Both stimulatory and inhibitory effects of dietary 5-hydroxytryptophan and tyrosine are found on urinary excretion of serotonin and dopamine in a large human population

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Department of Physiology and Pharmacology, University of MN Medical School Duluth, Duluth, MN, USA; ²Chief Medical Examiner, St. Louis County, Hibbing, MN, USA; ³Clinical Research, NeuroResearch Clinics, Inc., Duluth, MN, USA Abstract: Amino acid precursors of dopamine and serotonin have been administered for decades to treat a variety of clinical conditions including depression, anxiety, insomnia, obesity, and a host of other illnesses. Dietary administration of these amino acids is designed to increase dopamine and serotonin levels within the body, particularly the brain. Convincing evidence exists that these precursors normally elevate dopamine and serotonin levels within critical brain tissues and other organs. However, their effects on urinary excretion of neurotransmitters are described in few studies and the results appear equivocal. The purpose of this study was to define, as precisely as possible, the influence of both 5-hydroxytryptophan (5-HTP) and tyrosine on urinary excretion of serotonin and dopamine in a large human population consuming both 5-HTP and tyrosine. Curiously, only 5-HTP exhibited a marginal stimulatory influence on urinary serotonin excretion when 5-HTP doses were compared to urinary serotonin excretion; however, a robust relationship was observed when alterations in 5-HTP dose were compared to alterations in urinary serotonin excretion in individual patients. The data indicate three statistically discernible components to 5-HTP responses, including inverse, direct, and no relationships between urinary serotonin excretion and 5-HTP doses. The response to tyrosine was more consistent but primarily yielded an unexpected reduction in urinary dopamine excretion. These data indicate that the urinary excretion pattern of neurotransmitters after consumption of their precursors is far more complex than previously appreciated. These data on urinary neurotransmitter excretion might be relevant to understanding the effects of the precursors in other organs.

Keywords: dopamine, serotonin, depression, urinary neurotransmitters excretion

Introduction

Two critical neurotransmitters, serotonin (5-hydroxytryptamine; 5-HT) and dopamine, are synthesized from the amino acids tryptophan and tyrosine, respectively. 1.2 Serotonin synthesis *in vivo* is accomplished by a two-step process converting tryptophan to 5-hydroxytryptophan (5-HTP), facilitated by the enzyme tryptophan hydroxylase, and 5-HTP is then decarboxylated by dihydroxyphenalanine (DOPA) decarboxylase to form serotonin. Tyrosine is converted to dopamine by the combined action of tyrosine hydroxylase to form DOPA and DOPA decarboxylase to form dopamine. The synthesis of serotonin is commonly stimulated by dietary delivery of L-5-hydroxytryptophan (5-HTP)³ and dopamine synthesis is stimulated by dietary administration of either tyrosine or L-dihydroxyphenylalanine (L-DOPA). 4 Protein-containing foods such as meat and dairy products are good natural sources of both tyrosine and tryptophan.

Both 5-HTP and tyrosine are available in the United States as dietary supplements. These agents are utilized as natural supplements to augment brain levels of either serotonin

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or dopamine. This study investigates the effects of 5-HTP and tyrosine ingestion on urinary excretion of serotonin and dopamine in a large sample of humans ingesting 5-HTP and tyrosine. Curiously, the urinary excretion of these compounds after ingestion of 5-HTP or tyrosine has only been reported in human trials involving very small patient cohorts and the results involve anomalous responses. 5-7 Therefore, this study was designed to critically test the hypothesis that increased ingestion of 5-HTP or tyrosine elevates urinary excretion of serotonin and dopamine, respectively. The purpose of the study was to determine if urinary excretion of serotonin or dopamine reflect the adequacy of supplementation with 5 HTP or tyrosine.

Methodology

The study included 824 individuals ingesting 5-HTP, tyrosine, both 5-HTP and tyrosine, or neither. Multiple urine samples were obtained from all of these individuals and most received multiple doses of supplements to enable comparisons between doses of supplements and urinary excretion of mature neurotransmitters, as well as the relationship between changes in doses and changes in urinary neurotransmitter excretion. The primary rationale for using the dietary supplements was weight loss although a significant number of patients were treated for diseases other than obesity that were caused by, or associated with, serotonin and/or dopamine dysfunction. The participants resided throughout the United States. The dose range for 5-HTP ranged from 0 to 2700 mg per day. Tyrosine was taken in doses of 0 to 17,000 mg per day. The supplements were taken in divided doses two, three, or four times a day depending on the dosing of amino acid precursors administered.

