

Hyperthermic Syndromes Induced by Toxins

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Body temperature regulation is complex and requires a balance between heat production and dissipation. Hyperthermia occurs when metabolic heat production exceeds heat dissipation. Many exogenously administered xenobiotics are capable of altering the body's ability to maintain a constant temperature. For example, agents with anticholinergic activity may contribute to hyperthermia by eliminating sweating and evaporation [1]. Because both recognition and treatment vary with the cause of hyperthermia, it is important for clinicians to understand the various presentations and treatments of toxin-induced hyperthermic syndromes.

Body temperature regulation in warm-blooded (endothermic) animals is divided into obligatory and facultative thermogenesis. Metabolic processes required for normal basal function generate heat, which contributes to maintaining a constant body temperature in a process known as obligatory thermogenesis. Secondary to acute changes in environmental temperatures, however, humans and warm-blooded animals require an adaptive or facultative thermogenic process to adjust their body temperatures rapidly.

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This process is largely governed through hypothalamic regulation of the sympathetic nervous system [2] and mitochondrial oxidative phosphorylation, both of which may be adversely affected by a variety of toxins.

Normal thermogenesis

Adaptive thermogenesis refers to the body's ability rapidly to induce heat production through hypothalamic regulation of the sympathetic nervous system [2]. The preoptic nucleus of the anterior hypothalamus responds to core temperature changes and regulates the autonomic nervous system, inducing either cutaneous vasodilation, dissipating heat when body temperature is elevated, or vasoconstriction, conserving heat when the body is cold [3]. Similarly, through the activation of the autonomic nervous system, humans have the unique ability to sweat, dissipating heat by evaporative cooling. This process is affected by a patient's hydration status, ambient temperature, conditioning, and acclimation [4]. Increasing motor activity from either exercise or shivering also increases heat production, with shivering representing a unique feature of mammalian thermogenesis regulated by the coordinated interaction between the hypothalamus and motor neurons in the spinal cord [5].

Norepinephrine [6], dopamine [7], and serotonin [8] have all been suggested to play major roles in regulating hypothalamic control of body temperature. Drugs altering the hypothalamic levels of these neurotransmitters are therefore capable of altering body temperature regulation. Activation of the hypothalamic-pituitary-thyroid and the hypothalamic-pituitary-adrenal axes further assists in maintaining body temperature. Sympathetic nervous system activation contributes to effects on thermogenesis through cutaneous vasoconstriction and nonshivering thermogenesis [9]. Nonshivering thermogenesis occurs primarily by uncoupling of oxidative phosphorylation through the activity of a group of mitochondrial proteins known as uncoupling proteins (UCP).

Oxidative phosphorylation requires proteins in the mitochondrial inner membrane transport chain to shuttle electrons through a series of oxidation/reduction reactions that ultimately result in oxygen being converted to carbon dioxide, water, and protons being pumped from the cytosolic side of the inner membrane into the inner membrane space. This process creates an electrochemical gradient, with the inner membrane space being charged in comparison with the matrix. The potential energy of this gradient is then converted into adenosine triphosphate (ATP) through a protein known as ATP synthetase. To maintain ATP at a relatively constant level in cells, mitochondrial respiration is stoichiometrically coupled to and rate-limited by ATP synthesis or steady state levels of adenosine diphosphate (ADP) and ATP. This coupling is referred to simplistically as *respiratory control*. When any toxin or protein short circuits this system by facilitating the leak of protons across the inner membrane independent of ATP synthetase, this

can affect thermogenesis. Chronically, thyroid hormones have also been shown to regulate the synthesis of UCPs [20], giving them both acute and chronic effects on temperature regulation.

Serotonin and sympathomimetic syndromes

Although many texts distinguish between the sympathomimetic syndrome and the serotonin syndrome, at times they are clinically indistinguishable. Because of their similar presentations and mechanisms of toxicity, the authors do not differentiate between the two syndromes. Acute intoxication with cocaine [21] and agents in the phenethylamine class (eg, amphetamine [22], methamphetamine [23], and 3,4-methylenedioxymethamphetamine [MDMA] [24]) may cause serotonin syndrome. Along with abuse, therapeutic usage of stimulants in combination with antidepressants has been reported to induce a serotonin syndrome [25,26].

