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Review

Animal models of the serotonin syndrome: A systematic review

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HIGHLIGHTS

- There is no consistent procedure to model the serotonin syndrome (SS) in rodents.
- Provide a comprehensive review of rodent models of the SS.
- Analyzed behavioral and autonomic responses induced by serotonergic drugs.
- Standardized test methods will improve future studies using animal models of the SS.

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ABSTRACT

The serotonin syndrome (SS) is a potentially life-threatening disorder in humans which is induced by ingestion of an overdose or by combination of two or more serotonin (5-HT)-enhancing drugs. In animals, acute administration of direct and indirect 5-HT agonists also leads to a set of behavioral and autonomic responses. In the current review, we provide an overview of the existing versions of the animal model of the SS. With a focus on studies in rats and mice, we analyze the frequency of behavioral and autonomic responses following administration of 5-HT-enhancing drugs and direct 5-HT agonists administered alone or in combination, and we briefly discuss the receptor mediation of these responses. Considering species differences, we identify a distinct set of behavioral and autonomic responses that are consistently observed following administration of direct and indirect 5-HT agonists. Finally, we discuss the importance of a standardized assessment of SS responses in rodents and the utility of animal models of the SS in translational studies, and provide suggestions for future research.

Contents

Abbreviations: 5-HT, serotonin; 5-HTP, 5-hydroxy-L-tryptophan; 5-HTT, 5-HT transporter; MAO, monoamine oxidase; MAOA-I, monoamine oxidase type A inhibitor; MAOB-I, monoamine oxidase type A inhibitor; MAOA/B-I, monoamine oxidase type A/B inhibitor; SNRI, serotonin/norepinephrine reuptake inhibitor; SS, serotonin syndrome; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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1. Introduction

The serotonin syndrome (SS) in man is an adverse, toxic drug reaction which is a result of excessive serotonergic activity and is potentially life threatening. It typically occurs following ingestion of two or more drugs that enhance serotonin (5-HT) levels, but it can also be induced by an overdose of single drug use. Animal models of the SS can be helpful in uncovering drugs and drug combinations suspected in inducing the SS in humans, in addition to uncovering underlying neurobiological fundamentals of the SS. Whereas several reviews to date have focused on the SS in man [e.g. 1–19], only four reviews have focused on basic research and animal models of the SS [5,20–22].

The aim of the current review is to provide a comprehensive assessment of the existing versions of the animal model of an SS, including a historical perspective, the commonalities and differences between various animal models of the SS, and the discussion of the utility of these models. To that end, we provide a brief overview of the SS in humans, including the symptoms of the SS, drugs implicated in the SS, and the incidence of the SS. We then review animal models of the SS focused on rats and mice, highlighting behavioral and autonomic responses, in addition to a discussion of assessment and quantification procedures. Based on the frequency of the various behavioral and autonomic responses induced by widely used direct and indirect 5-HT agonists, we outline the common behavioral and autonomic effects. Additionally, we briefly consider the involvement of various 5-HT receptor subtypes in the responses. Finally, we discuss the importance of standardization of assessment of SS responses in experimental research, and suggest directions for future research involving animal models of the SS.

2. The SS in humans

2.1. Terminology

Although 5-HT was already identified in 1949 by Rapport, the understanding that low synaptic 5-HT concentrations are involved in the pathogenesis of mood disorders was first gained at the beginning of the 1960s [23]. The awareness of the link between 5-HT and psychiatric disorders and the introduction of 5-HT-enhancing drugs in therapy increased the attention of general practitioners for side-effects of serotonergic drugs and entailed the first descriptions of the symptoms in the 1960s [24–26]. Throughout the years, several terms have been used to describe the SS. Already in use in basic research, the term SS was first applied to the clinical syndrome in 1982 [27]. The SS is also referred to as a "toxidrome" as the syndrome consists of a pattern of characteristic unwanted symptoms and is induced by an overdose of drugs acting as direct or indirect 5-HT agonists [13]. Other terms including 5-HT toxicity [for a review: [12,28]] and 5-HT toxicity syndrome [29] have also been used.

2.2. Symptoms and diagnostic criteria

The symptoms of the SS in humans are categorized as a triad of signs which include mental state alterations (e.g. agitation, confusion), neuromuscular excitation (e.g. myoclonus, tremor), and autonomic dysregulation (e.g. hyperthermia, tachycardia) [for a review: [1]]. It is thought that many symptoms of the SS are centrally mediated [1], although excess serotonergic activity in the peripheral nervous system may also contribute to the spectrum of symptoms (e.g. vomiting, diarrhea, etc.) [30].

The first detailed diagnostic criteria for the SS were introduced in 1991. Based on an evaluation of published clinical cases, the Sternbach criteria identified ten symptoms as being characteristic of the SS: confusion, hypomania, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, and incoordination [4]. The SS was diagnosed based on the presence of three of these symptoms, and whether these symptoms appeared subsequent to ingestion of 5-HT-enhancing drugs [4]. In 2003, the Hunter 5-HT Toxicity Scale was proposed based on a retrospective analysis of more than 2000 patients by the Hunter Area Toxicology Service (HATS) and provided decision rules for the diagnosis of the SS [31]. Compared to the earlier Sternbach criteria, the Hunter criteria are more specific, are simpler to use, are less likely to produce false positives, and are