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Review

Perspectives on genetic animal models of serotonin toxicity

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Abstract

Serotonin syndrome, or serotonin toxicity, is a serious disorder attributable to exaggerated serotonergic function in the brain, most commonly after antidepressant overdose or after combining several psychotropic medications. Similar condition (serotonin syndrome-like behavior) can be evoked in animals experimentally, following administration of serotonergic drugs. In addition to pharmacological stimulation, some genetic and other factors may contribute to serotonin toxicity, prompting the need for new experimental genetic models relevant to this disorder. Here we discuss current problems and perspectives regarding genetic animal models of serotonin-related syndromes, and outline the potential utility of these models in experimental neurochemistry and clinical research.
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Keywords: Serotonin syndrome (toxicity); Genetic animal models; Mutant and transgenic mice; Serotonin transporter

1. Introduction

Serotonin (5-HT) is a key neurotransmitter that modulates normal and pathological brain mechanisms via multiple metabotropic and one ionotropic receptors (Aghajanian and Sanders-Bush, 2002; Serretti et al., 2006; Gingrich and Hen, 2001). High-affinity transmembrane serotonin transporter (SERT) regulates serotonergic neurotransmission and is a target for numerous psychotropic drugs, including selective serotonin reuptake inhibitors (SSRIs) (Blakely, 2001; D.L. Murphy et al., 2004; G.M. Murphy et al., 2004; Kalueff et al., 2007b; Kiss, in press; Murphy et al., 2001).

Acute serotonin toxicity events, such as the relatively common serotonin syndrome (SS) associated with increased serotonergic tone, may be serious life-threatening disorders (Insel et al., 1982; Sternbach, 1991; Mills, 1997; Mackay et al., 1999; Mason et al., 2000; Gillman, 2007; Hernandez et al., 2002; Goeringer et al., 2000). Also termed ''serotonin toxicity'' or ''toxidrome'', SS is commonly observed as a triad of neuromuscular, autonomic and mental symptoms (Table 1) that arise after an antidepressant overdose, or a combination of several serotonergic drugs (Mills, 1997; Gillman, 1999; Otte et al., 2003; Dunkley et al., 2003; Isbister et al., 2004; Gnanadesigan et al., 2005).

SS can be caused by the excess of serotonin precursors or agonists, increased release of serotonin, and reduced serotonin reuptake or metabolism (Bodner et al., 1995; Birmes et al., 2003; Bijl, 2004; Gillman, 2004). Mild forms of SS may also develop following intake of some recreational drugs, such as 3,4-methylenedioxymethamphetamine (MDMA) (Demirkiran et al., 1996; Mueller and Korey, 1998; McCann et al., 2000; Parrott, 2002). Additional factors that contribute to SS may include dietary supplements, lithium and electroconvulsive therapy, liver or renal diseases, genetic defects in xenobiotic-metabolizing enzymes, combination of psychotropic medication with inhibitors of these enzymes (Munhoz, 2004; Kaneda et al., 2002; Jaber et al., 2006; Turner et al., 2006) or some other non-psychotropic drugs (e.g., antibiotics with monoamine oxidase (MAO)-inhibiting actions; Lawrence et al., 2006). With the increase in antidepressant medication usage, accompanied by the design of new serotonin-selective psychotropic drugs, the rising occurrence of SS (Isbister, 2003; Kaufman et al., 2006; Silins et al., 2007) emerges as a key challenge in biomedicine.

Specific behavioral and physiological responses (SS-like or serotonin-like behavior) that generally resemble human SS (Table 1), have been reported in animals with pharmacologically elevated serotonin (Gwaltney-Brant et al., 2000; Borsini

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Table 1
Human serotonin syndrome and animal serotonin syndrome-like phenomena

