Research Exempt from IRB Committee Review Category 4:

EXISTING DATA: RECORDS REVIEW & PATHOLOGICAL SPECIMENS

IRB Use Only

#

Submission Instructions:
E-mail a copy of this application and any other materials required to the Research Subjects' Protections Programs Office: **RSPeev@umn.edu**

REDACTED

Electronically submitted protocols must be sent from a University of MN e-mail account. Original signatures are not required. U of M x.500 IDs have been deemed by the University of Minnesota to constitute a legal signature.

Academic Advisors and Co-Investigators should be carbon copied (Cc) on the submission e-mail.

For help with this form and to download additional appendices: see http://www.researc.umn.edu/irb/download/ or call 612-626-5654

1.1 Project Title (Project title must match grant title. If different, also provide grant title):

Ingestion of neurotransmitter precursors affect urinary neurotransmitter levels in humans

1.2 Principal Investigator (PI)

Name (Last name, First name MI): **T G**	Highest Earned Degree: Ph.D.
Mailing Address: DP Pharmacology University of Minnesota Medical School 1035 University Drive Duluth, MN 55812	Phone Number: 218-726-8 Pager or Cell Phone Number: Fax: 218-726-7906
U of M Employee/Student ID: 168344	Email: gt@d.umn.edu
U of M x.500 ID (ex. smith001): gt	University Department (if applicable): Physiology and Pharmacology
Occupational Position: ☒Faculty ☐Staff ☐Student ☐Fairview Researcher ☐Gillette Researcher ☐Other:	
Indicate the training and education completed in the protection of human subjects or human subjects records. Training is required for all research. Category four research projects require human subjects training. HIPAA training alone is not sufficient. ***Refer to training links at the end of this section**	
Human Subjects Training (one of these must be checked) ☐ CITI ☐ Investigator 101	HIPAA Training (Required if Data Contains PHI) ☐ HIPAA
As Principal Investigator of this study, I assure the IRB that the following statements are true: The information provided in this form is correct. I will seek and obtain prior written approval from the IRB for any substantive modifications in the proposal, including changes in procedures, co-investigators, funding agencies, etc. I will promptly report any unexpected or otherwise significant adverse events or unanticipated problems or incidents that may occur in the course of this study. I will report in writing any significant new findings which develop during the course of this study which may affect the risks and benefits to participation. I will not begin my research until I have received written notification of final IRB approval. I will comply with all IRB requests to report on the status of the study. I will maintain records of this research according to IRB guidelines. The grant that I have submitted to my funding agency which is submitted with this IRB submission accurately and completely reflects what is contained in this application. If these conditions are not met, I understand that approval of this research could be suspended or terminated.	
gt	**3/28/08**
x.500 of PI	Date

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1.3 Department, Division Head, or Dean Information

Please note as the researcher, you are responsible for confirming and following your departmental standards and requirements for research.

L W
Name of Department Head, Division Head, or Dean

Training Links
CITI - https://www.citiprogram.org/default.asp
FIRST - http://www.research.umn.edu/first/HumanSubjects.htm
Investigator 101 - http://www.research.umn.edu/irb/training/
HIPAA - http://www.research.umn.edu/first/AdditionalCourses.htm
See the Responsible Conduct of Research (RCR) web site for information of human subject protection training.

1.4 Are there additional Co-Investigators and Staff?

☐ Yes. Download an extra personnel sheet and include it with your application.
☒ **No.** Continue to 1.5.

1.5 Is the PI of this research a student?

☐ **Yes.** *Include Appendix J.*
Electronically submitted protocols must be carbon copied (Cc) to their advisor.
☒ **No.** Continue to 2.

Academic Advisor to the Student Investigator	
Advisor's Name (Last name, First name MI):	University Department:
Mailing Address:	Phone Number:
	Email:
	U of M x.500 ID (ex. smith001):

2. Funding

2.1 Is this research funded by an internal or external agency?

☒ **Yes.** *Include Appendix A.*
☐ **No.**

If no, explain how costs of research will be covered:

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3. Institutional Oversight

3.1 Will this research be utilizing Fairview Health System resources or medical records?

☐ Yes.
☒ No.

