

# The dual-gate lumen model of renal monoamine transport

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**Abstract:** The three-phase response of urinary serotonin and dopamine in subjects simultaneously taking amino acid precursors of serotonin and dopamine has been defined.<sup>1,2</sup> No model exists regarding the renal etiology of the three-phase response. This writing outlines a model explaining the origin of the three-phase response of urinary serotonin and dopamine. A “dual-gate lumen transporter model” for the basolateral monoamine transporters of the kidneys is proposed as being the etiology of the three-phase urinary serotonin and dopamine responses.

**Purpose:** The purpose of this writing is to document the internal renal function model that has evolved in research during large-scale assay with phase interpretation of urinary serotonin and dopamine.

**Patients and methods:** In excess of 10,000 urinary monoamine assays from more than 7,500 patients were analyzed. The serotonin and the dopamine phase were determined for specimens submitted in the competitive inhibition state. The phase determination findings were then correlated with peer-reviewed literature.

**Results:** The correlation between the three-phase response of urinary serotonin and dopamine with internal renal processes of the bilateral monoamine transporter and the apical monoamine transporter of the proximal convoluted renal tubule cells is defined.

**Conclusion:** The phase of urinary serotonin and dopamine is dependent on the status of the serotonin gate, dopamine gate, and lumen of the basolateral monoamine transporter while in the competitive inhibition state.

**Keywords:** serotonin, dopamine, basolateral, apical, kidney, proximal

## Introduction

The first step in development of the model was validation of peer-reviewed literature. Scientific knowledge of the monoamines (serotonin, dopamine, norepinephrine, and epinephrine) has grown significantly since 1990. Along with this growth in knowledge, some of the science originally thought to be correct has been discredited. In contrast to earlier writings it is now known that monoamines do not cross the blood-brain barrier. Monoamines are not simply filtered at the glomerulus then excreted into the urine. Urinary monoamine levels are not a direct assay of the peripheral or central nervous system monoamine levels. Interpretation of urinary monoamine assays is more complex than simply determining if urinary serotonin and dopamine levels found on assay are high or low. Under normal conditions, significant amounts of serotonin and dopamine filtered at the glomerulus do not make it to the final urine. Serotonin and dopamine (herein referred to as “monoamines”) found in the final urine are newly synthesized in the kidneys.<sup>1,2</sup>

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The monoamines and their amino acid precursors are filtered at the glomerulus then enter the proximal tubules of the kidneys. They are transported by organic cation transporters out of the proximal tubules into the proximal convoluted renal tubule cells. The monoamines filtered at the glomerulus are metabolized in the proximal convoluted renal tubule cells. Very little of these monoamines filtered at the glomerulus are found in the final urine of normal subjects. Monoamine amino acid precursors filtered at the glomerulus are synthesized in the proximal convoluted renal tubule cells into new monoamines, which are then detected in the final urine.<sup>2</sup>

Serotonin and dopamine exist in two states: the “endogenous state” found when no additional amino acid precursors are being administered, and the “competitive inhibition state” found when the amino acid precursors of both serotonin and dopamine are being administered.<sup>3</sup>

Prior to discussing the dual-gate lumen model, the following discussion of the three-phase urinary response is put forth based on previous peer reviewed literature.<sup>2</sup>

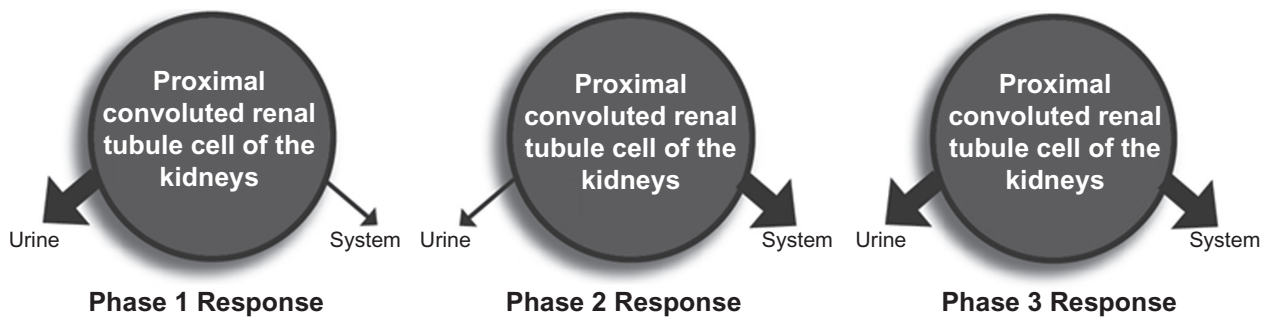
Literature notes: “Urinary monoamine neurotransmitter testing prior to initiation of serotonin and dopamine amino acid precursors is of no value. There is no correlation between