Human symptoms		Animal serotonin syndrome-like behavior	
Responses	References	Responses	References
Motor system (neurological symptoms)			
Hyperreflexia and muscle rigidity, tremor, clonus, myoclonus (seizures), incoordination and dizziness	Cohen et al. (1980), Sternbach (1991), Hegerl et al. (1998), Radomski et al. (2000), Dunkley et al. (2003)	Hypertonicity or rigidity, tremor, forepaw treading, head weaving and twitches, tics/back muscle contraction, flat/low body posture, hind limb abduction, backward gait	Jacobs (1976), Berendsen (1991), Coplan et al. (2000), Knapp et al. (2000), Ener et al. (2003), Van Oekelen et al. (2002, 2003), Isbister and Buckley (2005), Bert et al. (2006), Izumi et al. (2007)
Autonomic responses			
Temperature dysregulation (shivering, hyperthermia, diaphoresis, fever), hyperhydrosis (sweating), diarrhea; also: hypertonicity and tachycardia	Sternbach (1991), Hegerl et al. (1998), Radomski et al. (2000), Dunkley et al. (2003)	Temperature dysregulation (hyperthermia or hypothermia[a]), Straub tail, also: piloerection, salivation, hyperhydrosis, defecation	Jacobs (1976), Hwang and Woert (1979), Berendsen (1991), Bourin et al. (1996), Nisijima et al. (2003), Van Oekelen et al. (2002, 2003), Isbister and Buckley (2005), Bert et al. (2006), Fox and Murphy (2006b)
Mental status			
Agitation, confusion and hypomania	Sternbach (1991), Hegerl et al. (1998), Radomski et al. (2000), Dunkley et al. (2003)	Hyperactivity	Isbister and Buckley (2005)

[a] In addition to SS-like hyperthermia, mice and other species may also show hypothermic responses, especially to HTR1A agonists (e.g., Bert et al., 2006). Biphasic temperature responses, with hypothermia produced by relatively small increases in brain serotonin (mediated by HTR1A receptors) and hyperthermia following larger increases in serotonin concentrations (mediated by HTR2A receptors) in both brain and periphery, including muscle, and dependent upon ambient temperature (Abdel-Fattah et al., 1997).

et al., 2001; Izumi et al., 2006; Nisijima et al., 2000; Radomski et al., 2000; Jacobs and Fornal, 2002; Osei-Owusu et al., 2005; Piper et al., 2005). In fact, the term ''SS'' was originally used to describe an animal behavioral syndrome (Jacobs, 1976; Green and Grahame-Smith, 1976) and was first applied to clinical cases in 1982 by this laboratory (Insel et al., 1982), although earlier case reports described similar phenomena, without using this term (Oates and Sjoerdsma, 1960; Cohen et al., 1980; Mills, 1997).

Over the last years, there has been a growing body of literature on SS, reflecting the clinical importance of this disorder and emphasizing the role of different serotonin receptors (e.g., 5HT1AR, 5HT2AR, 5HT2CR, 5HT3R) in serotonin toxicity (Berendsen, 1991; Van Oekelen et al., 2002; Ener et al., 2003; Isbister and Buckley, 2005). However, the exact mechanisms of SS are still not yet fully understood (Bijl, 2004), and other mediators, in addition to serotonin, are thought to contribute to SS pathogenesis. Noradrenaline, glutamate, gamma-aminobutyric acid (GABA), opiate analogs and dopamine have been implicated in SS, most likely interacting and overlapping with serotonergic mechanisms (Shioda et al., 2004; Boyer and Shannon, 2005; Ener et al., 2003; Nisijima et al., 2000, 2004). Several comprehensive reviews have recently focused on SS pharmacology (Ener et al., 2003; Dunkley et al., 2003; Bijl, 2004; Boyer and Shannon, 2005), with evidence for parallel human and animal serotonin toxicity phenomena (Isbister and Buckley, 2005; Gillman, 2005a,b, 2006a,b).

During recent years, there has been a growing recognition of the importance of genetic factors in the pharmacology of serotonergic psychotropic drugs (D.L. Murphy et al., 2003, 2004; G.M. Murphy et al., 2003, 2004; Arias et al., 2005; Dorado et al., 2006; Popp et al., 2006; Toda et al., 2006; Oberlander et al., in press; Hu et al., 2007). Since genes regulating serotonergic function are attractive candidates in the search for risk factors of serotonin toxicity (Weiss et al., 2003), there is a need for new animal models of SS beyond the relatively well-modeled pharmacologic mechanisms. This paper evaluates recent animal genetic and neurochemical data relevant to modeling these disorders, and outlines future directions for research in this field.

