

REVIEW

THE ROLE OF THE SEROTONERGIC SYSTEM AT THE INTERFACE OF AGGRESSION AND SUICIDE

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Abstract—Alterations in serotonin (5-HT) neurochemistry have been implicated in the aetiology of all major neuropsychiatric disorders, ranging from schizophrenia to mood and anxiety-spectrum disorders. This review will focus on the multifaceted implications of 5-HT-ergic dysfunctions in the pathophysiology of aggressive and suicidal behaviours. After a brief overview of the anatomical distribution of the 5-HT-ergic system in the key brain areas that govern aggression and suicidal

behaviours, the implication of 5-HT markers (5-HT receptors, transporter as well as synthetic and metabolic enzymes) in these conditions is discussed. In this regard, particular emphasis is placed on the integration of pharmacological and genetic evidence from animal studies with the findings of human experimental and genetic association studies. Traditional views postulated an inverse relationship between 5-HT and aggression and suicidal behaviours; however, ample evidence has shown that this perspective may be overly simplistic, and that such pathological manifestations may reflect alterations in 5-HT homeostasis due to the interaction of genetic, environmental and gender-related factors, particularly during early critical developmental stages. The development of animal models that may capture the complexity of such interactions promises to afford a powerful tool to elucidate the pathophysiology of impulsive aggression and suicidability, and identify new effective therapies for these conditions. © 2013 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: impulsive-aggressive behaviours, suicide, 5-HT receptors, tryptophan hydroxylase, 5-HT transporter, monoamine oxidase A.

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; 5-HTT, 5-HT transporter; 5-HTTLPR, 5-HTT-linked promoter region; AAH, aromatic amino acid hydroxylase; AADC, L-aromatic amino acid decarboxylase; AP2, Activator Protein-2; BDHI, Buss-Durkee Hostility Inventory; CB, calbindin; DDC, dopa decarboxylase; DGGE, denaturing gradient gel electrophoresis; DRN, dorsal raphe nucleus; EPSPs, excitatory post-synaptic potentials; FAD, flavin-adenosine-dinucleotide; GI, gastrointestinal; His, histidine; IABs, impulsive-aggressive behaviours; IBTs, impulsive behavioural tendencies; INS/DEL, insertion/deletion; IPSP, inhibitory post-synaptic potentials; ir, immunoreactive; KO, knockout; MAO, monoamine oxidase; mPFC, medial prefrontal cortex; MRN, median raphe nucleus; NAC, nucleus accumbens; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; NRM, nucleus raphe magnus; NRO, nucleus raphe obscurus; NRP, nucleus raphe pallidus; NUDR/Deaf-1, nuclear-deformed epidermal auto regulatory factor-1; OFC, orbitofrontal cortex; PAG, periaqueductal gray; PET, positron emission tomography; PV, parvalbumin; SNPs, single nucleotide polymorphisms; SSRIs, serotonin selective reuptake blockers; TPH, tryptophan hydroxylase; Tyr, tyrosine; VNTR, variable number tandem repeat; VTA, ventral tegmental area; WT, wild-type.

Contents

Introduction: Challenging the 5-HT deficiency hypothesis in suicidal behaviour	161
The serotonergic system in aggression and suicide	162
Serotonergic innervation and 5-HT receptors distribution in PFC, amygdala and NAC	162
The 5-HT-ergic system in the PFC	162
The 5-HT-ergic system in the amygdala	163
The 5-HT-ergic system in the NAC	163
The role of 5-HT ₁ receptors in aggression and suicide	164
5-HT _{1A} receptors	164
5-HT _{1B} receptors	165
The role of 5-HT ₂ receptors in aggression and suicide	166
5-HT _{2A} receptors	166
5-HT _{2C} receptors	168
The role of other 5-HT receptors in aggression and suicide	168
5-HT ₃ receptors	168
5-HT ₄ , 5-HT ₆ and 5-HT ₇ receptors	168
The role of TPH in aggression and suicide	169
The role of 5-HTT in aggression and suicide	170
The role of MAO-A in aggression and suicide	172
Conclusions and research directions	173
Acknowledgments	174
References	174

INTRODUCTION: CHALLENGING THE 5-HT DEFICIENCY HYPOTHESIS IN SUICIDAL BEHAVIOUR

The definition of suicidal behaviours encompasses a broad constellation of heterogeneous entities, ranging from suicidal thoughts and death wishes to attempted and completed suicide. The great diversity of suicidal behaviours reflects their comorbidity with different psychiatric disorders, including affective disorders, psychoses, alcohol abuse and/or dependence, etc. In particular, numerous studies have shown a very robust association between multiple aspects of suicidal conduct and aggression. In keeping with this idea, multiple studies have pointed to pathological aggression and antisocial personality as major risk factors for suicide (Conner et al., 2001; Gureje et al., 2011).