baseline testing and urinary neurotransmitter phases once the patient is taking amino acid precursors. It is not necessary or even useful to measure baseline urinary neurotransmitters in treatment”.<sup>2,4</sup>

Urinary monoamine neurotransmitters are neurotransmitters that are synthesized by the kidneys and excreted into the urine or secreted into the system via the renal veins.<sup>1,2,5</sup> With simultaneous administration of serotonin and dopamine amino acid precursors, three phases of urinary neurotransmitter response have been identified on laboratory assay of the urine (Figures 1 and 2). The three phases of response apply to both serotonin and dopamine. In all the life forms tested that have kidneys along with serotonin and catecholamine systems, the three phases of urinary neurotransmitter response exist.<sup>40</sup> In review of the literature, it would appear that the three phases of urinary response to neurotransmitters were present in previous writings but were not identified as such. For example, a 1999 article notes that administration of L-dopa can increase urinary dopamine levels (phase 1) and decrease urinary serotonin levels (phase 1).<sup>2,6</sup> To determine the phase of serotonin and dopamine with certainty require two urinary monoamine neurotransmitter



**Figure 1** The three phases of urinary neurotransmitter excretion in response to amino acid dosing. The horizontal axis is not labeled with specific amounts; it reflects the general trend seen in the population. Amino acid dosing needs are highly individualized. The dosing level needed to inflect into the next level varies greatly throughout the general population. For example, some patients inflect into phase 3 on 37.5 mg of 5-HTP per day, while others need as high as 3,000 mg per day (source: DBS Labs database).



**Figure 2** The three phases of urinary response to amino acid dosing (Two urinary neurotransmitter tests are required to determine the phase with certainty). PHASE 1: In phase 1, as the amino acid dosing increases or decreases the urinary serotonin or dopamine decreases or increases respectively. In phase 1, there is inappropriate excretion of neurotransmitters into the urine instead of the system where they are needed. PHASE 2: In phase 2, as the amino acid dosing increases or decreases the urinary serotonin or dopamine is low ( $<80 \mu\text{g/g}$  creatinine for serotonin or  $<300 \mu\text{g/g}$  creatinine for dopamine). In phase 2, there is no inappropriate excretion of neurotransmitters into the urine. The neurotransmitters are being excreted appropriately into the system and the urine. PHASE 3: In phase 3, as the amino acid dosing increases or decreases the urinary serotonin or dopamine increases or decreases respectively. In phase 3, there are adequate systemic serotonin and dopamine levels. The excess serotonin and dopamine are appropriately excreted into the urine.

assays to be performed with the subject simultaneously taking a different amino acid dosing of dopamine and/or serotonin amino acid precursors on each test and comparing the results.<sup>1,2</sup>

In phase 1, monoamine neurotransmitters synthesized by the kidneys are excreted into the urine instead of being secreted into the system via the renal vein where they are needed (Figures 1 and 2). Increasing the amino acid dose in phase 1 will correct the problem of urinary monoamine excretion into the urine at the expense of secretion into the system. The amino acid precursor dosing of serotonin and dopamine, where the individual patient is in phase 1 varies widely in the population. The level at which the urinary serotonin is no longer in phase 1 ranges from dosing of 5-HTP per day to 3,000 mg of 5-HTP per day. The level at which the urinary dopamine is no longer in phase 1 ranges from no L-dopa (with the use of L-tyrosine only in some subjects) to 540 mg of L-dopa per day in the subjects not under treatment for Parkinsonism or Restless Leg Syndrome.<sup>1,2</sup>