3.2 Will this research be utilizing Gillette Children's Specialty Healthcare or medical records?

☐ Yes.
☒ No.

3.3 Is this research proposal being reviewed by any other institution or peer review committee?

☒ Yes. It is the responsibility of the PI to secure the appropriate approval from these committees and document that approval to the IRB. Attach a copy of documentation of approval, if received, and indicate committees below.
☐ No.

If yes, then please list which committees will review this proposal:

Whiteside Research Institute

4. Conflict of Interest

4.1 Do any of the investigators or personnel listed on this research have a potential conflict of interest associated with this study? Conflict of interest is defined in Appendix Y.

☐ **Yes.** *Include Appendix Y.*
☒ **No.**

5. Use of Protected Health Information (PHI): HIPAA Requirements

5.1 As part of this study, do you:

a. **Collect protected health information (PHI)* from subjects in the course of providing treaent/experimental care; or**
b. **Have access to PHI* in the subjects' records?**

Please read the definition of PHI below before answering.

*PHI is defined under HIPAA as health information transmitted or maintained in any form or medium that:

1. identifies or could be used to identify an individual;
2. is created or received by a healthcare provider, health plan, employer or healthcare clearinghouse; and
3. relates to the past, present or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present or future payment for the provision of healthcare to an individual.

The following records ARE EXEMPTED from the definition of PHI even though they may contain health-related information: student records maintained by an educational institution and employment records maintained by an employer related to employment status. If your study uses these kinds of records, it is not subject to HIPAA. However, existing IRB rules on informed consent and confidentiality still apply.

Health-related information is considered PHI if (any of the following are true):

1. the researcher obtains it directly from a provider, health plan, health clearinghouse or employer(other than records relating solely to employment status);
2. the records were created by any of the entities in "1" and the researcher obtains the records from an intermediate source which is NOT a school record or an employer record related solely to employment status; OR
3. the researcher obtains it directly from the study subject in the course of providing treatment to the subject.

Health-related information is not considered PHI if the researcher obtains it from:

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1. student records maintained by a school;
2. employee records maintained by an employer related to employment status; OR
3. the research subject directly, if the research does NOT involve treatment.

☐ **Yes. If yes to a or b above, complete Appendix H to show how you will satisfy HIPAA requirements for authorization to use PHI in research.**

☒ **No.**

6. Summary of Activities

Use lay language, do not cut and paste from or refer to grant or abstract.

6.1 Briefly state what is your research question.

The research examines how ingestion of serotonin or dopamine precursors affects urinary excretion of serotonin or dopamine. It was anticipated that increasing precursor ingestion would cause greater excretion of product. However, the data do not show a direct relationship between precursor intake and the excretion of their products in most of the samples. The study will examine whether subsets of patients respond anomolously to precursor intake by reducing the amount of serotonin or dopamine in the urine. This study uses previously collected urine samples.

6.2 Describe the source of the records; medical, educational, employment, existing data set, or pathological specimens (waste).

For approval in this category you must plan to use an existing data set without access to identifiers, records review to which you have permissible access to records when the chart is older than January 1, 1997, or where the patient has signed a consent form which is in the file after January 1, 1997, or collecting waste tissue after it has been released to pathology.

The existing data set will be obtained from a local firm, Neuroreplete. The data include a patient identification number, doses of serotonin and dopamine precursors, urinary levels of dopamine, serotonin, norepinephrine and epinephrine and the date of the sample collection.

6.3 Number of records or specimens to be used:

8200

6.4 How long do you anticipate this research study will last from the time you are determined to meet the criteria for exempt research?

Exempt research is generally considered short-term in nature. This office routinely inactivates exempt applications after six years from the time it was determined to meet the exempt criteria. If you think your project will extend beyond six years, contact the IRB office (612-626-5654 or **irb@umn.edu**).

6.5 Is the data you are gathering publicly available?

☐ **Yes.** Continue to 7.1

☒ **No**. Continue to 6.6

6.6 Do you already have permissible access to the records or specimens (i.e. through a job, volunteer work, internship etc.)

☒ **Yes.** Describe how you have permissible access to the records.

