



Serotonin and Epilepsy: The Story Continues

The 5-HT_{1A} receptor and 5-HT transporter in temporal lobe epilepsy.

Martinez A, Finegersh A, Cannon DM, Dustin I, Nugent A, Herscovitch P, Theodore WH. *Neurology* 2013;80:1465–1471.

OBJECTION: To study 5-HT transport and 5-HT_{1A} receptors in temporal lobe epilepsy (TLE) and depression. **METHODS:** Thirteen patients had PET with [¹¹C]DASB for 5-HTT and [¹⁸F]FCWAY for 5-HT_{1A} receptor binding, MRI, and psychiatric assessment. Sixteen healthy volunteers had [¹¹C]DASB, 19 had [¹⁸F]FCWAY, and 6 had both PET studies. We used a reference tissue model to estimate [¹¹C]DASB binding. [¹⁸F]FCWAY volume of distribution was corrected for plasma-free fraction. Images were normalized to common space. The main outcome was the regional asymmetry index. Positive asymmetry indicates relative reduced binding (reflecting transporter activity) ipsilateral to epileptic foci. **RESULTS:** Mean regional [¹¹C]DASB binding and asymmetry did not differ between patients and controls. [¹⁸F]FCWAY asymmetry was significantly greater for patients than controls in hippocampus, amygdala, and fusiform gyrus. On analysis of variance with region as a repeated measure, depression diagnosis had a significant effect on [¹¹C]DASB asymmetry, with significantly higher [¹¹C]DASB asymmetry in insular cortex (trend for fusiform gyrus). In insular cortex, patients had a significant correlation between [¹⁸F]FCWAY asymmetry and [¹¹C]DASB asymmetry. **CONCLUSIONS:** Our study showed increased [¹¹C]DASB asymmetry in insula and fusiform gyrus, and relatively reduced transporter activity, in subjects with both TLE and depression, as compared to subjects with TLE alone, implying reduced reuptake and thus increased synaptic 5-HT availability. This finding may represent a compensatory mechanism for 5-HT_{1A} receptor loss. Altered serotonergic mechanisms have an important role in TLE and concomitant depression.

Commentary

The observation that mood disorders and epilepsy often go hand in hand is certainly not new. Indeed, the reported prevalence of depression in patients with epilepsy has been reported to range between 12 and 40 percent in various patient populations and settings. One recent meta-analysis suggested an overall prevalence of active depression of about 24% (1). Left inadequately treated, depression may not only contribute to decreased quality of life but may also contribute to increased healthcare costs and decreased economic productivity (2). In patients with temporal lobe epilepsy (TLE) who have pharmacologically refractory seizures, depression may be even more common and severe. Despite common misperceptions, this apparent relationship is likely bidirectional. Not only are patients with epilepsy at increased risk of developing depression, but patients with psychiatric comorbidities are at substantially greater risk of developing epilepsy (3). Given this relationship, is it truly appropriate to consider mood and seizure disorders as simply comorbidities? The answer to that question will require an understanding of the neurobiological associations between the two disorders.

While much progress has been made in both highlighting the importance and clinical identification of this common,

debilitating comorbidity in our patients, our understanding of its neurobiological underpinnings is still rather unclear. While the biochemical causes of depression in patients with epilepsy are most certainly multifactorial (4, 5), the role of serotonin dysregulation and epilepsy has become an increasingly interesting story. Serotonin neurotransmission is important in modulating cortical excitatory and inhibitory balance in the brain. Both animal models and limited clinical experience suggest that reduced serotonergic tone is associated with seizure genesis and exacerbation (6) and that enhanced serotonergic activity may have anticonvulsant effects (7, 8).

Previous work using PET has demonstrated reductions in binding of serotonin (5-HT_{1A}) in mesial temporal structures in patients with TLE (9), and that patients with TLE with major depression may show greater reductions in 5HT_{1A} binding than patients with TLE who are not depressed (10, 11). Taken together, experimental data and studies in patients clearly demonstrate impaired 5-HT binding in patients with epilepsy. Alterations in 5-HT_{1A} receptor density is only one part of the story. The serotonin transporter (5-HTT) is the key regulator in serotonergic transmission and is primarily responsible for 5-HT inactivation via selective reuptake. Studies have suggested a possible role for genetic polymorphisms of this transporter in patients with TLE (12), with some data hinting that greater 5-HTT activity, leading to reduced synaptic 5-HT, might be associated with poorer response to antiepileptic drugs in patients with TLE (13).