Urine samples were collected six 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 Thomas Uncini, a hospital-based dual board certified laboratory pathologist). Urinary dopamine and serotonin were assayed utilizing commercially available radioimmunoassay kits (3 CAT RIA IB88501 and IB89527; Immuno Biological Laboratories, Inc., Minneapolis, MN, USA). The DBS Laboratories are accredited as a high complexity laboratory by Clinical Laboratory Improvement Amendments (CLIA) to perform these assays.

Statistical evaluations utilized either two-way ANOVA to compare dose-response curves or regression analyses to establish correlations between precursor doses and urinary

excretion of serotonin and dopamine. We also correlated changes in precursor doses with changes in urinary neurotransmitter levels. These regression analyses were conducted to determine if a statistically definable relationship existed between dose of precursor and excretion of the resulting neurotransmitter. Comparison of mean values was performed using Student's t test. Data are presented as individual data points or as means \pm SE. A p value \leq 0.05 was considered statistically significant. JMP (SAS Institute, Cary, NC, USA) software was used to perform the statistical analysis.

Data were evaluated further by subdividing responses into the following: 1) those representing inverse relationships between dietary supplement intake and urinary excretion of neurotransmitter, deemed phase 1; 2) those exhibiting no relationship between dietary supplement intake and neurotransmitter excretion, deemed phase 2; and 3) those exhibiting a direct relationship between dietary supplement consumption and neurotransmitter excretion in the urine (phase 3). These groups were identified by dividing alterations in neurotransmitter excretion by alterations in supplement dose to obtain the slope of the relationship. Phases 1, 2, and 3 had negative, 0, and positive slopes, respectively. These curves were compared by two-way ANOVA. They also were compared with daily fluctuations in urinary neurotransmitter efflux in the absence of supplement ingestion (ie, phase 0). This analysis was performed to determine if the alterations in serotonin or dopamine excretion in phases 1, 2, or 3 could be accounted for by circadian rhythms and/or daily fluctuations in neurotransmitter excretion resulting from stress or other factors. The latter comparison involved the Students t test comparing the absolute value of deviations in neurotransmitter excretion in all groups. The conversion to absolute values was necessary because samples contained both positive and negative alterations in neurotransmitter excretion that conformed to the appropriate response for a specific phase. For instance, a reduction in precursor dose in phase 3 resulted in a reduction in neurotransmitter excretion. Although the change in neurotransmitter excretion was negative in this example, it represented the appropriate directional change for samples in phase 3.

This study was exempt from Institutional Review Board review at the University of Minnesota because it was a retrospective study of deidentified data.

Results

The dose response to 5-HTP on urinary serotonin excretion is shown in Figure 1. The correlation between 5 HTP doses and

urinary sertotonin excretion was not statistically significant (r = 0.040; p = 0.09). All of these individuals also were consuming tyrosine, therefore we sought an interaction with tyrosine as well, but there was none (p = 0.50). Surprisingly, the data from these experiments indicate only a marginal relationship between administration of a serotonin precursor and urinary excretion of serotonin.

We then sought a more convincing relationship by analyzing the effect of 5-HTP dosing alterations on changes in urinary serotonin excretion in individual patients. These experiments were conceived to ascertain whether individuals exhibited dramatically different basal levels of urinary serotonin excretion but consistently responded to changes in precursor administration with increased excretion of the serotonin. Figure 2 depicts a statistically significant relationship between changes in 5-HTP administration and alterations in urinary efflux of serotonin (p < 0.0001; r = 0.145). These data indicate a relationship between ingested 5-HTP and urinary serotonin excretion, but this effect remains modest based on the regression coefficient.