With the plethora of serotonergically based antidepressant agents currently on the market and the increased popularity of the drug of abuse MDMA, there has been a marked increase in the number of case reports of and research conducted into serotonin syndrome. Although serotonin syndrome might appear to be a modern phenomenon, history is rich in cases. Numerous outbreaks of convulsive ergotism, from the contamination of grain with the fungus *Claviceps purpurea*, have been reported since the Middle Ages [27]. From one such outbreak it has been speculated that the Salem witch trials arose [28]. In the earliest medical case attributed to serotonin syndrome, reported in 1955, a patient experienced a recurrent drug reaction to the combination of meperidine and the monoamine oxidase inhibitor iproniazid [29]. In 1984, a possible case of serotonin syndrome would forever change the course of medical education in the United States. In that year, 18-year-old Libby Zion died of a presumed drug interaction between meperidine and phenelzine, a monoamine oxidase inhibitor [30]. Zion's father, an attorney and writer for the *New York Times*, used his influence to obtain a grand jury investigation into the conditions surrounding his daughter's death. The lasting ramifications of the jury's findings would include policies addressing resident supervision, resident duty hours, regulation of the use of restraints, and systems to prevent drug interactions [30].

Several good reviews on the clinical effects of serotonin syndrome have been conducted to date [26,31–34]. Although differences exist in the incidence of certain features seen in these reviews, the clinical findings are consistent. In most cases, patients present with the triad of altered mental status, autonomic instability, and abnormal neuromuscular activity. Altered mental status may manifest as coma, somnolence, confusion, agitation, and seizures, with some patients manifesting multiple symptoms in one presentation. Autonomic instability has been reported as fever, diaphoresis, tachycardia, hypertension or hypotension, and mydriasis. The neuromuscular derangements reported in serotonin syndrome include clonus,

myoclonus, rigidity, and hyperreflexia; all are more commonly reported in the lower than the upper extremities. Although the literature contains published criteria for the diagnosis of serotonin syndrome [32,34], they tend to be either nonspecific or impractical for practicing physicians. Instead, the authors recommend the consideration of serotonin syndrome in any patient on serotonergic agents who presents with the triad of altered mental status, autonomic instability, and neuromuscular abnormalities.

Although most cases of serotonin syndrome are mild and self limited, severe and fatal cases have been reported [24,29]. Fatal intoxications usually produce a clinical picture characterized by diaphoresis, tachycardia, muscle rigidity, rhabdomyolysis, metabolic acidosis, seizures, hyperkalemia, coagulopathy, and marked hyperpyrexia, with temperatures as high as 43.9°C being reported [35]. In cases of serotonin syndrome from MDMA, mortality directly correlates with core body temperatures, with cases in which body temperature was greater than 41.5°C resulting in fatality two thirds of the time [36]. Although severe hyperthermia represents the most serious manifestation of serotonin syndrome, it is reported in only about a third of cases [37]. The onset of serotonin syndrome typically occurs within hours of medication initiation; however, as many as a quarter of patients may not present until more than 24 hours after taking their medication [37].

Numerous compounds have been associated with serotonin syndrome; several articles review these [26,31–34,37]. Essentially, any drug capable of increasing the concentration of serotonin in the central nervous system has the potential to cause this syndrome (Fig. 2). Although it is most common with a combination of drugs (ie, monoamine oxidase inhibitor and tricyclic antidepressants), serotonin syndrome has also been reported with single-agent therapy [38,39]. Although the serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and many of the newer antidepressants are recognized by most physicians as having serotonergic activity, several commonly prescribed medications that can cause serotonin syndrome may not be as well recognized. Included in this group are dextromethorphan [40], meperidine [41], L-dopa [42], bromocriptine [42], tramadol [43], and lithium [44].