The firm, Neuror, will provide the data to me to analyze.

☐ **No.** Continue to 6.6a

6.6a Will the records you receive be stripped of all identifiers that would make it possible for you to identify a subject?

☒ **Yes.** Continue to 6.7

☐ **No.** This research does not qualify for exempt status. Please complete the full IRB application, requesting expedited review if appropriate.

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6.7 Confirm that the data/specimens you wish to review already exist

☒ **The data set exists.**

☐ **The data set does not already exist.**

If the data is not already collected, the research does not qualify for exempt category four research. Please complete the full IRB application requesting expedited review if appropriate.

6.8 Please confirm that you will not have access to, or create a link, which would make it possible to identify subjects.

☒ **I will not have access to, or create, a link.**

☐ **I will have access to a link.**

If you have access to, or create a link you do not qualify for exempt category four research. Please complete the full IRB application requesting expedited review if appropriate.

6.9 Describe the identifying information to which you will have access to prior to recording data:

None

6.10 Describe the identifying information you will record:

Please note in order to proceed with exempt research under category four, you may not record information in such a manner that subjects can be identified directly or through identifiers linked to subjects.

None

7. Confidentiality

See Protecting Private Data Guideline from the Office of Information Technology (OIT) for information about protecting the privacy of research data.

7.1 Describe provisions taken to maintain confidentiality of data:

All data are deidentified. No names, locations or other identifying information are included in the data set.

7.2 Describe the security plan for data including how and where stored and duration of storage (i.e., password protection, encrypted data, etc.):

The data will be stored in a University database requiring password access.

7.3 Will identifiable data be made available to anyone other than the PI?

☐ Yes.

☒ No.

If yes, explain who and why they will have access to the identifiable data:

This regulation does not apply to FDA regulated research.

You have reached the end of this form. Please make sure that you have responded to every question on this application (even if your response is "not applicable").

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Title: **Ingestion of neurotransmitter precursors affect urinary neurotransmitter levels in humans**

G T
Professor, Department of Physiology and Pharmacology
University of Minnesota Medical School Duluth

Introduction. Amino acid precursors of neurotransmitters such as serotonin and dopamine are frequently used as dietary supplements in attempts to influence endogenous levels of these critical neurotransmitters. The serotonin precursor is usually 5-hydroxy Tryptophan, whereas either Tyrosine or dihydroxy-Phenylalanine (L-DOPA) is typically utilized to elevate dopamine concentrations. The purpose of this investigation is to assess the effect of the amino acid precursors on urinary concentrations of serotonin and dopamine, as well as norepinephrine and epinephrine. The literature on this subject indicates the intuitive expectation that increasing dietary levels of the precursors increases the amount of neurotransmitter product excreted in the urine (Arterberry and Conley, 1967; Agharanya and Wurtman, 1982; Garcia et al., 1999).

This basic hypothesis has been questioned by recent findings by a commercial enterprise examining the effects of the amino acid precursors in a large sample of subjects. The subjects consumed the amino acid precursors primarily for weight loss but the rationale included a plethora of other medical conditions. The company, Neuroreplete, provides the amino acid precursors and also analyzes urinary serotonin and catecholamine (i.e., dopamine, norepinephrine and epinephrine) concentrations. Their findings indicate that approximately one-third of patients respond to increased ingestion of 5 Hydroxy Tryptophan or Tyrosine with a decrease in urinary neurotransmitter concentrations. Furthermore, one-third of these same patients fail to exhibit any change in urinary neurotransmitter concentrations after increasing consumption of these amino acids. Finally increases in the dose of the amino acids eventually elevate urinary serotonin and dopamine concentrations in approximately one-third of the subjects. The prominent response to L-DOPA was to raise urinary dopamine concentrations in virtually all of the subjects, as is widely expected and reported (Barthelmebs et al., 1993; Grossman et al., 1999; Davidson et al., 2007). The Neuroreplete experience with two of the three supplements questions the accepted notion that a simple relationship exists between amino acid consumption and urinary excretion of the neurotransmitters formed from them. **The hypothesis to be tested in the proposed work is that increased consumption of neurotransmitter precursors increases urinary excretion of the resulting neurotransmitters.**

The major advantage of the proposed analysis is the volume of data available in the Neuroreplete database. Approximately 8000 samples are available to compare the relationship between amino acid precursor and eventual urinary excretion of neurotransmitters. Many of these samples, 30%, are obtained from the same patient. The sequential samples from the same patient allow a direct test of the hypothesis that increased consumption of neurotransmitter precursors results in an increase in neurotransmitter excretion in the urine.