By increasing the amino acid dosing of serotonin and dopamine precursors above the dosing of phase 1, the phase 2 response is observed (Figures 1 and 2). In phase 2, urinary monoamine levels are low ( $<475$  micrograms dopamine per gram of creatinine or  $<80$  micrograms serotonin per gram of creatinine, the neurotransmitter – creatinine ratio compensates for dilution of the urine), and the inappropriate excretion of neurotransmitters into the urine has ceased. When in phase 2, serotonin and/or dopamine is being primarily secreted into the system and not excreted into the urine. The model used to explain phase 2 is, “inappropriate excretion of neurotransmitters has now ceased as the amino acid precursor dosing is increased and systemic levels are not increasing appropriately.”<sup>1,2</sup>

As serotonin and dopamine amino acid precursors are increased above the phase 1 and the phase 2 levels, all subjects enter the phase 3 response (Figures 1 and 2). Further increases in the amino acid dosing lead to increases in urinary dopamine and serotonin neurotransmitter levels if they are in phase 3. Phase 3 represents appropriate secretion into the system and appropriate excretion of excess neurotransmitters synthesized by the kidneys into the urine.<sup>1,2</sup>

## Material and methods

Prior to this writing there has been no peer-reviewed publication setting forth an internal renal model to explain the etiology of the three-phase response of urinary serotonin and dopamine. This model is based on analysis of in excess of 75,000 monoamine assays (serotonin, dopamine, norepinephrine, and epinephrine) from more than 7,500 human subjects with samples obtained either in the endogenous state or the competitive inhibition state under conditions covered in previous writings on the three-phase response.<sup>1,2</sup> The urinary phase of serotonin and dopamine was determined for assay samples obtained in the competitive inhibition state. Knowledge gained through large-scale phase interpretation in correlation with peer-reviewed renal literature is the basis for the model.

Urine samples were collected 6 hours prior to bedtime with 4:00 PM being the most frequent collection time point. The samples were obtained in 6 N HCl to preserve dopamine and serotonin. The urine samples were collected after a minimum of one week at a specific dose of the precursor being consumed. Samples were shipped to DBS Laboratories (Duluth, MN, USA) under the direction of one of the authors (Dr T Uncini, hospital-based dual board certified laboratory pathologist). Urinary dopamine and serotonin were assayed

utilizing commercially available radioimmunoassay kits (3 CAT RIA IB88501 and IB89527, both from Immuno Biological Laboratories, Inc., Minneapolis, MN, USA). The DBS laboratory is accredited as a high complexity laboratory by CLIA to perform these assays.

## Results

When in the three-phase response, the two systems become completely intertwined to the point that changes in one system will affect not just that system but the other system as well.<sup>2</sup> With administration of the dopamine precursor L-dopa and the serotonin precursor 5-HTP there is no biochemical feedback regulation in the synthesis of dopamine and/or serotonin, respectively. There is a direct proportion between the amount of L-dopa and 5-HTP administered and the amount of dopamine and serotonin synthesized.<sup>1,2</sup>

The three-phase response occurs only in the competitive inhibition state. It is the response of the newly synthesized renal serotonin and dopamine found in the urine to the manipulation of serotonin and/or dopamine amino acid precursor dosing. With each simultaneous urinary assay of serotonin and dopamine in the competitive inhibition state, a three-phase model for serotonin and dopamine must be independently conceptualized. Serotonin and dopamine may be in any one of the three phases simultaneously, with one exception. Urinary serotonin and dopamine are never found in phase 1 simultaneously.<sup>1,2</sup>

In Figure 1, increasing or decreasing one or both amino acid precursors of serotonin or dopamine in the competitive inhibition state allows for determination of the urinary phase of both serotonin and dopamine.