The mechanism of serotonin syndrome is complex and involves interaction between the environment, the central catecholamine release, the hypothalamic-pituitary-thyroid-adrenal axis, the sympathetic nervous system, and skeletal muscle (Fig. 3). The effect of ambient temperature on drugs that can cause serotonin syndrome has been well documented. In several animal studies, researchers have shown that elevating ambient temperature increases the body temperature and toxicity associated with MDMA [45] and methamphetamine [46,47], whereas lowering ambient temperature decreases these factors. This evidence supports the idea that MDMA and similar serotonergic agents cause a central deregulation of thermogenesis [48]. This idea is supported by the finding that deaths from cocaine are more frequent during months with elevated ambient temperatures [49], and it has important

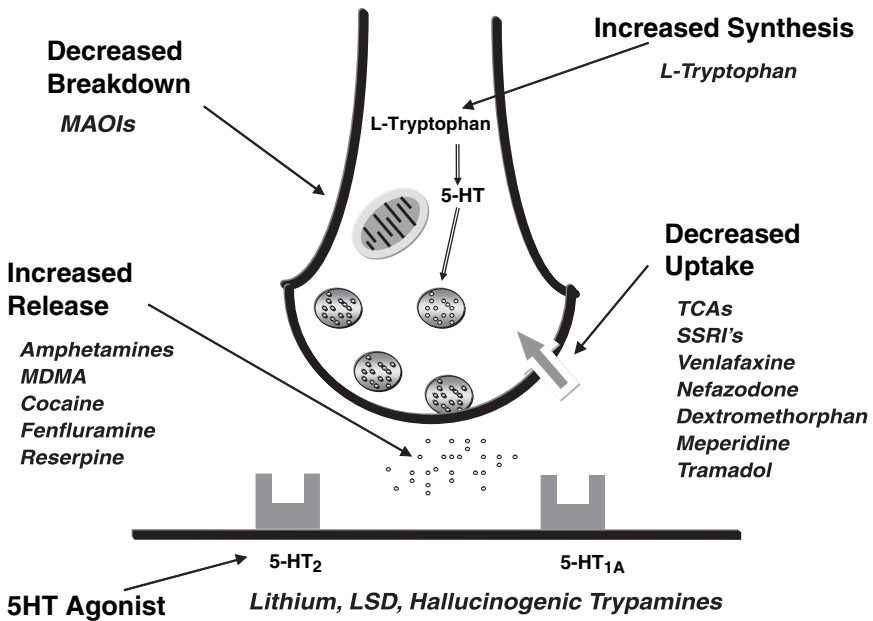


Fig. 2. Agents causing serotonin syndrome. Representative examples of agents and their various actions involving serotonin. Any agent capable of increasing serotonin concentrations in the synaptic cleft, increasing activity of or stimulating 5-HT_{2a} receptors, or decreasing the activity of or inhibiting 5-HT_{1a} receptors may, in theory, cause or contribute to hyperthermia from serotonin syndrome. MAOIs, monoamine oxidase inhibitors; SSRIs, serotonin selective reuptake inhibitors; TCAs, tricyclic antidepressants.

implications for users of recreational drugs such as MDMA in hot and crowded dance clubs.

Along with elevated ambient temperature, motor activity increases the toxicity of stimulants such as amphetamine and MDMA. Because motor activity can increase body temperature and exhaust supplies of ATP, it is not surprising that the combination of increased motor activity and stimulant use results in exaggerated toxicity [50,51]. This finding is particularly relevant to MDMA, which is typically taken at all-night dance parties. Recent work in the authors' laboratory using nuclear magnetic resonance has shown that MDMA decreases ATP in skeletal muscle of MDMA-treated anesthetized immobile rats, suggesting that MDMA impairs energy production in skeletal muscle [52]. When combined with the increased motor activity seen with MDMA, this impairment is a likely mechanism for the rhabdomyolysis seen in both humans [53] and experimental animals [54].