Methodology. The proposed study will be a retrospective study of the relationship between the amount of amino acid precursors of neurotransmitters consumed and the amount of neurotransmitters excreted in the urine. Only de-identified data will be used in the study. Data obtained from Neuroreplete will include the following: patient identification number; date of test; dose of amino acid precursor (5 Hydroxy Tryptophan, Tyrosine, L-DOPA); and urinary concentration of neurotransmitter (serotonin, dopamine, norepineprhine, epinephrine). The data also will include a preliminary designation of whether neurotransmitter excretion is decreasing with precursor dose (phase 1), not changing (phase 2) or increasing with the dose of precursor (phase 3). The initial analysis will test for a relationship between amino acid precursor dose and urinary neurotransmitter excretion in the entire sample and among the different phases. Analysis of Variance will be utilized to test for differences between individual phases. The Analysis of Variance will identify the phase and the dose of the precursor as independent variables and the urinary excretion of neurotransmitter as the dependent variable.

Statistical Identification of Groups: A statistically-based analysis for the different groups will then be undertaken. Individuals, identified by identification numbers, will be examined for one of the following: a decrease; no response; or an increase in urinary neurotransmitter excretion, in response to an increased consumption of the precursor amino acid. Individuals will be designated group 1 if they respond either to an increased consumption of the amino acids with a decrease in the urinary excretion of the resulting neurotransmitter or to a decreased amino acid consumption with an increase in urinary neurotransmitter excretion. Group 2 individuals will be defined as those showing virtually no urinary response to an increase or decrease in intake of amino acid precursors of neurotransmitters. Group 3 will be identified by an increased excretion of neurotransmitters in response to increased ingestion of their respective precursors or a decreased excretion in response to a decreased consumption of amino acids. This aspect of the study will be limited to individuals consuming different doses of supplements over time. A control group of patients not taking any supplements also will be included to define basal fluctuations of urinary neurotransmitter levels unrelated to therapeutic consumption of amino acid precursors. The **basic hypothesis** to be tested is that increased consumption of neurotransmitter precursors (i.e., amino acids) will lead to increased excretion of the resulting neurotransmitters in the urine. The **alternative hypothesis** to be tested is that subsets of responses will be observed indicating that elevated consumption of neurotransmitter precursors (i.e., amino acids) leads to one of the following: decreased excretion of resulting neurotransmitters in the urine; no change in the excretion of the resulting neurotransmitters in the urine; or increased urinary excretion of the resulting neurotransmitters. The three groups will be compared to the control group by Analysis of Variance to determine if the different groupings are simply a reflection of random variation in urinary neurotransmitter levels. The final analysis will compare the accuracy of the Neuroreplete method of phase determination to the groups identified with the statistical method.

Statistical Methods: The initial test of the basic hypothesis will be performed by analysis of variance seeking a dose-response effect with the dose of either 5-Hydroxy Tryptophan, Tyrosine or L-DOPA representing the independent variable and urinary excretion of neurotransmitters representing the dependent variable. Analysis of Variance also will be performed with change in dose of the amino acids 5-Hydroxy Tryptophan,

Tyrosine or L-DOPA as the independent variable and the change in urinary neurotransmitter excretion as the dependent variable. The hypotheses will be explored further by subdividing the responses into phases or groups (as described above). Analysis of Variance will be conducted with the independent variables being phase (group) and precursor amount and the dependent variable being urinary neurotransmitter content. Analysis of Variance will be conducted with independent variables being phase/group and change in amino acid precursor dose and the dependent variable being alteration in urinary neurotransmitter content. It is anticipated that the relationship between alterations in dietary precursor vs. alterations in urinary content of neurotransmitter will differ statistically for the different phases. A p value of 0.05 will be considered statistically significant. JMP software (SAS) will be employed for statistical evaluation.