Further examination of the data in Figure 2 indicated that, of the 1671 individual data points, 390 demonstrated an inverse relationship between changes in urinary serotonin

excretion and 5-HTP administration, 375 showed virtually no change in urinary serotonin excretion (ie, an alteration of less than 2000 µg/g creatinine) after altering the 5-HTP dose and 860 experienced the anticipated direct relationship between changes in urinary serotonin excretion and 5-HTP dose. Furthermore, 46 samples represented the random variation in urinary serotonin excretion when no 5-HTP or tyrosine dosing occurred. Thus the relationship between alterations in 5-HTP dose and urinary serotonin excretion demonstrated in Figure 2 appears to derive from three distinct responses being summed in the data presented. The average value of each of these three different responses, plus the random daily fluctuation in the absence of precursors, is shown in Figure 3. The results in the absence of any alteration in 5-HTP dose (ie, normal circadian rhythms or other disturbances) are compared to those representing the three different responses when 5-HTP dosing was varied. This comparison was necessary to determine if there is a de facto statistical difference between the different patterns of responses and whether the responses are distinctly different than random fluctuations in serotonin excretion. The data are presented as absolute values of changes in serotonin excretion because the magnitude of the change in serotonin excretion is the critical variable.

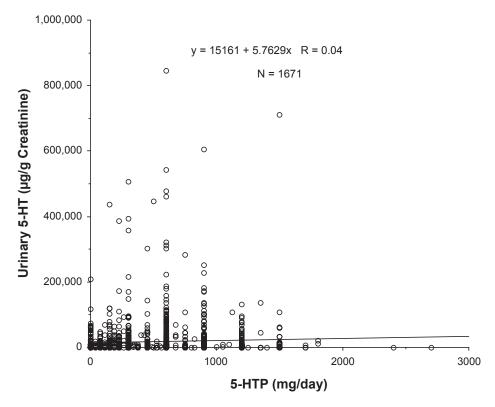


Figure I Relationship between 5-hydroxytryptophan (5-HTP) dose and urinary serotonin (5-HT) excretion. All data represent individual values from patients providing multiple samples over time. N represents the total number of samples and the regression coefficient was not statistically significant (p = 0.09).

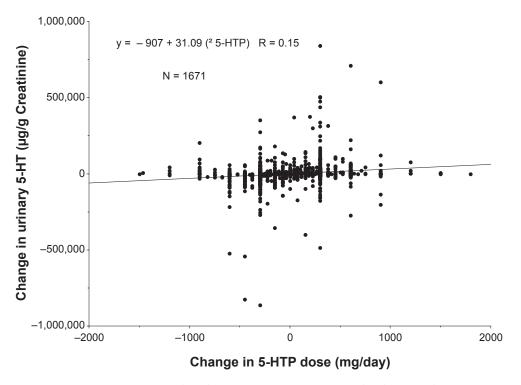


Figure 2 Relationship between change in 5-hydroxytryptophan (5-HTP) dose and change in urinary serotonin (5-HT) excretion. All values are individual points obtained from patients providing multiple samples over time. A statistically significant relationship was identified by linear regression (p < 0.0001). The equation describing the linear regression is provided in the figure.

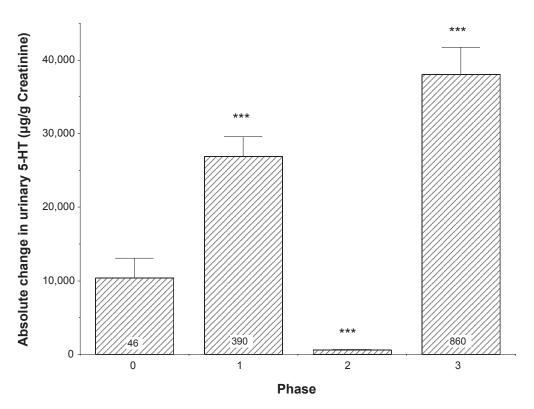


Figure 3 Absolute change in serotonin (5-HT) excretion when responses are segregated by change in urinary serotonin excretion as follows: no 5-hydroxytryptophan (5-HTP) dose (phase 0); inverse responses of urinary serotonin excretion to changes in 5-HTP (phase 1); no change in urinary serotonin excretion in response to changes in 5-HTP dose (phase 2); and direct correlation between changes in urinary serotonin excretion and changes in 5-HTP dose (phase 3). All values are means + SE. Values in both phases 1 and 3 were greater than phases 0 (random fluctuation) or 2 (****p < 0.0001). Phase 2 responses were less than phase 0 (****p < 0.001) and the N was 375.