The hypothalamus is known to be a key thermoregulatory site in the central nervous system and is activated following MDMA treatment [55]. Thermoregulation within the hypothalamus has been suggested to be controlled by serotonin [7], dopamine [6], and norepinephrine [8]. Animal models of serotonin syndrome have likewise demonstrated acute elevations

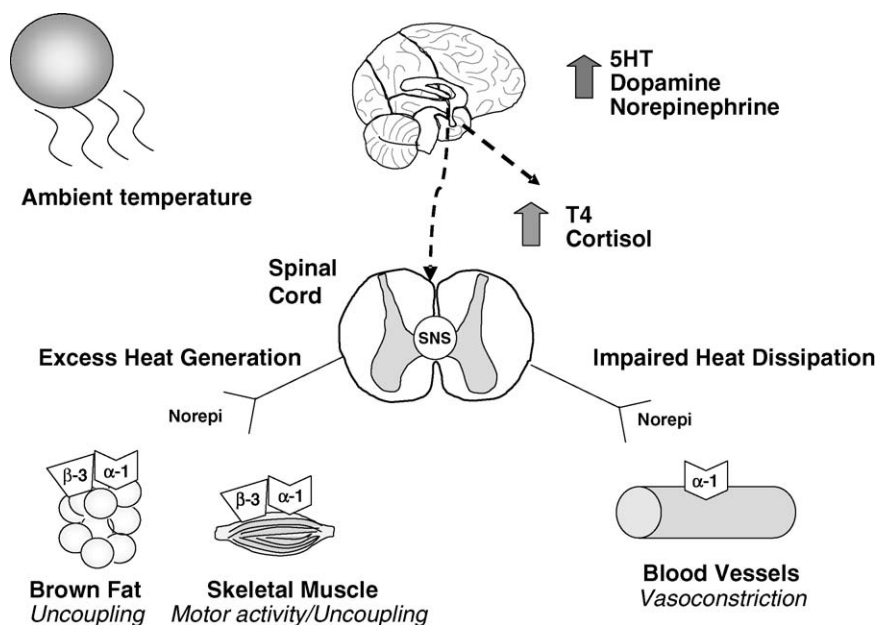


Fig. 3. Thermogenesis from serotonin syndrome. Serotonergic drugs increase central catecholamine release, activating the hypothalamus. The hypothalamus activates the pituitary/thyroid/adrenal glands to increase circulation levels of thyroid hormones and cortisol and the sympathetic nervous system to increase the peripheral release of norepinephrine. Norepinephrine activates α_1 and β_3 receptors on brown fat (rodents) and skeletal muscle (humans and rodents), causing uncoupling of oxidative phosphorylation and heat generation. Excess motor activity, which often accompanies serotonin syndrome, also increases heat generation. Elevated levels of norepinephrine cause vasoconstriction, impairing heat dissipation. Finally, ambient temperature plays an important role, with elevations resulting in higher body temperatures and increased morbidity and mortality. Norepi, norepinephrine; SNS, sympathetic nervous system.

in serotonin, norepinephrine, and dopamine in the anterior hypothalamus [56–58]. These findings correlate with elevated cerebrospinal fluid levels of these neurotransmitters in human cases of serotonin syndrome [59,60]. Direct and indirect stimulation of the hypothalamus by agents such as MDMA and methamphetamine activates the hypothalamic-pituitary-thyroid-adrenal axis, with subsequent thermogenesis and toxicity being dependent on the circulating levels of thyroid and adrenal hormones [61–64]. When activated neurons in the anterior hypothalamus stimulate the sympathetic nervous system, norepinephrine is released from nerve endings into the circulatory system. Significant elevations of norepinephrine have been shown by the authors' laboratory in rats treated with MDMA and have similarly been demonstrated in human users [65,66]. Acting through vascular α_1 -adrenoreceptors (AR), norepinephrine release from MDMA in rats and cocaine in humans induces vasoconstriction and impaired heat