A summary of the statistical comparisons is as follows:

1) Amino Acid precursor vs. urinary neurotransmitter excretion (Analysis of Variance for all data)

a) 5 Hydroxy Tryptophan dose vs. urinary Serotonin concentration
b) Tyrosine dose vs. urinary Dopamine (also norepinephrine & Epinephrine)
c) L-DOPA dose vs. urinary Dopamine (also norepinephrine & Epinephrine)

2) Amino Acid precursor vs urinary neurotransmitter excretion (Two-Way Analysis of Variance for different phases defined by Neuroreplete)

a) phases and 5 Hydroxy Tryptophan dose vs. urinary Serotonin concentration
b) phases and Tyrosine dose vs. urinary Dopamine (also norepinephrine & Epinephrine)
c) phases and L-DOPA dose vs. urinary Dopamine (also norepinephrine & Epinephrine)

3) Amino Acid precursor vs urinary neurotransmitter excretion (Two Way Analysis of Variance for different groups defined by Statistical means)

a) Groups (including control) and 5 Hydroxy Tryptophan dose vs. urinary Serotonin concentration
b) Groups (including control) and Tyrosine dose vs. urinary Dopamine (also norepinephrine & Epinephrine)
c) Groups (including control) and L-DOPA dose vs. urinary Dopamine (also norepinephrine & Epinephrine)
d) Groups (including control) and *change* in 5 Hydroxy Tryptophan dose vs. *change* urinary Serotonin concentration
e) Groups (including control) and *change* in Tyrosine dose vs. *change* in urinary Dopamine (also norepinephrine & Epinephrine)
f) Groups (including control) and *change in* L-DOPA dose vs. *change in* urinary Dopamine (also norepinephrine & Epinephrine)

4) Comparison of phases defined by Neuroreplete vs. Groups defined by Statistical means (Two Way Analysis of Variance)

a) Phase #1 or Group #1 & precursor dose vs. urinary excretion of

neurotransmitter

b) Phase #2 or Group #2 & precursor dose vs. urinary excretion of neurotransmitter

c) Phase #3 or Group #3 & precursor dose vs. urinary excretion of neurotransmitter

d) Phase #1 or Group #1 & change in precursor dose vs. change in urinary excretion of neurotransmitter

e) Phase #2 or Group #2 & change in precursor dose vs. change in urinary excretion of neurotransmitter

f) Phase #3 or Group #3 & change in precursor dose vs. change in urinary excretion of neurotransmitter

Discussion. The value of this study is to validate or refute the observation that urinary serotonin or catecholamine levels do not necessarily directly relate to the amount of amino acid precursor consumed. A potential explanation for the lack of correlation is that urinary serotonin and catecholamines are not believed to originate from blood borne neurotransmitters. The most discerning studies have found that these urinary neurotransmitters are actually synthesized in the proximal tubules of the kidney (Wahbe et al., 1982; Hayashi et al., 1990). Furthermore, other studies have found anomalous reductions in serotonin excretion associated with increased consumption of Tryptophan (Arterberry and Conley, 1967). Thus, current thinking regarding the significance of urinary neurotransmitters as an indicator of the amount of dietary supplement added could be erroneous. The major advantage of the proposed analysis is the magnitude of the database analyzed. It is far larger than any of the studies on this topic reported in the literature. The other studies typically report 10 to 20 subjects in a study. The conclusions from this larger study should be more accurate and provide a more rigorous test of the hypothesis. None of the analyses to be performed address the efficacy of amino acid therapy for any clinical condition. The analysis will be limited to amino acid influences on urinary neurotransmitter excretion. This information will be valuable in assessing the predictive significance of these urinary neurotransmitter levels in determining efficacy of neurotransmitter precursor dosing in clinical studies and should add significant novel information to the scientific literature.