Now, in a report by Martinez and colleagues, 13 patients with TLE were compared with 29 healthy volunteers who



had never met criteria for a major psychiatric disorder. Of the patients, four had a history of major depression, with two of these individuals reporting symptoms of depression at the time of study. Using PET, 5-HTT and 5-HT_{1A} binding was assessed in the insula, hippocampus, amygdala, parahippocampal gyrus, fusiform gyrus, and cingulate cortex. In agreement with previous studies, the investigators found that 5-HT_{1A} binding was reduced in the limbic areas on the ipsilateral side in patients with TLE, and that 5-HT_{1A}-binding asymmetry was greater for patients as compared with healthy controls. Overall, 5-HTT-binding differences in patients with TLE, however, were not apparent. Neither sex, nor AED use, nor side of epilepsy focus appeared to affect 5-HTT binding. Of interest, differences in 5-HTT binding were noted in patients with TLE and a history of major depression. In these patients, greater asymmetry in transporter activity was seen in the insular cortex (likely an important neural structure in major depression) (14) and in the fusiform gyrus on the ipsilateral side. Correlations between 5-HT_{1A} and 5-HTT asymmetry in the insular cortex were also seen in TLE patients but not healthy controls. These observations suggest several things. First, patients with TLE appear to have subtle alterations in 5-HT neurotransmission as compared with healthy individuals. Those patients with clinical expressions of depression may have a somewhat different neurochemical marker. In the patient with TLE and depression, a compensatory mechanism may exist. Perhaps, in response to markedly reduced 5-HT_{1A}-receptor density, uptake, the primary mechanism terminating serotonin activity, is also reduced, allowing for increased synaptic serotonin concentrations.

Clearly, one must be cautious not to overinterpret these findings. Subtle differences in clinical expression of TLE and depressive symptoms may have been obscured by the relatively small sample size. These findings do raise interesting questions. Could it be that in patients with TLE and depression, there is an endogenous mechanism in place to try and increase synaptic serotonin concentrations? If so, clearly this compensatory mechanism is not entirely sufficient in all patients. Of note, in this report, there was a trend (albeit not statistically significant) toward a correlation between higher Beck Depression scores and increased insular 5-HTT asymmetry. Perhaps these neurochemical markers are indicative of either severity of the mood disorder or of differing clinical syndromes in patients with TLE. It is possible therefore that neuroimaging might lend insight as to potential patient subtypes that might benefit from treatment with selective serotonin reuptake inhibitors (SSRIs).

Finally, the observations of Martinez and colleagues also prompts one to ask whether it is entirely appropriate to consider depression simply a comorbid finding in patients with epilepsy. As it is commonly defined, comorbidity refers to the presence of more than one diagnosis occurring at the same time in a given patient. This implies a distinct clinical disorder occurring during the course of the “index” disease. This might be imprecise, if not frankly inaccurate, in this patient population. Given the observed bidirectionality of epilepsy and depression, common neurochemical markers, and perhaps compensatory neurotransmitter adaptations, it is perhaps

more correct to view epilepsy and depression as different expressions of a single disorder. Clearly, TLE is a heterogeneous disorder. Perhaps patients with TLE and significant mood disturbance represent a subgroup of patients with a unique neurochemical signature. These observations take us one step closer to understanding the mechanistic underpinnings of this common debilitating “comorbidity” and, perhaps, to designing personalized screening and treatment approaches.

