OXFORD

International Journal of Neuropsychopharmacology, 2015, 1–3

doi:10.1093/ijnp/pyv050
Focus Paper

FOCUS PAPER

The Role of Serotonin (5-HT) in Behavioral Control: Findings from Animal Research and Clinical Implications

CL Sanchez, PhD; CS Biskup, MD; S Herpertz, MD; TJ Gaber, Dipl.-Psych; CM Kuhn, PhD; SH Hood, MBBS, MSc, FRANZCP; FD Zepf, MD

Clinic for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, RWTH Aachen University, Aachen, Germany (Drs Sanchez, Biskup, and Mr Gaber); Jülich Aachen Research Alliance, JARA Translational Brain Medicine, Aachen & Jülich, Germany (Drs Sanchez, Biskup, and Mr Gaber); Department of Pharmacology and Cancer Biology, Duke University, Durham, NC (Drs Sanchez and Kuhn); Department of Psychiatry, Psychotherapy and Psychosomatics, University of Heidelberg, Heidelberg, Germany (Dr Herpertz); School of Psychiatry and Clinical Neurosciences (Dr Hood), and Department of Child and Adolescent Psychiatry, School of Psychiatry and Clinical Neurosciences & School of Paediatrics and Child Health (Dr ZEPF), Faculty of Medicine, Dentistry and Health Sciences, The University of Western Australia, Perth, WA, Australia; Specialised Child and Adolescent Mental Health Services, Department of Health in Western Australia, Perth, WA, Australia (Dr ZEPF)

Correspondence: Florian Daniel Zepf, MD, Chair and Winthrop Professor of Child and Adolescent Psychiatry, University of Western Australia, The University of Western Australia (M561), 35 Stirling Highway, Crawley WA 6009, Perth, Australia (florian.zepf@uwa.edu.au).

Abstract

The neurotransmitters serotonin and dopamine both have a critical role in the underlying neurobiology of different behaviors. With focus on the interplay between dopamine and serotonin, it has been proposed that dopamine biases behavior towards habitual responding, and with serotonin offsetting this phenomenon and directing the balance toward more flexible, goal-directed responding. The present focus paper stands in close relationship to the publication by Worbe et al. (2015), which deals with the effects of acute tryptophan depletion, a neurodietary physiological method to decrease central nervous serotonin synthesis in humans for a short period of time, on the balance between hypothetical goal-directed and habitual systems. In that research, acute tryptophan depletion challenge administration and a following short-term reduction in central nervous serotonin synthesis were associated with a shift of behavioral performance towards habitual responding, providing further evidence that central nervous serotonin function modulates the balance between goal-directed and stimulus-response habitual systems of behavioral control. In the present focus paper, we discuss the findings by Worbe and colleagues in light of animal experiments as well as clinical implications and discuss potential future avenues for related research.

Keywords: Serotonin, dopamine, behavior, habitual responding, goal-directed behavior

Received: April 28, 2015; **Accepted:** April 29, 2015

Introduction

Disentangling the role between goal-directed and habitual systems of behavioral control and how the neurotransmitter serotonin (5-HT) contributes to this is clinically important. Under normal conditions, human behavior can be flexible and adaptive, with actions directed by the value of the outcome in terms of goal-directed behaviors. When needed, more mechanistic and automatic responses to contextual cues can be elicited by stimulus-response actions, which are insensitive to goal value. The balance of both systems is crucial for correct instrumental learning (de Wit et al., 2009; Thrailkill and Bouton, 2015). Deficits in the balance of behavioral control between goal-directed and habit processes may lead to psychological problems such as drug addiction, schizophrenia, or obsessive-compulsive disorder. These systems can be distinguished experimentally by devaluing the reinforcer after an instrumental response has been learned and evaluating the frequency of responses to the devalued reinforcer using an instrumental discrimination task developed by de Wit et al. (2007).

Previous studies have yielded contradictory results about the interaction of dopamine (DA) and 5-HT in this balance. It has been suggested that DA biases behavior towards habitual responding, with 5-HT offsetting this phenomenon and directing the balance toward more flexible, goal-directed responding. However, previous research in animals and humans suggests roles for DA in both goal-directed and habitual action (De Wit et al., 2012). Furthermore, 5-HT has been implicated in punishment and behavioral inhibition and, more specifically, a reduced incentive motivation when 5-HT is low (Sanders et al., 2007; Cools et al., 2008; Hebart and Gläscher, 2014). Therefore, the relative and multiple roles of DA and 5-HT in the balance of goal-directed and habitual responding are unclear.