References

Agharanya, J.C. and Wurtman, R.J. Studies on the mechanism by which tyrosine raises urinary catecholamines. Biochem. Pharmacology 31: 3577-3580, 1982

Arterberry, J.D. and Conley, M.P. Urinary excretion of serotonin (5-hydroxytryptamine) and related indoles in normal subjects. Clinica Chimica Acta 17: 431-440, 1967

Barthelmebs, M., Mbou, P., Stephan, D., Grima, M. and Imbs, J.L. renal dopamine excretion in healthy volunteers after oral ingestion of L-DOPA. Fundamentals Clin. Pharmacol. 7: 11-16, 1993.

Davidson, D.F., Grosset, K. and Grosset, D. Parkinson's disease: the effect of L-DOPA therapy on urinary free catecholamines and metabolites. Ann. Clin. Biochem. 44: 364-368, 2007

Garcia, N.H., Berndt, T.J., Tyce, G.M. and Knox, F.G. Chronic oral L-DOPA increases dopamine and decreases serotonin excretions. Am. J. Physiol. 277: R1476-R1480, 1999.

Grossman, E., Shenkar, A., Peleg, E., Thaler, M. and Goldstein, D.S. Renal effects of L-DOPA in heart failure. J. Cardiovasc. Pharmacol. 33: 922-928, 1999.

Wahbe, F., Hagege, J., Loreau, N. and Ardaillou, R. Endogenous dopamine synthesis and DOPA-Decarboxylase activity in rat renal cortex. Mol. & Cell. Endocrinology 27: 45-54, 1982.

Project Budget (support supplied by Neuroreplete):

G T	20% time for summer salary	$4073	
	Fringe benefits	$1288	
Statistician (TBD)		$5650	
Personnel Total			$11,011
Computer for analysis			$ 1,000
Indirect Cost (overhead at 10%)			$ 1,201
Total……			$ 13,212

Budget Justification: Tr will take responsibility for overseeing the statistical analysis, performing an extensive literature search and an analysis of the data, and preparation of any manuscripts resulting from the study.

The statistician will be consulted to ensure the validity of the statistical analyses performed and for advise in "fine tuning" the analysis.

A computer devoted to this project should be purchased to facilitate the data entry.

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Edit IRB Study

Study Search: Study Number Search

Print Version | Flag as High Priority | Create Label(s) | Create Form Letter

Study: **0806E36521**
PI: **T G**
Status: Inactive
Title: Ingestion of neurotransmitter precursors affect urinary neurotransmitter levels in humans

Approval date: 06/20/2008
Expiration date:

Type: (E) Exempt
Subtype: General
Exempt Category: EXMT4
Committee: Expedited
Status: Inactive
Update

- Submissions
- Titles (1)
- Personnel (1)
- Funding (1)
- Details
- Notes (0)
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Date: 06/20/2008
To: G T (gt@umn.edu)
From: irb@umn.edu
Subject: #STUDYNBR# - PI #PILASTNAME# - IRB - Exempt Study Notification
Message: The IRB: Human Subjects Committee determined that the referenced study is exempt from review under federal guidelines 45 CFR Part 46.101(b) category #4 EXISTING DATA; RECORDS REVIEW; PATHOLOGICAL SPECIMENS. Study Number: 0806E36521 Principal Investigator: G T Title(s): Ingestion of neurotransmitter precursors affect urinary neurotransmitter levels in humans

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This e-mail confirmation is your official University of Minnesota RSPP notification of exemption from full committee review. You will not receive a hard copy or letter. This secure electronic notification between password protected authentications has been deemed by the University of Minnesota to constitute a legal signature. The study number above is assigned to your research. That number and the title of your study must be used in all communication with the IRB office. If you requested a waiver of HIPAA Authorization and received this e-mail, the waiver was granted. Please note that under a waiver of the HIPAA Authorization, the HIPAA regulation [164.528] states that the subject has the right to request and receive an accounting of Disclosures of PHI made by the covered entity in the six years prior to the date on which the accounting is requested. If you are accessing a limited Data Set and received this email, receipt of the Data Use Agreement is acknowledged. You will receive a notification prior to inactivation.

Upon receipt of this email, you may begin your research. If you have questions, please call the IRB office at (612) 626-5654. You may go to the View Completed section of eResearch Central at http://eresearch.umn.edu/ to view further details on your study. The IRB wishes you success with this research.

Attachments: None

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