The following renal model is the basis for conceptualization of the dual-gate lumen model. While numerous transport and cell wall crossing mechanisms exist in the proximal convoluted renal tubule cells, primary transport out of the proximal convoluted renal tubule cells of the newly synthesized serotonin and dopamine is via the organic cation transporters (OCT). Newly synthesized serotonin and dopamine exit the proximal convoluted renal tubule cells primarily by one of two routes. They are either transported across the basolateral membrane via the basolateral transporter (an OCT transporter) or transported across the apical membrane via the apical transporter (an OCT transporter).<sup>7,8</sup> For the purpose of this model, the basolateral membrane transporter (OCT) is deemed as being dominant. Newly synthesized serotonin and dopamine, not transported across the dominant basolateral membrane, are transported out of the proximal convoluted renal tubule cells by the apical transporters and detected

in the final urine as waste. In reviewing urinary assays of serotonin and dopamine in the competitive inhibition state, the interpreter is viewing monoamines not transported by the basolateral monoamine transporters (organic cation transporters). While numerous other renal functions and interactions have been described, these forces are viewed as minor to insignificant in comparison to the dominating force of the basolateral and apical transport on the newly synthesized monoamines.

## Discussion

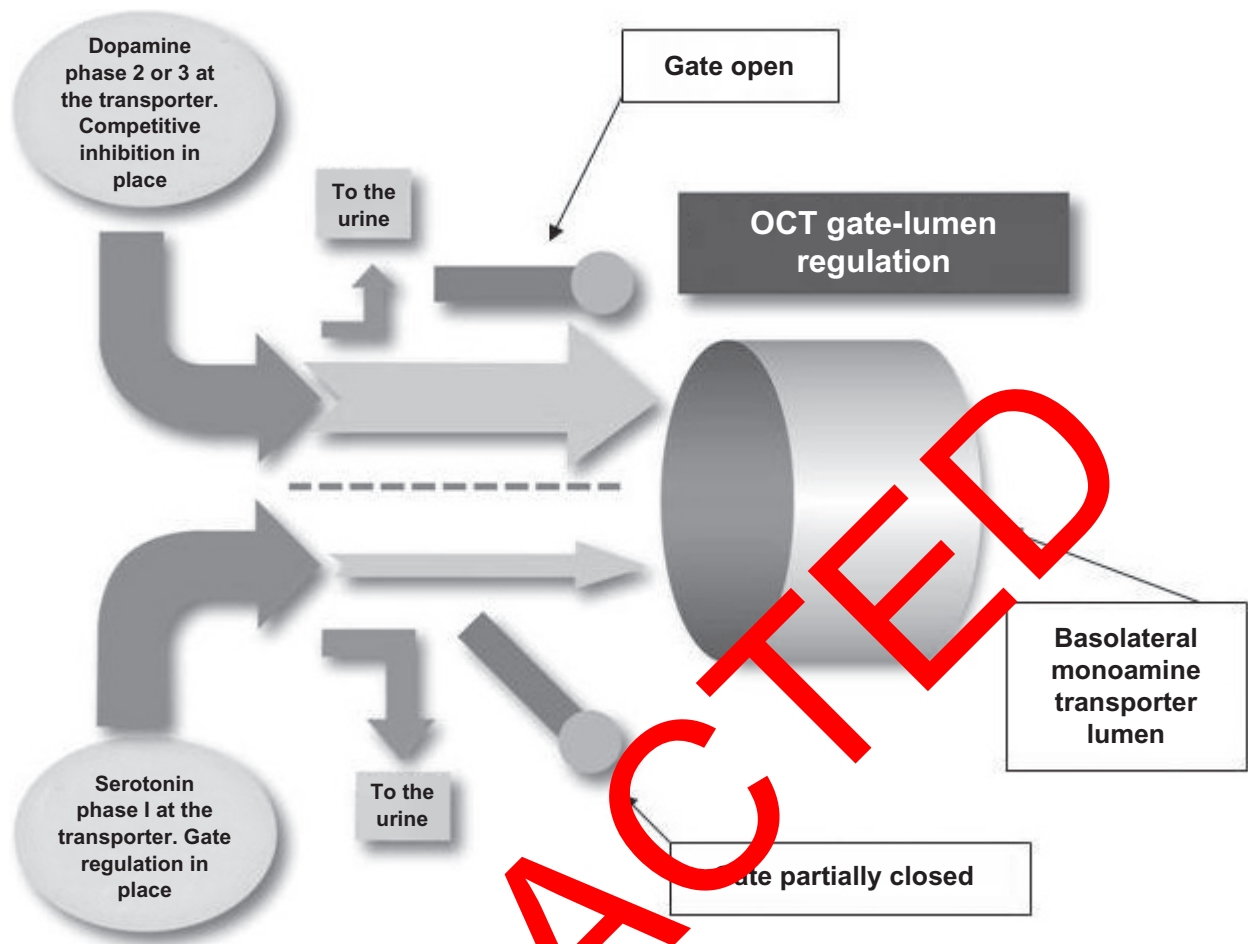
Models of organic cation transporters of serotonin and dopamine have been defined in the past. One such model was the "gate-lumen-gate model".<sup>9</sup> The gate-lumen-gate model and other models do not explain the phenomenon observed under the three-phase urinary response when both serotonin and dopamine are in the competitive inhibition state.