dissipation [67,68]. In concert with the thyroid hormones, norepinephrine also binds to and activates α_1 - and β_3 -AR regulating the activity of thermogenic tissues, such as brown fat, through UCP [69]. Although the role of skeletal muscle UCPs in thermogenesis has been controversial, recent work suggests they may have an integral role in MDMA-induced hyperthermia [70]. Support for this notion comes from animal work showing that the combination of an α_1 - and β_3 -AR antagonist can prevent hyperthermia and mortality in a rat model of MDMA intoxication [62]. Similarly, mice lacking UCP3 express a blunted hyperthermic response to MDMA and are protected against its subsequent mortality [71]. In summary, serotonin syndrome appears to be a concerted action between central and peripheral catecholamine release, with resultant hypothalamic activation causing both impaired heat dissipation through vasoconstriction and excess heat generation through motor work and uncoupling (see Fig. 3).

Although mechanisms of serotonin syndrome are slowly beginning to come to light, the development of specific treatments has lagged behind. Part of the problem with developing treatments has been the incomplete understanding of which receptors are important for the generation and propagation of serotonin syndrome. In his original review article on the topic, Sternbach [32] made a case for the role of 5-hydroxytryptamine (5-HT_{1a}) receptors in the development and treatment of serotonin syndrome. More recently, however, studies have placed an emphasis on 5-HT_{2a} and D-1 receptors in mediating hyperthermia [72–74]. But these studies typically employ pretreatment models, which, although helpful in delineating mechanisms, offer little in the way of support for clinical treatments. Pretreatment models are particularly problematic with MDMA, because any drug that lowers core body temperature in rats, regardless of mechanism, is protective in MDMA intoxication. To date, the authors know of only two animal studies in which treatments employed after the establishment of MDMA-mediated hyperthermia showed a benefit. In one of these studies, the commonly used antipsychotics olanzapine and clozapine reduced MDMA hyperthermia and cutaneous vasoconstriction; in the other, carvedilol reduced MDMA hyperthermia and rhabdomyolysis [65,75]. Olanzapine and clozapine affect a variety of receptor systems, including 5-HT_{2a}, 5-HT_{1a}, D-1, D-2, and α_1 receptors, although which of these is responsible for its effects in MDMA hyperthermia is currently unknown. Carvedilol is an antagonist of $\beta_{1,2,3}$ -AR, as well as α_1 -AR. Hence it is a more attractive treatment choice for sympathomimetic and serotonin syndromes than other nonselective β -blockers, such as propranolol and nadolol. These lack affinity for α_1 - or β_3 -AR and so may enhance α_1 -AR-mediated vasoconstriction and heat retention. In both of these studies, however, the agents were used at significantly larger doses than are commonly used in humans, and we lack any clinical reports or studies of their role in humans.

Given similarities in the clinical presentation of serotonin syndrome and malignant hyperthermia, it has become tempting to speculate and even

assume that the molecular underpinnings of anesthesia- and MDMA-induced hyperthermic syndromes are the same. To date, however, both animal and human studies have shown mixed results, without convincing evidence of the usefulness of dantrolene in cases of serotonin syndrome [64,76–79].

The two most commonly reported beneficial drugs for serotonin syndrome are cyproheptadine and chlorpromazine [80–82]. Although both are reported to be beneficial, their utility is derived solely from case reports [82]. The purported benefits of these agents are thought to be mediated by their central serotonin antagonist properties. The recommended starting dose is 50 mg intramuscular (IM) for chlorpromazine and 4 to 16 mg of cyproheptadine orally. Other agents used in case reports include benzodiazepines, propranolol, and methysergide [82]. Of note is the theoretic benefit of benzodiazepines, which hyperpolarize neurons, reducing central mediated catecholamine release [83], and decrease hyperthermia from serotonin syndrome in rats [56]. Their anticonvulsant and anxiolytic properties, safety and availability, numerous routes of administration, potential titration to effect, and lack of contraindication in other causes of drug-induced hyperthermia make benzodiazepines a reasonable treatment choice in cases of sympathomimetic and serotonin syndromes.