As shown in Figure 3, both phase 1 (inverse correlation between altered 5-HTP dosing and serotonin excretion) and phase 3 (direct correlation between altered 5-HTP dosing and serotonin excretion) had much larger, statistically significant variations in comparison to the values representing random fluctuation of serotonin excretion (indicated as phase 0) (p < 0.0001 both phases). Phase 2 responses (ie, indicative of virtually no change in serotonin excretion in response to a change in 5-HTP administration) also were statistically different from either phases 0, 1, or 3 (p < 0.0001).

The dose-response curves for 5-HTP vs. urinary serotonin excretion for the three phases are shown in Figure 4. The 5-HTP suppressed urinary serotonin excretion in the phase 1 samples and augmented excretion in the phase 3 samples. The phase 0 and phase 2 samples had extremely low urinary serotonin levels and the concentrations did not fluctuate in response to alterations in 5-HTP dosing. Phase 2 values were significantly lower than urinary serotonin levels in either phase 1 or phase 3 samples (p < 0.0001) and the slopes of the curves for phases 1, 2, and 3 differed significantly (p \leq 0.0022). Urinary serotonin excretion in the absence of 5-HTP dosing was statistically higher in the phase 1 samples than any of the other groups. This finding is consistent with the phase 1 group demonstrating large declines in urinary serotonin levels in response to increased administration of 5-HTP. The stimulatory effect of 5-HTP observed in phase 3 samples occurred primarily in the dose range of 150 to 900 mg 5-HTP. A maximal effect appeared to be achieved at the 900 mg 5-HTP dose and no further increment in urinary serotonin concentrations was observed at higher 5-HTP doses.

Tyrosine ingestion produced a scenario starkly different from the 5-HTP data. Tyrosine consistently produced a paradoxical effect to reduce urinary dopamine excretion. The effect of tyrosine is shown in Figure 5. The inhibitory effect of tyrosine was statistically significant and yielded a concentration-dependent effect based on linear regression analysis (p < 0.0001, R = 0.086).

As with the relationship between 5-HTP consumption and serotonin excretion, the tyrosine effect on urinary dopamine excretion represented a summation of responses exhibiting one of the following: an inverse correlation; no effect; or a direct correlation. These data are shown in Figure 6. Consistent with the data shown in Figure 5, the fluctuations in dopamine excretion were smaller in samples obtained from patients ingesting incrementally greater amounts of tyrosine; and this difference for the combined phases 1, 2, and 3 reached a high level of statistical significance (p < 0.0001) when compared to phase 0 samples. The fluctuations in the phase 2 samples were less than any other phase (p \leq 0.005). The levels in phase 1 and 3 samples were not statistically different from levels in phase 0 samples (p = 0.09 for both).

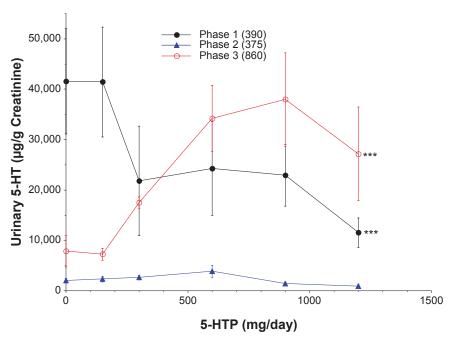


Figure 4 Influence of 5-hydroxytryptophan (5-HTP) dose on urinary excretion of serotonin (5-HT). All values are means \pm SE. The number of samples in each phase is indicated in parentheses. The slopes of the curves differed statistically for phases 1, 2, and 3 (p = 0.0022). Urinary serotonin levels for both phases 1 and 3 were significantly greater than phase 2 by analyses of variance (***p < 0.0001), but did not differ from each other.

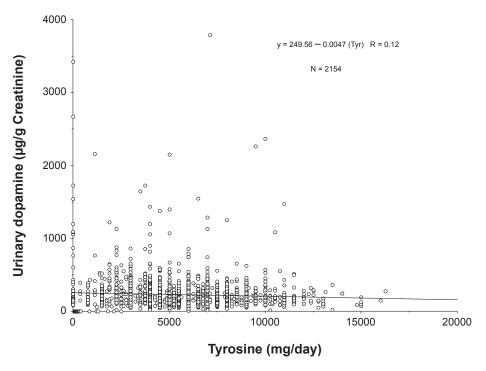


Figure 5 Effect of tyrosine on urinary dopamine excretion. All values are individual data points from patients ingesting tyrosine. Tyrosine significantly suppressed urinary dopamine excretion, resulting in a statistically significant regression (p < 0.0001).