2. Methodological considerations

Clinical diagnostics of SS is complicated by a broad range of symptoms with varying severity, and the lack of definitive laboratory tests (Hegerl et al., 1998; Isbister et al., 2001; Munhoz, 2004; Gillman, 2004, 2007; Terao and Hikichi, 2007). Diagnostic criteria for SS recently underwent a marked sophistication and improvement (Hegerl et al., 1998; Radomski et al., 2000; Dunkley et al., 2003; Isbister and Buckley, 2005), providing a better clinical focus for the development of animal models of serotonin toxicity (Table 1). However, as clinical criteria for SS are still unclear (Dunkley et al., 2003; Garside and Rosebush, 2003; Nelson et al., 2007), mild or atypical SS cases may be missed, while other illnesses, such as neuroleptic malignant syndrome, poisoning or seizures, may be mistaken for SS (Ames and Wirshing, 1993; Bodner et al., 1995; Demirkiran et al., 1996; Ener et al., 2003; Koppel, 2002; Gillman, 2005a,b, 2006a,b; Kaufman et al., 2006).

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In animals, the exact SS-like behaviors and the methods of their assessment are also the subject of debate (Hwang and Woert, 1979; Nagata and Izumi, 1991; Darmani and Ahmad, 1999; Van Oekelen et al., 2002; Weiss et al., 2003; Izumi et al., 2006, 2007), with most models mimicking motor and autonomic human SS responses (Table 1). At the same time, states that resemble SS-like behavior can be evoked in animals by drugs without direct serotonergic actions—opioids, convulsants or psychostimulants (e.g. Sotnikova et al., 2004) and hormones (e.g., thyrotropin releasing hormone; Pranzatelli, 1988), although some of these agents seem to have indirect pro-serotonergic effects (Gnanadesigan et al., 2005). These states may also partially resemble aberrant behavioral/neurological phenotypes unrelated to SS, such as Tourette's-like ticking or stereotypic behavior (Nordstrom and Burton, 2002), parkinsonism (tics, incoordination, low posture; Baik et al., 1995) or epilepsy (twitches, myoclonus, Straub tail, hyperthermia, backward gait; e.g., Schmitt et al., 2005). Psychogenic stress may also mimic some SS-like behaviors, including Straub tail (Katz, 1979), hyperthermia (Olivier et al., 2003), hyperactivity, low/flat body posture or backward gait (especially in some mouse strains listed in the Mouse Phenome Database; MPD, 2007), further complicating interpretations of animal SS-like phenotypes. The continuing paucity of relevant animal studies has recently been remarked upon (Gillman, 1999, 2005a,b, 2006a). While there may be some face validity in such findings, caution is needed when developing new animal models of SS, and special attention has to be paid to their construct validity, reflecting pathogenic mechanisms.

3. Genetic mouse models potentially related to SS

In general, two situations are relevant to experimental modeling of SS and its risk factors. Some genetically modified animals may display spontaneous SS-like phenotype, while other animals may show hypersensitivity to drugs that induce SS-like behaviors, or both. Human genetic vulnerability may be suggested by case reports of the development of SS following single, low doses of a MAO inhibitor, or treatment with cytochrome oxidase inhibitors (Boyer and Shannon, 2005; Terao and Hikichi, 2007). Mounting data evidences that individual sensitivity to antidepressant drugs (a potential predictor of the risks of SS) is related to genetic polymorphisms in human SERT (Smeraldi et al., 1998; Arias et al., 2005; Hu et al., 2007; Serretti et al., 2006, 2007), indicating the likely importance of SERT in SS (also see similar data on genetic polymorphisms in human 5HTR2A; D.L. Murphy et al., 2003; G.M. Murphy et al., 2003). SERT knockout (−/−) mice are a useful tool to assess the role of serotonin and SERT in various brain disorders (Bengel et al., 1998; D.L. Murphy et al., 2004). These mice display increased extracellular serotonin, altered expression of several serotonin receptors, and numerous behavioral anomalies, including hypolocomotion and anxiety (Holmes et al., 2002a,b, 2003a,b; Kim et al., 2005; Li, 2006).

