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Review

The role of serotonin in reward, punishment and behavioural inhibition in humans: Insights from studies with acute tryptophan depletion

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ABSTRACT

Deakin and Graeff proposed that forebrain 5-hydroxytryptamine (5-HT) projections are activated by aversive events and mediate anticipatory coping responses including avoidance learning and suppression of the fight-flight escape/panic response. Other theories proposed 5-HT mediates aspects of behavioural inhibition or reward. Most of the evidence comes from rodent studies. We review 36 experimental studies in humans in which the technique of acute tryptophan depletion (ATD) was used to explicitly address the role of 5-HT in response inhibition, punishment and reward. ATD did not cause disinhibition of responding in the absence of rewards or punishments (9 studies). A major role for 5-HT in reward processing is unlikely but further tests are warranted by some ATD findings. Remarkably, ATD lessened the ability of punishments (losing points or notional money) to restrain behaviour without affecting reward processing in 7 studies. Two of these studies strongly indicate that ATD blocks 5-HT mediated aversively conditioned Pavlovian inhibition and this can explain a number of the behavioural effects of ATD.

Contents

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1. Introduction

1.1. Overview

The behavioural functions of 5-HT have been a matter of speculation, experiment and controversy since 5-HT was identified in the brain over 60 years ago. Many experiments using drugs or lesions to reduce 5-HT function have reported disinhibitory effects on a wide variety of animal behaviours. This has lead to 40 years of debate on the question of whether 5-HT systems have a general role in suppressing behaviour (Harvey et al., 1975) or have a more specific central role in processing aversive stimuli, as first suggested by Wise et al. (1970). Soubrié (1986) concluded that 5-HT neurones generally restrain behaviour in any competition between action and restraint, for example, in restraining responding for small rewards in order to obtain larger delayed rewards. Others have proposed that different 5-HT topographic systems and associated receptors orchestrate specific adaptive responses to aversive events and environments (Deakin, 1983, 2013; Deakin and Graeff, 1991; Lowry, 2002; Paul and Lowry, 2013). More recently a role of 5-HT in reward mechanisms has been proposed (see Roberts, 2011). These theories have had a predominantly animal behavioural perspective. However, the last decade has seen a number of studies with human participants that have employed cognitive neuroscience decision-making paradigms in order to isolate the effects of 5-HT manipulation on impulsivity and the processing of rewards and punishments. The implications of these studies for the behavioural functions of 5-HT are the subject of this review.

We confine our attention to human studies in which acute tryptophan depletion (ATD) was used to decrease 5-HT functioning because this has been by far the most common manipulation. This ingenious dietary manipulation markedly decreases circulating concentrations of tryptophan, the precursor of 5-HT, which is presumed to impair 5-HT synthesis and release. Compelling evidence that ATD decreases 5-HT release in humans or animals is lacking and the technique has been criticised on these grounds by van Donkelaar et al. (2011) and defended by Crockett et al. (2012a). We conclude that ATD effects on release are likely to be mild and that some 5HT projections may be more susceptible than others to ATD (see Supplementary material). Therefore absence of an ATD effect is an uncertain basis on which to reject a function of 5-HT.

The present review focuses on the implications of ATD effects on performance on tasks relevant to theories of 5-HT and inhibition, reward and punishment. We have not reviewed studies in clinical populations because our focus is on healthy mechanisms and there are recent extensive reviews of the cognitive neuropsychopharmacology of depression that cover ATD effects (Roiser et al., 2012; Elliott et al., 2011). For the same reason we have not reviewed ATD effects on emotion processing. Mendelsohn et al. (2009) comprehensively reviewed the effects of ATD on cognitive performance across a broad range of cognitive-perceptual domains. Their main conclusion was that ATD has a consistent effect in impairing declarative memory mainly on verbal list-learning tasks in the visual rather than auditory domain. Other forms of memory were not consistently affected. ATD had no consistent effects on executive or percepto-motor function that might affect studies of reward and punishment.

The last 10 years have seen attempts to formalise the role of 5-HT in behavioural inhibition and motivation using computational modelling of information processing during reward and punishment learning. For example temporal difference reinforcement learning (TDRL) models provide well established computational accounts of how learning proceeds in proportion to the unexpectedness of rewards (reward prediction error; RPE) which is signalled by dopamine neurones (Schultz et al., 1997). Several 'dopamine opponency' theories propose that 5-HT signals punishment prediction error (PPE) as an opponent to dopamine, and together they compute the trade-off between rewards and punishments that control activation and inhibition (Daw et al., 2002; Cools et al., 2011; Boureau and Dayan, 2011). According to such accounts 5-HT function is not specifically associated with inhibition or with punishment processing, but rather their combination. The suggestion that 5-HT governs the rate at which rewards devalue with delay (Doya, 2002) initiated another computational theme in understanding 5-HT functions. We discuss computational and other theories of 5-HT function that have been co-evolving from 10 years of ATD studies and their implications for Deakin and Graeff's (1991) anatomical theory of 5-HT and aversive coping.

1.2. Panic disorder in the context of 5-HT and punishment

Since the early behavioural pharmacology experiments of Graeff and others in animals, 5-HT has appeared to have opposite roles in different forms of anxiety (Graeff and Schoenfeld, 1970; Schütz et al., 1985). Deakin and Graeff (1991) and others (McNaughton and Corr, 2004; Deakin, 2013; Paul and Lowry, 2013) proposed a resolution in which different 5-HT systems mediate different adaptive responses (defences) depending on the imminence of the threat, as follows.