The bulk of evidence points to the existence of at least two major subtypes of aggression, characterized by distinct behavioural profiles and neural underpinnings: *proactive aggression*, typically calculated and instrumental to gaining rewards; and *reactive aggression*, which is generally enacted impulsively as a stress-coping response to potentially threatening contingencies (Poulin and Boivin, 2000). Research has shown that both subtypes of aggression may influence suicidal conduct. Indeed, reactive aggression and impulsive personality characteristics have been recently highlighted as major risk factors for suicidal ideation and behaviour (Pfeffer et al., 2000; Conner et al., 2003; Dougherty et al., 2004; Hull-Blanks et al., 2004; Smith et al., 2008). Although impulsive actions often result in higher likelihood of self-inflicted painful and provocative experiences, they are rarely conducive to attempted and completed suicide, which typically require prior planning (Baca-Garcia et al., 2005; Wyder and De Leo, 2007; Smith et al., 2008; Witte et al., 2008). Conversely, while proactive aggression has been often regarded as unrelated to suicide, recent studies have shown that this subtype is actually associated to suicide attempt in men, but not women (Conner et al., 2009). Taken together,

these findings underscore the complex, multifaceted relationship between aggressive manifestations and suicidal behaviours.

The neurobiological link between aggression and suicide is apparently contributed by imbalances in serotonin (5-HT) neurotransmission. Findings from preclinical and clinical studies have indicated that dysregulations of 5-HT release, signalling and/or turnover may be robust correlates of violent reactivity (Virkkunen et al., 1995; Higley and Linnoila, 1997; Stanley et al., 2000) and impulsive-aggressive behaviours (IABs), which have been recently highlighted as critical intermediate phenotypes for suicidal conduct (Turecki, 2005; Zouk et al., 2007; Mann et al., 2009). Notably, both reactive aggression and suicide are affected by multiple biological variables that influence the regulation of 5-HT-ergic neurotransmission, including psychosocial stress, traumatic experiences, pathological personality traits, mental disorders, alcohol abuse and nicotine addiction (Turecki, 2001; Gibb et al., 2006; Nock et al., 2008; Mann et al., 2009; Pivac et al., 2010). For several decades the link between 5-HT and aggression was explained by a “5-HT deficiency hypothesis”, which posited a direct association of reduced CSF concentrations of 5-HT and/or its metabolite 5-hydroxyindoleacetic acid (5-HIAA) and suicidal/aggressive behaviour. Accumulating evidence, however, shows that this theory is inadequate to account for the pleiotropic role of 5-HT in the modulation of pathological aggression and suicidal behaviours; thus, current views postulate that IABs may be the final outcome of different homeostatic imbalances of the 5-HT system.

In the following section, we will briefly describe the 5-HT innervations of the forebrain regions involved in IABs and suicidal behaviours, such as the prefrontal cortex (PFC), amygdala and nucleus accumbens (NAc) (Davidson et al., 2000) (Fig. 1). In addition, we will overview the preclinical and clinical evidence on the best-characterized 5-HT-ergic targets implicated in violent and suicidal behaviours, including its receptors,

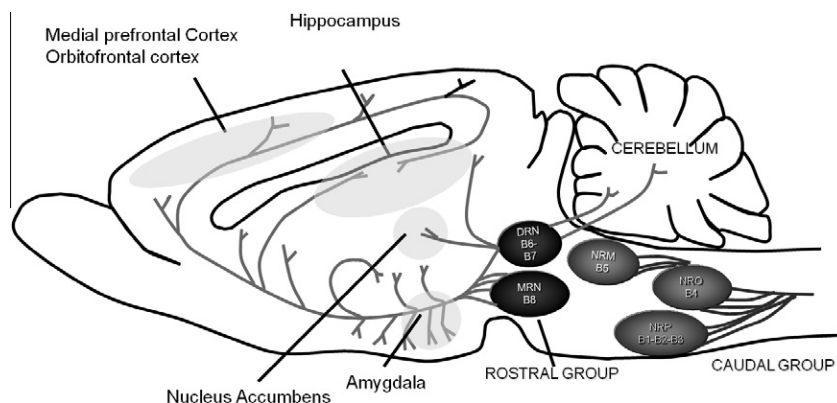


Fig. 1. Midsagittal view of the rat brainstem with serotonin-immunoreactive cell body groups. The ovals encompass the two major subdivisions of the brain serotonergic system. *Abbreviations:* DRN, dorsal raphe nucleus; MRN, medial raphe nucleus; NRM; nucleus raphe magnus; NRO, nucleus raphe obscurus. Cell groups B1 to B9 according to the terminology of Dahlstrom and Fuxe (1964). 5-HT innervations of the areas involved in aggression and suicide are depicted.

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