Interestingly, SERT−/− mice spontaneously display Straub tail, tremor, tics, hind leg abduction, backward gait and flat back/low posture (Kalueff et al., 2007a)—a behavioral phenotype resembling SS-like behavior (Table 2; also see similar effects in saline-treated SERT−/− mice in: Fox et al., in press). Given the >10-fold increase in extracellular fluid serotonin concentrations in SERT−/− mice (Mathews et al., 2004), these mutants may represent a genetic model of SS, similar to that produced pharmacologically. Consistent with this, baseline hyperthermia, observed in some cases of SS, has also been reported in SERT−/− mice (Holmes et al., 2003c). Finally, recent pharmacological studies showed several exaggerated SS-like behaviors in SERT−/− versus SERT+/+ mice treated with serotonin-enhancing drugs (Fox and Murphy, 2006a; Fox et al., in press); also see hyperthermic responses in SERT−/− mice (Numachi et al., in press) treated with methamphetamine, representing a risk factor for clinical SS (Silins et al., 2007). Similarly, heterozygous SERT+/− mice display hypersensitivity to SSRIs and are highly relevant to human SERT genetic polymorphisms (Montanez et al., 2003; Kalueff et al., 2007b). These mice are characterized by multiple dysregulation in serotonergic systems (Li, 2006) and display exaggerated drug-induced SS-like responses (Fox and Murphy, 2006a; Fox et al., in press; Numachi et al., in press). Collectively, this suggests that SERT−/− and +/− mice may have significant face, predictive and construct validity as a mouse model relevant to serotonin toxicity.

Furthermore, there is a growing recognition of important neurochemical and genetic interactions between serotonin, SERT and brain-derived neurotrophic factor (BDNF) (D.L. Murphy et al., 2003; Mattson et al., 2004; Ren-Patterson et al., 2005, 2006; Yoshida et al., in press). A recent neurochemical study in mutant mice lacking one BDNF allele (BDNF+/− mice) showed a hippocampal hyper-serotonergic phenotype (Guiard et al., in press), suggesting that these mice (and possibly double mutant SERT−/− × BDNF+/− mice) may also be relevant to modeling genetically determined serotonergic dysregulation. In contrast, sensitivity to SSRIs was reduced in BDNF+/− mice in this and some previous studies (rev: Guiard et al., in press), thus limiting the utility of this model for targeting ''pharmacogenic'' SS.

Although there may be sufficient differences in human and animal receptor mechanisms of SS, several receptors, such as HTR1A (Sternbach, 1991; Birmes et al., 2003), HTR2A and HTR2C (Nisijima et al., 2001, 2003; Isbister and Buckley, 2005) receptors, have been strongly implicated in different aspects of serotonin toxicity. Therefore, it is logical to expect that mice with up-regulated HTR1A receptors may be prone to serotonin toxicity. Although transgenic mice over-expressing these receptors in cortex and dentate gyrus showed no alterations in baseline brain serotonin levels (Bert et al., 2006), they do display exacerbated SS-like behaviors (Table 2) following administration of HTR1A agonist 8-hydroxy-2-di-*n*-propylaminotetralin (8-OHDPAT), suggesting the utility of these transgenic mice as a second genetic model relevant to SS, with a particular focus on HTR1A-related mechanisms.

Interestingly, mutant mice that lack HTR1A receptors exhibit enhanced anxiety, elevated serotonin levels and hypersensitivity to SSRIs (Heisler et al., 2001; Parsons et al., 2001). Although somewhat opposite to mice over-expressing HTR1A receptors,

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Table 2
Phenotypes of selected genetically modified mice and their relevance to serotonin syndrome (SS)

Model	Selected responses (as in Table 1)									References
	"Core" SS-like responses (Jacobs, 1976)				Other typical SS-like responses			Related behaviors		
	Tremor, paw treading	Head weaving	Hind leg abduction	Straub tail	Tics	Flat/low body position	Backward gait	Basal hyperthermia	Incoordination	Anxiety	
Serotonin receptors											
Transgenic mice over-expressing HTR1A receptor + 8-OH-DPAT		+		–		–	+				Bert et al. (2006)
Serotonin transporter (SERT)											
Serotonin transporter knockout (−/−) mice	+			+	+	+	+		+	+	Kalueff et al. (2007a)
+ serotonin-enhancing drugs	+	+	+	+		+	+	+	+		Holmes et al. (2002a,b, 2003c) Fox et al. (in press)
Other models											
Dopamine D2 receptor knockout (−/−) mice			–			+	+		+	+	Baik et al. (1995)