Because hyperthermia represents one of the most serious complications of serotonin syndrome, it makes intuitive sense for physicians to seek actively to cool their patients. Few studies, however, have looked at the role of active cooling in serotonin syndrome. In one of these studies, dogs cooled through a femoral artery catheter after a lethal dose of amphetamine had dramatically increased survival times [84]. Although researchers have largely ignored this simple treatment step, teenagers and young adults have employed this method of treatment in the form of the chilled rooms available at rave parties, so-called “chill out” rooms. However, no research has been done on this topic in humans except in the setting of exertional and nonexertional heat stroke. In heat stroke, various means of external cooling, including cool water submersion and evaporative cooling with misting and fans, have shown rapid cooling of hyperthermic patients [85] and increased survival in animals [86]. Based on current knowledge, it appears prudent to recommend similar methods of cooling for patients with life-threatening hyperthermia from serotonin syndrome.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a rare idiosyncratic reaction typically occurring in persons taking neuroleptics or after the sudden withdrawal of dopamine agonists. The prevalence of NMS is typically reported as between 0.02% and 2.44% for patients taking neuroleptics [87]. These numbers, however, were typically generated by retrospective reviews of the older, higher-potency neuroleptic agents. With the recent advent of the atypical antipsychotics, it was hoped that lower prevalence and severity

of NMS would ensue, but a recent review of published cases casts doubt on this possibility [88].

NMS patients typically present with a clinical syndrome of hyperthermia, altered mental status, skeletal muscle rigidity, and autonomic dysfunction [89–93]. Hyperthermia is one of the most consistent features of NMS, with temperatures greater than 38°C being one of the key diagnostic features. Manifestations of altered mental status in NMS are variable, however, and include delirium, somnolence, coma, and mutism [93]. The muscle rigidity associated with NMS is typically described as “lead pipe,” denoting a resistance to passive motion. Finally, autonomic dysfunction is typically seen, with tachycardia, hyper- or hypotension, and diaphoresis. Other symptoms seen in NMS include tremor, cogwheeling, dystonic reactions, and choreiform movements [92,94]. The clinical presentation of NMS may vary, and it can occur in the absence of some or all of the classic clinical features [89,90]. Although the sequential development of signs and symptoms is variable in patients with NMS, symptom progression has been suggested to proceed from mental status changes to muscle rigidity, autonomic instability, and hyperthermia [95]. Common laboratory abnormalities seen in NMS include leukocytosis, elevated creatine phosphokinase (CPK), and low serum iron [92,96].

With the increased use of atypical antipsychotics and serotonergic antidepressants, it may be difficult to differentiate between NMS and serotonin syndrome in patients presenting with fever, muscle rigidity, autonomic instability, and altered mental status on concomitant medications. The authors believe that the speed of onset of symptoms and the finding of hyperreflexia/clonus are the most distinguishing features between these two syndromes. Patients who have serotonin syndrome typically present acutely, within 24 hours of starting their medication, whereas patients who have NMS may present at any time in their drug course, with peak symptoms not occurring for days [93]. In patients who have serotonin syndrome, clonus, hyperreflexia, and myoclonus are commonly reported, whereas these symptoms are rarely reported in NMS [31].

Although NMS is most commonly reported with the use of high-potency neuroleptics, such as haloperidol, it does occur with the atypical neuroleptics (eg, risperidone, olanzapine) [88], as well as with nonneuroleptic drugs, including metaclopramide [97], prochlorperazine [98], and promethazine [99]; it may also result from the acute withdrawal of antiparkinsonian agents [100].

Difficulties in establishing an animal model for NMS have led to difficulties in understanding the cause [101]. Although NMS is believed to be due to central dopamine antagonism, particularly within the hypothalamus [102], the sympathetic nervous system also appears to play a critical role [103]. In patients with NMS, peripheral and cerebral spinal fluid catecholamines have been shown to be markedly elevated [104–106]. In particular, cerebral spinal fluid levels of norepinephrine during the acute phase of

illness were two times greater than those of matched controls or during convalescence [104]. Similar findings have been reported for plasma concentrations of serotonin and epinephrine [107]. Although less is known about the cellular events leading to NMS, overlap between the clinical features and catecholamine levels of NMS and serotonin syndrome suggests similar mechanisms.