The paper by Worbe et al. (2015), which was recently published in this journal, focuses on the effects of acute tryptophan (TRP) depletion (ATD), a neurodietary physiological method to decrease central nervous 5-HT synthesis in humans for a short period of time, on the balance between hypothetical goal-directed and habitual systems. In this particular study conducted in healthy adult volunteers, a short-term serotonergic deficit induced by ATD was associated with a shift of behavioral performance towards habitual responding, the magnitude of which was predicted by a steeper decline in plasma levels of TRP, the physiological precursor amino acid of 5-HT. This finding is of particular relevance, as it shows that central nervous 5-HT function modulates the balance between goal-directed and stimulus-response habitual systems of behavioral control. In particular, Worbe et al. (2015) used the de Wit methodology to disentangle the role of 5-HT in goal-directed vs habitual action with careful controls for its other actions. They used ATD, which is a widely used translational research method, to lower serotonergic function with a TRP-deficient beverage (Young et al., 1985; Hood et al., 2005; Zepf et al., 2014). The authors showed that after an ATD challenge, subjects increased responding for devalued stimuli during the slip-of-action stage, indicating a devaluation of the outcome without changes in response-outcome learning. This effect implies a shift in the balance of action toward habitual responding during ATD. One useful feature of the present study was the use of several controls for other potential actions of 5-HT. No differences for valuable outcomes were found between groups, in contrast to previous reports suggesting insensitivity to reward value after pharmacological 5-HT reduction (Rogers et al., 2003; Line et al., 2014). Furthermore, ATD had no effect during a control test of response disinhibition, while other studies indicated a dual role of 5-HT in negative affect and behavioral inhibition (Cools et al., 2008).

However, various studies suggest that altered DA function during ATD could have contributed to the present results. Both animal (Yin et al., 2004; Faure et al., 2005) and human studies including those from the same laboratory have shown dopaminergic contribution to habit control. Recent findings from our laboratory indicate that ATD has the potential to influence both 5-HT and DA. Sánchez et al. (2014) in a mouse study showed that ATD not only impaired serotonergic function as previously described, but also lowered tyrosine (a semi-essential amino acid precursor of DA) and homovanillic acid (major end-product of DA metabolism). This finding suggests that nonserotonergic effects of ATD might contribute to its behavioral effects. The potential specificity of these formulations was previously questioned (Badawy et al., 2010). Future studies will hopefully explore the role of catecholaminergic function in this important type of behavioral control.

The impact of a short-term reduction in central nervous 5-HT synthesis by means of ATD on behavioral characteristics has been the subject of many studies (eg, see Bell et al., 2005; Biskup et al., 2012; Zepf et al., 2014). In particular, the effects of ATD on aggressive and impulsive behaviors and related behavioral constructs such as behavioral inhibition have attracted much attention. A recent study from our group on the underlying neural correlates of impulsivity in adult female volunteers combined the Moja-De ATD methodology with functional neuroimaging techniques employing a modified Go/No-Go task that implements punishment and reward (Helmbold et al., 2015). In this particular study, neural activation during No-Go trials in punishment conditions was positively correlated with ATD-related depletion magnitude in the ventral and subgenual anterior cingulate cortices (ACC), and neural activation in the medial orbitofrontal cortex and the dorsal ACC were also positively correlated with baseline impulsivity (Helmbold et al., 2015). Neural sensitivity to punishment after ATD administration in brain areas known to be associated with emotion regulation increased with depletion magnitude and in brain areas related to appraisal and expression of emotions (medial orbitofrontal cortex and dorsal ACC), increasing with baseline impulsivity (Helmbold et al., 2015). These findings support the conclusion that 5-HT modulates neural circuits related to impulsive behaviors, emotion regulation, and punishment processing, and the found effects somewhat map on the found relationship between depletion magnitude and the tendency detected by Worbe et al. (2015) towards habitual responding.

Conclusion

Studying the effects of other neuropharmacological challenge tests such as TRP enhancement (ie, within a loading paradigm) on both goal-directed and habit behavior could help to verify the role of 5-HT with regard to the outlined behaviors. Understanding the complex role of 5-HT and DA is crucial with regard to their critical position in the underlying neurobiology of neuropsychiatric disorders. In this context, the paper by Worbe et al. (2015) published in this journal relates to a component of the OCD clinical syndrome, namely a shift from goal-directed to habit-based behavior, that is sensitive to acute serotonergic manipulation that previous ATD in OCD studies have not examined or elicited. Future analysis of this variable might provide similar insights in related disorders with compulsive behavioral components, such as eating disorders (Kaye et al., 2000, 2003) and substance addiction (Liang and Ho, 2012).

Acknowledgments

The research leading to these results is funded by the European Union's Seventh Framework Programme (FP7/2007- 2013) under grant agreement no 602407.

Statement of Interest

In the past 6 years, F.D.Z. was the recipient of an unrestricted award donated by the American Psychiatric Association, the American Psychiatric Institute for Research and Education, and AstraZeneca (Young Minds in Psychiatry Award). He has also received research support from the German Federal Ministry for Economics and Technology, the German Society for Social Pediatrics and Adolescent Medicine, the Paul and Ursula Klein Foundation, the Dr. August Scheidel Foundation, and the IZKF of RWTH Aachen University and a travel stipend donated by the GlaxoSmithKline Foundation. He is the recipient of an unrestricted education grant, travel support, and speaker honoraria by Shire Pharmaceuticals, Germany, as well as editorial fees from Co-Action Publishing (Sweden). In addition, he has received support from the Raine Foundation for Medical Research (Raine Visiting Professorship). The other authors have nothing to disclose or report.