These data add support to the surprising observation that tyrosine ingestion suppresses urinary dopamine excretion.

The relationship between tyrosine doses and urinary dopamine excretion in the three response phases is shown in Figure 7. These data were presented as mean data with standard errors for clarity necessitated by substantial overlap of raw data points. Phase 1 responses were characterized by decreasing excretion of dopamine as tyrosine doses increased. The slope of this curve was negative and statistically different from the curves representing phases 2 or 3 (p < 0.0001). Phase 2 and 3 did not exhibit statistically discernable slopes (p = 0.32), but the urinary dopamine levels were statistically greater in phase 3 samples (p = 0.0007).

Discussion

The data presented in this study indicate that consumption of specific dietary precursors of serotonin or dopamine only increases the urinary excretion of these neurotransmitters approximately 50% of the time. Probably the most surprising finding of this study is that 20% to 40% of these same individuals respond to the precursors with an unexpected reduction in excretion of the neurotransmitters, particularly dopamine. These observations indicate that the simplistic expectation that increased ingestion of neurotransmitter precursors will increase excretion of the mature neurotransmitters in the urine

is frequently not observed. In fact, the prominent response to tyrosine was a suppression of dopamine excretion.

The uncoupling of neurotransmitter excretion from the ingestion of precursors for the neurotransmitter is most likely caused by the degradation of blood-borne neurotransmitter in the kidney.^{8,9} Most of the serotonin or dopamine found in the urine is synthesized in the kidney. 9-12 Therefore, the excreted neurotransmitters must be synthesized in the kidneys and escape reabsorption into the blood in order to be excreted in the urine. Most of the serotonin formed by the kidneys is typically catabolized² or reabsorbed and not excreted in the urine. 8,11,13 Alternatively, dopamine synthesized in the kidney is secreted across the apical surface into the urine¹⁴ probably by an organic cation transporter^{9,15} resulting in greater urinary than interstitial dopamine concentrations. 12,13 Larger doses of tyrosine and 5-HTP have been observed to increase both urinary dopamine and serotonin excretion. 16-18 The array of catabolic and reabsorptive events probably accounts for the far more complex responses than expected to 5-HTP or tyrosine ingestion observed in this study.

In spite of the complex sequence of renal events accounting for the appearance of neurotransmitter in urine, the presence of opposing responses (ie, phases 1 and 3) does not seem possible without a direct effect of either the precursors or the formed neurotransmitters to cause an aberration in the series

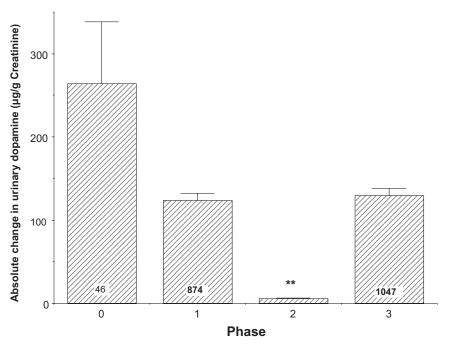


Figure 6 The average change in urinary dopamine excretion from baseline in the different phases including random fluctuation of dopamine excretion (phase 0). All values are means + SE with the number of samples per group indicated except for phase 2 (N = 187). The fluctuation in phase 2 was significantly less than daily fluctuations in the control (phase 0) group, as well as phases 1 and 3 (p < 0.001).

of events leading to the presence of urinary neurotransmitters. Based on a large volume of studies in the literature, it is likely that administration of 5-HTP increases the synthesis of serotonin within the kidney.^{2,3,8} Transporters for serotonin then transfer it into the blood stream to prevent it from being excreted in the urine. The phase 1 response we observed for serotonin could be explained by either a neurotransmitterinduced allosteric alteration of a reabsorptive transporter to increase activity or an induction of the synthesis of the transporter. Increased transport of the neurotransmitters out of the region of the nephron would theoretically reduce urinary excretion of the neurotransmitter, as observed in phase 1. If the alteration or induction were great enough, essentially all of the neurotransmitter would be reabsorbed and little or none would appear in the urine, as observed in phase 2. A conversion to phase 3 would be possible if the supply of neurotransmitter eventually increased enough to saturate the transport process and result in spillage of neurotransmitter into the urine. All three phases have been observed in the same individual and the three phases could represent different stages of renal processing of 5-HTP. We currently have no evidence explaining the different phases and the potential for increased activity or induction of neurotransmitter transporters merely appears to be the most likely possibility explaining these observations at this point in time.