It is proposed that the basolateral monoamine transporter is a "dual-gate lumen transporter" (Figure 3). The transporter has a serotonin gate and a dopamine gate at the transporter entrance, which function independently of each other.

Primary forces affecting transport through the basolateral monoamine transporter and the apical monoamine transporter are the status of the basolateral monoamine transporter serotonin and dopamine gates, and lumen saturation. The serotonin and dopamine gates at the entrance of the basolateral monoamine transporters can be either partially closed (impeding transporter lumen access by the monoamines) or open (with no impedance). The status of the basolateral monoamine transporter lumen is either saturated or not saturated.

Correlations of the three-phase model and dual-gate lumen model considerations are as follows. In phase 1 the monoamine gate is partially closed impeding access to the transporter lumen. In phase 2 and phase 3 the monoamine gate is open giving full access of the monoamine to the transporter lumen. In phase 1 and phase 2 basolateral monoamine transport through the lumen is not saturated. In phase 3 the basolateral monoamine transport through the lumen is saturated. Opening and closing of a gate is not solely dependent on changes in associated monoamine levels. The opening and closing of the gates is dependent on the total amount of serotonin and dopamine presenting at the transporter.

In the competitive inhibition state, a serotonin gate or a dopamine gate in phase 1 (partially closed) can be opened or closed by adding or subtracting the total amount of amino acid precursors administered. This causes an increase or decrease in the total amount of serotonin and dopamine



**Figure 3** The dual-gate lumen model. The basolateral monoamine transporters contain three key components: a serotonin gate, a dopamine gate, and a lumen.

presenting at the transporter. As the gate opens, more monoamine has access to the transporter and is transported, causing a drop in the amount of monoamine transported by the apical transporter and found in the final urine.

In phase 2 the gate is open with full access to the transporter by monoamine. The transporter effectively transports most of the monoamine through the lumen leading to a very small amount of monoamine being transported by the apical transporter and found in the final urine.

In phase 3 the gate is open and the transporter is saturated. Increases or decreases in the total amount of the monoamine presenting at the transporter will lead to an increase or decrease in the amount of monoamine found in the final urine. When both serotonin and dopamine are in phase 3, increasing the amino acid precursor dosing of one monoamine will cause increased transport of the associated monoamine at both the basolateral and apical transporters. Due to competitive inhibition, transport of the other monoamine will decrease at the basolateral transporter and increase at the apical transporter. Administration of one amino acid precursor with both

serotonin and dopamine in phase 3 leads to an increase in apical transport of both monoamines with associated increase of urinary levels of both on assay.

## Conclusion

Assay of the urinary monoamines, serotonin and dopamine, in the competitive inhibition state is an assay of the newly synthesized serotonin and dopamine of the kidneys not transported by the basolateral monoamine transport. The two primary forces affecting transport across the basolateral membrane and responsible for the three-phase response are the status of the basolateral monoamine transporter gates and the saturation of the lumen. Proper assay interpretation in the competitive inhibition state is a determination of the states of serotonin and dopamine phases relative to the basolateral monoamine transporter status. It is not the intent of this writing to explore all known aspects of the basolateral monoamine transporter, apical monoamine transporter properties, or renal properties in the context of the three-phase response. The model presented here is intended to

be used as a foundation and reference point for continuing discussion, further studies, refinement of the model, and future investigation of renal and urinary serotonin and dopamine response to amino acid manipulation in the competitive inhibition state.

## Acknowledgment/disclosure

Marty Hinze and Thomas Uncini are owner and medical director of DBS Labs Duluth, Minnesota. Alvin Stein reports no disclosure.

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