References

Badawy AA, Dougherty DM, Richard DM (2010) Specificity of the acute tryptophan and tyrosine plus phenylalanine depletion and loading tests I. Review of biochemical aspects and poor specificity of current amino acid formulations. Int J Tryptophan Res 2010:23–34

Bell CJ, Hood SD, Nutt DJ (2005) Acute tryptophan depletion. Part II: clinical effects and implications. Aust N Z J Psychiatry 39:565–574.

Biskup CS, Sánchez CL, Arrant A, Van Swearingen AED, Kuhn C, Zepf FD (2012) Effects of acute tryptophan depletion on brain serotonin function and concentrations of dopamine and norepinephrine in C57BL/6J and BALB/cJ mice. PLoS One 7:e35916

Cools R, Roberts AC, Robbins TW (2008) Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci 12:31–40.

De Wit S, Niry D, Wariyar R, Aitken MRF, Dickinson A (2007) Stimulus-outcome interactions during instrumental discrimination learning by rats and humans. J Exp Psychol Anim Behav Process 33:1–11.

De Wit S, Corlett PR, Aitken MR, Dickinson A, Fletcher PC (2009) Differential engagement of the ventromedial prefrontal cortex by goal-directed and habitual behavior toward food pictures in humans. J Neurosci 29:11330–11338.

De Wit S, Standing HR, Devito EE, Robinson OJ, Ridderinkhof KR, Robbins TW, Sahakian BJ (2012) Reliance on habits at the expense of goal-directed control following dopamine precursor depletion. Psychopharmacology (Berl) 219:621–631.

Faure A, Haberland U, Condé F, El Massioui N (2005) Lesion to the nigrostriatal dopamine system disrupts stimulus-response habit formation. J Neurosci 25:2771–2780.

Hebart MN, Gläscher J (2014) Serotonin and dopamine differentially affect appetitive and aversive general Pavlovian-to-instrumental transfer. Psychopharmacology (Berl) 232:437–451.

Helmbold K, Zvyagintsev M, Dahmen B, Bubenzer-Busch S, Gaber TJ, Crockett MJ, Klasen M, Sanchez CL, Eisert A, Konrad K, Habel U, Herpertz-Dahlmann B, Zepf FD (2015) Effects of serotonin depletion on punishment processing in the orbitofrontal and anterior cingulate cortices of healthy women. Eur Neuropsychopharmacol. Available at: http://dx.doi.org/10.1016/j.euroneuro.2015.02.007. Retrieved 27 Apr 2015.

Hood SD, Bell CJ, Nutt DJ (2005) Acute tryptophan depletion. Part I: rationale and methodology. Aust N Z J Psychiatry 39:558–564.

Kaye WH, Gendall KA, Fernstrom MH, Fernstrom JD, McConaha CW, Weltzin TE (2000) Effects of acute tryptophan depletion on mood in bulimia nervosa. Biol Psychiatry 47:151–157.

Kaye WH, Barbarich NC, Putnam K, Gendall KA, Fernstrom J, Fernstrom M, McConaha CW, Kishore A (2003) Anxiolytic effects of acute tryptophan depletion in anorexia nervosa. Int J Eat Disord 33:257–267.

Liang CS, Ho PS (2012) Tryptophan depletion in addictive behaviours. Br J Psychiatry 201:73.

Line SJ, Barkus C, Rawlings N, Jennings K, McHugh S, Sharp T, Bannerman DM (2014) Reduced sensitivity to both positive and negative reinforcement in mice over-expressing the 5-hydroxytryptamine transporter. Eur J Neurosci 40:3735–3745. Available at: http://doi.wiley.com/10.1111/ejn.12744. Retrieved 27 Apr 2015.

Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS (2003) Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. Neuropsychopharmacology 28:153–162.

Sánchez CL, Van Swearingen AED, Arrant AE, Kuhn CM, Zepf FD (2014) Dietary manipulation of serotonergic and dopaminergic function in C57BL/6J mice with amino acid depletion mixtures. J Neural Transm 121:153–162.

Sanders AC, Hussain AJ, Hen R, Zhuang X (2007) Chronic blockade or constitutive deletion of the serotonin transporter reduces operant responding for food reward. Neuropsychopharmacology 32:2321–2329.

Thrailkill EA, Bouton ME (2015) Contextual control of instrumental actions and habits. J Exp Psychol Anim Learn Cogn 41:69–80.

Worbe Y, Savulich G, de Wit S, Fernandez-Egea E, Robbins TW (2015) Tryptophan depletion promotes habitual over goal-directed control of appetitive responding in humans. Int J Neuropsychopharmacol:1–9 Available at: http://ijnp.oxfordjournals.org/cgi/doi/10.1093/ijnp/pyv013. Retrieved 27 Apr 2015.

Yin HH, Knowlton BJ, Balleine BW (2004) Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. Eur J Neurosci 19:181–189.

Young SN, Smith SE, Pihp RO, Ervin FR (1985) Psychopharmacology Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology (Berl) 87:173–177.

Zepf FD et al. (2014) Acute tryptophan depletion: converging evidence for decreasing central nervous serotonin synthesis in rodents and humans. Acta Psychiatr Scand 129:157–159.