Responses: (+) increased; (−) reduced or absent. *Drug:* 8-OH-DPAT: 8-hydroxy-2-(di-*n*-propylamino) tetralin, a HTR1A agonist.

they share many phenotypical features with SERT−/− mutant mice (as discussed above). Demonstrating disinhibition of central serotonergic neurotransmission and hypersensitivity to serotonergic drugs (Parsons et al., 2001; Richer et al., 2002), HTR1A−/− mice may be attractive for modeling SS-like phenotype and assessing the role of other serotonin receptors in serotonin toxicity. Thus, testing SS-like profiles of these mice, including SERT/HTR1A double knockout mice may be an interesting direction of research. Other particularly relevant mouse strains may be MAO A or A/B knockout mice (Evrard et al., 2002; Chen et al., 2004) or double knockout mice lacking MAO A and SERT or 5-HT1B receptors, displaying both elevated brain serotonin and altered sensitivity to serotonergic drugs (Salichon et al., 2001; D.L. Murphy et al., 2003).

As already mentioned, other mediators beyond serotonin contribute to pathogenesis of SS (Boyer and Shannon, 2005). For example, the adrenergic system modulates central serotonergic activity (Judge and Gartside, 2006), and targeted inactivation of α2c-adrenoreceptors (modulating both serotonin and dopamine) in mice leads to increases in specific drug-induced SS-like responses (Sallinen et al., 1998; Weiss et al., 2003). While both elevated serotonin and dopamine have been implicated in mouse SS-like behaviors (Shioda et al., 2004), recent data on dopaminergic modulation of SS-like hyperthermia in mice (Sugimoto et al., 2001) imply that genetically modified mice with disturbed dopaminergic pathways merit further scrutiny. For example, mice lacking dopamine D2 receptors (Baik et al., 1995) display spontaneous behaviors that resemble some SS-like responses (Table 2), and may be relevant to targeting dopaminergic components of SS pathogenesis. Dopamine transporter (DAT) is a key regulator of brain dopamine (Torres et al., 2003; Kalueff et al., 2007b), and may also be an interesting candidate for genetic models of serotonin toxicity. Consistent with this notion, Shen et al. (2004) have shown increased serotonin levels in SERT−/− mice after treatment with selective or non-selective DAT blockers. Likewise, recent studies also showed modulation of glutamatergic neurotransmission by serotonergic neurons (Marcoli et al., 2006), elevated glutametergic tone in animal models of SS (Shioda et al., 2004) and anti-SS activity of antagonists of glutamate receptors (Nisijima et al., 2004). Together, these findings suggest that modifications (including genetic manipulations) of the glutamatergic system may be relevant to new genetic models of SS.

Importantly, although gene-knockout techniques are powerful tools for understanding mechanisms of serotonin toxicity, they have certain significant limitations. For instance, when the product of a crucial gene is knocked out, the embryonic development may be altered and substantial compensatory changes may occur. Therefore, the mouse models with conditional knockout, or knockdown via RNAi, of specific serotonergic genes (such as SERT or HTR1A receptor genes) may lead to novel animal models which should be very useful in the studies of SS. Other genetic manipulations within SS-related pathways may include the use of antisense oligonucleotides to silence specific receptors and examine their role in SS. Using this approach, Van Oekelen et al. (2003) showed that

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silencing of HTR2A receptors in rodents reduces some of their SS-like responses, offering new insights into the pharmacogenetics of SS.

In addition to directed gene targeting (top-down strategy), genetic screens for SS-like behaviors (bottom-up strategy) have also been successful in experiments with non-specific chemically induced or gene-trap-induced mutagenesis (Weiss et al., 2003; Zhao et al., 2006). Identification of heritable mutations responsible for hypersensitivity to serotonergic drugs and specific SS-like behaviors (such as those used in the Weiss et al., 2003 study) can lead to new interesting animal models, further unraveling the genetics of SS (also see: Wieland and Lucki, 1991). Likewise, selective breeding of mice for their SS-like responses (similar to that already performed in rats; Knapp et al., 2000) may be a promising direction of research in this field.