The response to tyrosine was dominated by suppressed urinary dopamine excretion. This scenario probably necessitates either an inhibition of dopamine secretion into the nephron lumen or a reduction in renal dopamine synthesis. Two reports indicate that newly synthesized dopamine is normally secreted into the nephron, 12,13 thus an inhibition of this secretion could account for the inhibitory effect. It is likely that tyrosine could interfere with the secretion of dopamine into the lumen of the nephron but we are unaware of any reports supporting this site of action.

Tyrosine appears to be an unlikely inhibitor of renal dopamine synthesis because it is widely recognized as a dopamine precursor. However, tyrosine suppresses L-DOPA uptake into proximal tubule cells^{14,19} and L-DOPA uptake is required for renal dopamine synthesis. ²⁰ L-DOPA is the immediate precursor to dopamine in the synthetic pathway; therefore, inhibition of its uptake could impair dopamine synthesis. Proximal tubule cells accumulate tyrosine¹⁴ but the kidney lacks extraneuronal tyrosine hydroxylase^{1,21,22} and cannot convert it to dopamine. Thus, tyrosine could have a paradoxical inhibition of dopamine synthesis in the kidney by suppressing L-DOPA uptake into proximal tubule cells. This scenario represents a potential mechanism accounting for phase 1 responses to tyrosine. An alternative scenario potentially accounting for phase 3 responses to tyrosine

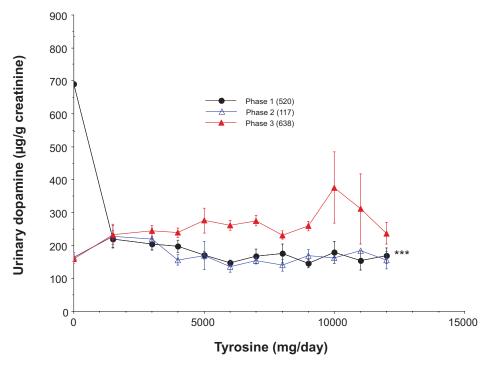


Figure 7 The relationship between tyrosine administration and urinary dopamine excretion for the different phases of dopamine excretion. The number of samples per group is indicated in parentheses. All values are means \pm SE. The slope for phase 1 differed significantly from slopes for phases 2 or 3 (****p < 0.0001).

involves the peripheral conversion of tyrosine to L-DOPA in neuronal tissue. The L-DOPA entering the kidney could serve as a precursor to dopamine and result in increased dopamine secretion observed in phase 3. The observation of the inhibitory (ie, phase 1) response to tyrosine has not been reported previously. A plethora of reports indicate that phase 3 stimulatory effects of tyrosine on urinary dopamine excretion is the predominant response in most studies in rats^{4,22,23} and protein has been widely used as a tyrosine source to increase dopamine excretion in humans.²⁴ It is possible that the phase 1 response to tyrosine in humans has not been noted previously because of the limited number of studies specifically investigating tyrosine effects on human dopamine excretion.

The novel observations noted in this study include a somewhat variable relationship between ingested 5-HTP and urinary serotonin excretion and the unexpected influence of tyrosine to reduce urinary dopamine excretion. The description of the three phases demonstrating the relationship between 5-HTP and urinary serotonin excretion is also novel and probably is a reflection of serotonin reabsorption in the kidney. The consistent and statistically discernable ability of tyrosine to dampen fluctuations in urinary dopamine excretion is also noteworthy. These processes might be

reflective of similar processes occurring in other organs and suggest that urine sampling for neurotransmitters requires multiple samples to determine the direction of the response and, potentially, the adequacy of dosing.

Disclosure

The authors report no conflicts of interest in this work.

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