Published in final edited form as:

Biol Psychiatry. 2010 June 1; 67(11): e61–e62. doi:10.1016/j.biopsych.2009.12.036.

In Reply to: Childhood Maltreatment and Hypothalamic-Pituitary-Adrenal Axis Reactivity

Audrey R. Tyrka,

Mood Disorders Research Program and Laboratory for Clinical Neuroscience, Butler Hospital and the Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, 345 Blackstone Boulevard, Providence, RI 02906

Lawrence H. Price,

Mood Disorders Research Program and Laboratory for Clinical Neuroscience, Butler Hospital and the Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, 345 Blackstone Boulevard, Providence, RI 02906

Linda L. Carpenter, and

Mood Disorders Research Program and Laboratory for Clinical Neuroscience, Butler Hospital and the Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, 345 Blackstone Boulevard, Providence, RI 02906

George M. Anderson

Yale Child Study Center, Yale University School of Medicine, New Haven, CT

Audrey R. Tyrka: Audrey_Tyrka@Brown.edu

To the Editor

We published a report demonstrating an interaction of reported childhood maltreatment with variation in the corticotropin-releasing hormone (CRH) Type I receptor gene that was associated with altered cortisol responses to the dexamethasone (Dex)/CRH test in a sample of healthy adults (1). We noted that our findings are of particular interest because two recent studies that examined the same single nucleotide polymorphisms in the CRH Type I receptor gene showed similar gene-by-childhood maltreatment interactions in the prediction of depressive symptoms (2) or major depressive disorder (3). In the abstract and discussion, we speculated about the possible mechanisms and implications of our findings, taking into account previous related findings from the literature.

Dr. Carroll has taken issue with four of the five speculative statements included in the article. He states that “the data do not permit these conclusions” and that “there is no basis in these data” to support these speculations. In addition, he asserts that there are “several problematic aspects of the data and of the study design.” In support of these assertions, Dr. Carroll refers to two aspects of our study: first, that we did not have adrenocorticotropin (ACTH) data and, second, that the Dex/CRH test delivers a nonphysiologic stimulus.

Dr. Carroll contends that because our study involved cortisol data but not ACTH, we have no basis to speculate about the sensitivity of the CRH Type I receptor. Although we did not have ACTH data and, as we noted in the article, it is not known whether the polymorphisms

studied are functional, we believe it is entirely appropriate to *speculate* that our findings regarding the CRH Type I receptor gene might involve sensitivity of that receptor. Dr. Carroll refers to a study published by our group on temperament in relation to Dex/ CRH test responses to argue that ACTH is not likely to support conclusions drawn from our cortisol data. Given that the study at hand concerns childhood maltreatment and not temperament, we would refer Dr. Carroll to our more relevant study of childhood maltreatment in relation to cortisol and ACTH responses to the Trier Social Stress Test, which did indeed show that childhood maltreatment had effects on ACTH responses that corresponded to its effects on cortisol responses (4). Although we agree that ACTH data would be helpful in elucidating the mechanism of our finding, we believe that our report is of substantial interest without that data.

Second, Dr. Carroll makes the point that the response characteristics of the Dex/CRH test do not resemble those of physiologic stressors such as the Trier Social Stress Test. We appreciate this point and that this test likely reflects the response capacity in addition to sensitivity of the hypothalamic- pituitary-adrenal axis. However, we note that although ecological validity is one important aspect of a test, it does not represent the sine qua non of a scientifically informative neuroendocrine challenge test. Dr. Carroll asserts that our Dex/CRH test results argue against the possibility of “altered receptor feedback regulation” because the participants had suppressed plasma cortisol concentrations following administration of dexamethasone. However, the inhibitory effect of dexamethasone is primarily due to activity at pituitary glucocorticoid receptors (5), so that alterations of central corticosteroid receptor feedback cannot be ruled out. The Dex/CRH test is sensitive to increases in central CRH and vasopressin, which may result from impaired central glucocorticoid receptor signaling (6). It is also important to consider that the time frame and corticosteroid feedback mechanisms governing cortisol concentrations 16 hours following dexamethasone administration are likely different from those that are involved in acute CRH-induced secretion (7). Moreover, additional regulatory mechanisms, including possible autoregulatory effects of CRH on the CRH Type 1 receptor (8), could be involved.