4. Other aspects and research strategies

Setting the priorities for experimental modeling of serotonin toxicity is another important issue. Based on clinical manifestations of SS, a rational, clinically relevant strategy may be targeting life-threatening symptoms, such as hyperthermia (Boyer and Shannon, 2005), reported in an estimated 30% of clinical cases of SS. Therefore, animal models of serotonergically mediated hyperthermic responses (e.g., Nisijima et al., 2001, 2003, 2004, 2007), may represent an A-list priority for genetic modeling in this field. As a complementary strategy (by analogy with clinical criteria for SS; Table 1), good experimental models may be required to mimic several distinct SS-like responses from the spectrum. As already mentioned, animal SS-like responses mimic mostly autonomic and motor features of SS, and tend to ignore key mental symptoms of this disorder (Table 1). Therefore, a more balanced approach to animal models of SS is needed, also targeting mental symptoms such as agitation, hypomania and confusion, or states that commonly co-exist with SS, such as anxiety (Goitz, 2002).

Although the latter aspect of SS remains under-explored in both clinical and animal studies, it should be considered further. Are stress and anxiety relevant to SS pathogenesis? Recent animal data on attenuation of some SS-like behaviors by anxiolytic drugs (Nisijima et al., 2003) parallel well-known clinical data on partial benzodiazepine efficacy in clinical SS, and support the link between anxiety and SS. In fact, the growing practice of treating anxiety disorders with various SSRIs (Masand and Gupta, 2003), may provoke SS-related anxiety, leading to further clinical complications. Thus, mouse models characterized by both SS-like behaviors and anxiety (e.g., Table 2), may be useful for targeting mental symptoms of SS and/or the comorbidity aspect of its pathogenesis [also see interesting rat data showing correlation between anxiety, SS-like responses to serotonergic drugs and HTR1A receptor function; Knapp et al., 2000].

Another important issue in experimental models concerns the role of central versus peripheral mechanisms in serotonin toxicity (Hegerl et al., 1998; Isbister and Whyte, 2002; Squires et al., in press). For example, while central mechanisms play a key pathogenetic role in SS (Sternbach, 1991), some SS-like states may also be produced by peripheral factors (Berendsen, 1991; Van Oekelen et al., 2002), also consistent with more common neuromuscular and autonomic (versus mental) symptoms of SS (see above). Likewise, serotonin does not cross the blood–brain barrier, and direct effects of serotonin on muscle (resembling some symptoms of SS) have been clearly shown to contribute to other toxic syndromes (Wappler, 2001; Krause et al., 2004).

The involvement of peripheral mechanisms may have several implications for genetic modeling of serotonin toxicity. For example, some aspects of SS may sometimes be exaggerated by serotonin/dopamine-excreting carcinoid tumors, resembling the human carcinoid syndrome (Feldman and Plonk, 1977; McCormick, 2001; Russo et al., 2003, 2004). Therefore, it is possible to assume that mice with carcinoid tumors may represent interesting models relevant to SS, especially peripheral aspects of its pathogenesis (also see Bourin et al., 1996). For example, mutant mice spontaneously developing carcinoid tumors have been recently reported in the literature (Crabtree et al., 2001; Bertolino et al., 2003), meriting further evaluation of possible SS-like phenotypes. In line with a recent notion of similarities between the SERT−/− mouse phenotype and carcinoid syndrome (Mekontso-Dessap et al., 2006), mutant mice prone to carcinoid tumors, as well as double mutants that also lack SERT, HTR1A receptors and/or MAOA may help dissect peripheral and central aspects of SS. Another direction for further genetic dissection of central versus peripheral mechanisms of serotonin toxicity may be tissue-specific mutant or transgenic mice, as well as selected global mutant mice (such as tryptophan hydroxylase 1 and 2 knockout mice; Veenstra-VanderWeele and Cook, 2003) with the serotonergic system differentially affected in the brain and in the periphery.