by Barry E. Gidal, PharmD

References

1. Fiest KM, Dykman J, Patten S, Wiebe S, Kaplan GG, Maxwell CJ, Bulloch A, Jette N. Depression in epilepsy: A systematic review and meta-analysis. *Neurology* 2013;80:590–599.
2. Cramer J, Blum D, Fanning K, Reed M; Epilepsy Impact Project Group. The impact of comorbid depression on health resource utilization in a community sample of people with epilepsy. *Epilepsy Behav* 2004;5:337–342.
3. Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: A bidirectional association. *Ann Neurol* 2012;72:184–191.
4. Kandratavicius L, Ruggiero RN, Hallak JE, Garcia-Cairasco N, Leite JP. Pathophysiology of mood disorders in temporal lobe epilepsy. *Rev Bras Psiquiatr* 2012;34(suppl 2):S233–S259.
5. Lang UE, Borgwardt S. Molecular mechanisms of depression: Perspectives on new treatment strategies. *Cell Physiol Biochem* 2013;31:761–777.
6. Epps SA, Weinshenker D. Rhythm and blues: Animal models of epilepsy and depression comorbidity. *Biochem Pharmacol* 2013;85:135–146.
7. Ingelstrom KM. Preclinical antiepileptic actions of selective serotonin reuptake inhibitors: Implications for clinical trial design. *Epilepsia* 2012;53:596–605.
8. Hamid H, Kanner AM. Should antidepressant drugs of the selective serotonin reuptake inhibitor family be tested as antiepileptic drugs? *Epilepsy Behav* 2013;26:261–265.
9. Savik I, Lindstrom, Gulyas B, Halldin C, Andree B, Farde L. Limbic reductions of 5-HT_{1A} receptor binding in human temporal lobe epilepsy. *Neurology* 2004;60:749–756.
10. Theodore WH, Giovacchini G, Bonwetsch R, et al. The effect of antiepileptic drugs on 5-HT_{1A} receptor binding measured by positron emission tomography. *Epilepsia* 2006;47:499–503.
11. Theodore WH, Hasler G, Giovacchini, et al. Reduced hippocampal 5-HT_{1A} PET receptor binding and depression in temporal lobe epilepsy. *Epilepsia* 2007;48:1526–1530.
12. Manna I, Labate A, Gambardella A, Forbosco P, La Russa A, Piane EL, Aguglia U, Quattrone A. Serotonin transporter gene (5-Htt): Association analysis with temporal lobe epilepsy. *Neurosci Lett* 2007;421:52–56.
13. Hrovje H, Jasminka S, Lipa C, Vida D, Branimir J. Association of serotonin transporter promoter (5-HTTLPR) and intron 2 (VNTR-2) polymorphisms with treatment response in temporal lobe epilepsy. *Epilepsy Res* 2010;91:35–38.
14. Sprengelmeyer R, Steele JD, Mwangi B, Kumar P, Christmas D, Milders M, Matthews K. The insular cortex and neuroanatomy of major depression. *J Affect Disord* 2011;133:120–127.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 11/22/13
2. First Name Barry Last Name Gidal Degree PharmD
3. Are you the Main Assigned Author? Yes No
If no, enter your name as co-author:
4. Manuscript/Article Title:
5. Journal Issue you are submitting for: 13.6

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	<input checked="" type="checkbox"/>				
2. Consulting fee or honorarium	<input checked="" type="checkbox"/>				
3. Support for travel to meetings for the study or other purposes	<input checked="" type="checkbox"/>				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>				
5. Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>				
6. Provision of writing assistance, medicines, equipment, or administrative support.	<input checked="" type="checkbox"/>				
7. Other	<input checked="" type="checkbox"/>				

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section #3 Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	<input checked="" type="checkbox"/>				
2. Consultancy	<input type="checkbox"/>	6,000		Eisai, Upsher-Smith	
3. Employment	<input checked="" type="checkbox"/>				
4. Expert testimony	<input checked="" type="checkbox"/>				
5. Grants/grants pending	<input checked="" type="checkbox"/>				
6. Payment for lectures including service on speakers bureaus	<input type="checkbox"/>	7,500		UCB	, GSK
7. Payment for manuscript preparation.	<input checked="" type="checkbox"/>				
8. Patents (planned, pending or issued)	<input checked="" type="checkbox"/>				
9. Royalties	<input checked="" type="checkbox"/>				
10. Payment for development of educational presentations	<input checked="" type="checkbox"/>				
11. Stock/stock options	<input checked="" type="checkbox"/>				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	<input checked="" type="checkbox"/>				
13. Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>				

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- No other relationships/conditions/circumstances that present a potential conflict of interest.
 Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.
Epilepsy Currents Editorial Board