In summary, Dr. Carroll raises a useful issue regarding the nature of the Dex/CRH test, and his comments highlight that ACTH data could be informative as to the mechanism of our findings. However, we submit that the findings described in our brief report are sound and of substantial interest and that our speculations about the possible mechanisms and implications of our findings are reasonable. In contrast to Dr. Carroll’s opening assertion that there are “several problematic aspects of the data and of the study design,” we believe that while the issues he raised are of interest, they do not represent problems with the data or the design and do not invalidate our findings.

Acknowledgments

The authors disclose the following biomedical financial interests and sources of support over the past 2 years and the foreseeable future. Drs. Tyrka, Price, and Carpenter have received grant/research support from the National Institutes of Health, National Alliance for Research on Schizophrenia and Depression, Department of Defense, Sepracor, Cyberonics, Neuronetics, UCB Pharma, and Medtronic. Dr. Tyrka received an honorarium for continuing medical education from the American Psychiatric Association from Lundbeck/Takeda. Dr. Anderson has received grant/research support from the National Institutes of Health, the Korczak Foundation (Amsterdam), and the Alan B. Slifka Foundation (New York City). Dr. Price has received speakers bureau honoraria from Jazz Pharmaceuticals

and MD Conferences/Psychiatry Review Course, consultant income from Gerson Lehrman, Wiley, Qatar National Research Fund, Alberta Heritage Foundation for Medical Research, Springer, and Lundbeck. Dr. Carpenter has served as a consultant or on an advisory board for AstraZeneca, Cyberonics, Novartis, Neuronetics, and Wyeth, and has received honoraria for continuing medical education from AstraZeneca and Speakers' Bureau honoraria from Cyberonics and Neuronetics and reimbursement for travel from Neuronetics.

References

1. Tyrka AR, Price LH, Gelernter J, Schepker C, Anderson GM, Carpenter LL. Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor Gene: Effects on hypothalamic-pituitary-adrenal axis reactivity. *Biol Psychiatry*. 2009; 66:681–685. [PubMed: 19596121]
2. Bradley RG, Binder EB, Epstein MP, Tang Y, Nair HP, Liu W, et al. Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. *Arch Gen Psychiatry*. 2008; 65:190–200. [PubMed: 18250257]
3. Polanczyk G, Caspi A, Williams B, Price TS, Danese A, Sugden K, et al. Protective effect of CRHR1 gene variants on the development of adult depression following childhood maltreatment: Replication and extension. *Arch Gen Psychiatry*. 2009; 66:978–985. [PubMed: 19736354]
4. Carpenter LL, Carvalho JP, Tyrka AR, Wier LM, Mello AF, Mello MF, et al. Decreased adrenocorticotropic hormone and cortisol responses to stress in healthy adults with a history of significant childhood maltreatment. *Biol Psychiatry*. 2007; 62:1080–1087. [PubMed: 17662255]
5. Cole MA, Kim PJ, Kalman BA, Spencer RL. Dexamethasone suppression of corticosteroid secretion: Evaluation of the site of action by receptor measures and functional studies. *Psychoneuroendocrinology*. 2000; 25:151–167. [PubMed: 10674279]
6. Ising M, Kunzel HE, Binder EB, Nickel T, Modell S, Holsboer F. The combined dexamethasone/CRH test as a potential surrogate marker in depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005; 29:1085–1093. [PubMed: 15950349]
7. Keller-Wood ME, Dallman MF. Corticosteroid inhibition of ACTH secretion. *Endocr Rev*. 1984; 5:1–24. [PubMed: 6323158]
8. Makino S, Hashimoto K, Gold PW. Multiple feedback mechanisms activating corticotropin-releasing hormone system in the brain during stress. *Pharmacol Biochem Behav*. 2002; 73:147–158. [PubMed: 12076734]