affects neuronal maturation, plasticity and higher cognitive functions.

Excess glutamate signaling, and its effects, has been termed “excitotoxicity” and is considered a contributing factor in the neurodegeneration seen in Huntington’s disease, Alzheimer’s disease,
amyotrophic lateral sclerosis (ALS), multiple sclerosis, stroke and fibromyalgia. Animal studies indicate that acute stressors may cause transient elevations in extracellular glutamate. Glutamate signaling may occur through a variety of glutamate receptors. N-methyl-D-aspartate (NMDA) receptor signals are the most complex, requiring both glutamate and glycine to function.

The blood-brain barrier prevents the passage of glutamate. Astroglial cells are the primary source of glutamate in the CNS. Any glutamate released into the synapse is cleared by excitatory amino acid transporters (EAAT) found on the astroglia. EEATs, unless damaged or defective, keep extracellular glutamate levels low and insufficient for glutamate receptor signaling. EAAT functions are inhibited by oxidative stress. Extracellular glutamate may alter activity by binding with extra-synaptic high affinity glutamate receptors. Extracellular glutamate levels may also accumulate due to defects in the glutamate-glutamine cycle which removes ammonia from the CNS.

Enteric glial cells in the gastrointestinal tract may be important in glutamate signaling within the gut as neurotransmitter receptors and glial cells respond to dietary L-glutamate and monosodium glutamate (MSG). Gastrointestinal microbes may also affect glutamate levels.

References:

Akiba, Y; Kaunitz, JD. (2009), Luminal chemo sensing and upper gastrointestinal mucosal defenses. Am J Clin Nutr vol. 90 (3) p. 826S-831

Bridges, R; Lutgen, V; Lobner, D; et al (2012), Thinking outside the cleft to understand synaptic activity: contribution of the cystine-glutamate antiporter (System xc-) to normal and pathological glutamatergic signaling. Pharmacological Reviews vol. 64 (3) p. 780-802

Bridges, RJ; Natale, NR; Patel, SA. (2012), System xc(c) cystine/glutamate antiporter: an update on molecular pharmacology and roles within the CNS. British Journal of Pharmacology vol. 165 (1) p. 20-34.

Burrin, DG; Stoll, B. (2009), Metabolic fate and function of dietary glutamate in the gut. Am J Clin Nutr vol. 90 (3) p. 850S-56S.

Cotman, CW; Kahle, JS; Miller, SE; et al. (2000), Excitatory Amino Acid Neurotransmission Neuropsychopharmacology û 5th Generation of Progress. Lippincott, Williams, & Wilkins, Philadelphia, Pennsylvania.


Labow, BI; Soubia, WW; Abcouwer, SF. (2001), Mechanisms governing the expression of the enzymes of glutamine metabolism- glutaminase and glutamine synthetase. J. Nutr. vol. 131 (9) p. 2467S-2474


© 1999-2015  Doctor's Data, Inc.


Glycine High

The level of glycine is higher than expected in this sample. Glycine is a non-essential amino acid that acts as a neurotransmitter in the central nervous system (CNS). Glycine is inhibitory when bound to glycine receptors in the spinal cord, brain or retina, and is considered inhibitory in the CNS. The presence of glycine transporters on glial cells suggests that glycine may also have neuromodulatory effects. Glycine is an essential ligand with glutamate for N-methyl-D-aspartate (NDMA) receptor excitatory signaling.

Animal studies indicate that elevated glycine levels may severely impair energy use in the CNS. Genetic defects may result in glycine encephalopathy. Elevated levels of glycine in the CNS may result in intellectual disability, poor muscle tone, chorea, and respiratory or feeding difficulties (infants). This condition is characterized by non-ketotic hyperglycinemia (NHK) and elevated urinary glycine. Most cases are diagnosed during infancy, although occasionally a patient will have a milder, atypical form of NHK with onset from late infancy to adulthood. Genetic variation in the glycine receptor may contribute to seizure disorders, and may also affect neuronal excitability and plasticity. Mutations of glycine receptor subunits have been associated with hereditary hyperekplexia (startle disease). Glycine supplements may be used in conjunction with pharmaceutical supports for schizophrenia or psychosis, and may result in elevated urinary glycine.

The glycine cleavage complex (GCC) metabolizes glycine and is comprised of four different proteins. GCC requires vitamin B6 and tetrahydrofolate as cofactors. Alternately, glycine may be converted to serine by serine hydroxymethyltransferase, which also requires vitamin B6.

High levels of glycine may interact with clozapine and decrease the drug’s effect.

References:


Busanello, ENB; Moura, AP; Viegas, CM; et al. (2010), Neurochemical evidence that glycine induces bioenergetical dysfunction. Neurochemistry International vol. 56 (8) p. 948-954.

Petrus, C; Badenhorst, S; Erasmus, E. (2014), A new perspective on the importance of glycine conjugation in the metabolism of aromatic acids. Drug Metab Rev. 2014; 46(3):343-61 (ISSN: 1097-9883)

Creatinine

The urinary creatinine concentration (CC) presented in this report represents the actual creatinine concentration in the specimen that was submitted. Under normal conditions, the rate of excretion of creatinine is quite constant and highly correlated with lean body mass (muscle). However, the CC can vary significantly as a function of urine volume. An unusually high CC most likely indicates poor hydration of the patient at the time of the urine collection. A very low CC most likely indicates unusually high fluid consumption, or perhaps the influence of diuretics. If the urine specimen is very dilute (extremely low CC), the accuracy of the neurotransmitter analysis may be compromised due to analytical detection limits. It is emphasized that the CC in this specimen should not be utilized to assess renal function or glomerular filtration. For that purpose, one should perform a bona fide creatinine clearance test.

For a given age and gender, intra-individual variability in daily creatinine excretion can vary by as much as two-fold. Therefore, to more accurately assess neurotransmitter status using a random collection, the reported values for each analyte are expressed per gram "normalized" creatinine.