In addition to pharmacodynamics-related genetic differences in side effects of serotonergic agents (D.L. Murphy et al., 2003; G.M. Murphy et al., 2003), metabolic factors may also play a role in serotonin toxicity (Dorado et al., 2006). Antidepressant drugs are metabolized by liver P450 cytochrome oxidases (Ramamoorthy et al., 2001), whose genetic polymorphisms in humans have been linked to SS (Sallee et al., 2000; Kaneda et al., 2002; Gonzalez, 2003; Sato et al., 2004; Scordo et al., 2005; Ueda et al., 2006). Given the importance of drug pharmacokinetics in SS (Ener et al., 2003), it is possible to expect that mice with genetic defects in cytochrome P450 enzymes may show exaggerated SS-like responses following administration of serotonergic drugs, thus making them potentially relevant to modeling risk factors of SS (see, for example, recent human data on SS associated with mutated cytochrome P450 enzyme in Sato et al., 2004).

Since genetic background influences behavioral and neurochemical (especially serotonin-mediated) phenotypes of mutant animals (e.g., Holmes et al., 2003a,b; D.L. Murphy et al., 2003), special attention has to be paid to background strains used in putative animal models of serotonin neurotoxic reactions. As recent data show marked strain differences in brain and peripheral serotonin levels (Cervo et al., 2005) and

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SS-like behaviors (Weiss et al., 2003), generation of SS-prone transgenic or mutant mice on selected ''SS-sensitive'' genetic backgrounds may be a useful research strategy for the development of new models of SS. Likewise, it may also be interesting to assess SS-like behaviors in a SERT−/− rat model recently described in the literature (Homberg et al., 2007).

Moreover, experimental modeling of serotonin toxicity may benefit markedly from using other models beyond relatively well-studied rodent species. The similarity of mode of action, behavior and gene response between insect and mammalian systems makes the insects (including genetically modified *Drosophila*) an attractive system to study brain disorders, as well as their pharmacology and genetics (Colas et al., 1995; Soehnge et al., 1996; Yellman et al., 1997; Feany and Bender, 2000; Nichols et al., 2002; Kalueff et al., 2007c). Empowered by a relatively easy experimental genetics, and low-cost maintenance of insects, this line of research may lead to new feasible high-throughput genetic and pharmacogenetic insect models relevant to mimicking different aspects of serotonin toxic reactions.

Finally, a number of studies have examined SS-like responses in various non-human primates (e.g., Curzon et al., 1960; Mizuta et al., 1990; Taffe et al., 2006). Therefore, cross-species experimental modeling of SS may be fostered by a wider use of non-human primate models, whose serotonergic genetics (Lesch et al., 1997; Barr et al., 2003, 2004) resembles that of humans, and whose behavioral, physiological and neurochemical reactions (Garrick et al., 1984; Garrick et al., 1985; Campbell et al., 1982; Meyer et al., 2006; Taffe et al., 2006) may be a close approximation to human serotonin toxicity.

5. Conclusions

The growing recognition of genetic factors in brain disorders caused by serotonergic dysregulation, including anxiety and depressive disorders (D.L. Murphy et al., 2003; G.M. Murphy et al., 2003; D.L. Murphy et al., 2004; G.M. Murphy et al., 2004; Serretti et al., 2006) and toxic reactions such as neuroleptic malignant syndrome and malignant hyperthermia (Wappler, 2001; Wappler et al., 2001; Isbister and Whyte, 2002; Galli et al., 2006; Nisijima et al., 2007; Carbone, 2000; Caroff and Mann, 1993), suggests a need for new genetic and pharmacogenetic models of serotonin toxicity. Although the exact pathogenetic mechanisms of these disorders and their clinical features differ (Rusyniak and Sprague, 2005, 2006; Kaufman et al., 2006; Sakkas et al., 1991; Kline et al., 1989), it is also possible to expect that they may share some common genetic determinants, and that these genes may be an important target for modeling a wider spectrum of serotonin-related toxic disorders. Some potentially relevant models, as well as directions for further research in this field, have been discussed here.

Over the last decades, there has been some progress in this area, leading to several animal models that may provide further insights into neurobiological and genetic mechanisms of serotonin toxicity, its risk factors and overlap with other illnesses. These models may further dissect serotonergic and other mechanisms, assess the role of different receptors, genetic interactions as well as central versus peripheral mechanisms, and thereby target models of different clinical subtypes of serotonin toxic reactions. In addition, such models may enable further *in vivo* studies of drug interactions in SS, also fostering the search for antidepressants and other drugs devoid of serotonergic toxic side effects, as well as new selective agents with specific therapeutic effects in SS.

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