In NMS, as in all cases of drug-induced hyperthermia, the first step in managing the patient is the removal of the offending drug. The most commonly recommended drugs in the treatment of NMS are bromocriptine and dantrolene. The recommendations for the use of bromocriptine and dantrolene are based solely on case reports and retrospective reviews.

Bromocriptine is an orally administered dopamine agonist and has been used with reported success in treating NMS [108–110]. In one study, early discontinuation of bromocriptine resulted in recrudescence of NMS in two patients who responded to reinstatement of therapy [108]. Similarities between the clinical features of NMS and malignant hyperthermia have prompted many physicians to use dantrolene for patients with NMS, with some reported success [111]. A case-controlled analysis comparing dantrolene and dopamine agonists in treating NMS reported evidence for significant reduction in the mortality when dantrolene, bromocriptine, amantadine, and other dopamine agonists were used alone or in combination [112]. Other authors, however, have concluded the opposite and suggested that the use of dantrolene and bromocriptine may actually worsen the course of NMS over the use of supportive measures alone [113].

In patients with mild symptoms, drug withdrawal and supportive care are the mainstays of treatment. In patients with severe symptoms (ie, temperature greater than 40°C, coma, and severe rhabdomyolysis), the combined use of dantrolene and bromocriptine may be warranted [114,115]. The usual dose of bromocriptine to treat NMS ranges from 5 to 20 mg every 6 hours, with the most common side effects being hypotension, dyskinesia, and erythematous, tender lower extremities (erythromelalgia) [101,108]. Dantrolene should be administered intravenously at a dose ranging from 3 to 5 mg/kg divided three times a day. When patients are able to take oral medications, dantrolene may be given orally at a dose of 100 to 400 mg/d divided four times a day. The most serious side effect of dantrolene is liver toxicity; it should be avoided in patients with underlying liver disease. Treatment should be continued for 10 days beyond symptom resolution to prevent the recrudescence of NMS [115]. Benzodiazepines have also been used for the treatment of anxiety and catatonia associated with NMS [116,117] and may be effective single agents in mild cases [118]. Other agents that have been used in treatment include carbidopa/levodopa, L-dopa, carbamazepine, amantadine, and methylprednisolone [90]. More recently, a randomized clinical trial suggested some benefit in patients who have NMS and are treated with methylprednisolone [119]. For patients refractory to pharmacotherapy and supportive measures, electroconvulsive therapy

(ECT) may prove beneficial, but controlled studies comparing ECT, pharmacotherapy, and supportive care are lacking [101,115]. In those patients in whom NMS and serotonin syndrome cannot be differentiated, the authors recommend the use of benzodiazepines for treatment, because bromocriptine can potentially worsen serotonin syndrome and chlorpromazine could worsen NMS.

Because many patients are dependent on neuroleptic agents for the control of their mental illness, the question of when to reinstitute therapy is crucial. Although safe reinstatement of therapy with the same drug has been reported [120], reoccurrence has been reported as well [101]. Based on the unpredictable nature of the disease and the risk for recurrence, it is generally recommended to withhold therapy for at least 2 weeks after a case of NMS [120] and then reinstitute it, if possible with a lower-potency agent.

Malignant hyperthermia

Malignant hyperthermia (MH) was first described in 1960, when a 21-year-old Australian student requiring orthopedic surgery developed hyperthermia, hypotension, and cyanosis during anesthesia with halothane. A detailed family history revealed that 10 of his close relatives had died during or after anesthesia, clearly establishing a genetic link to his anesthesia reaction [121]. Before adequate screening and treatment for MH, the initial fatality rate of MH was approximately 70%, whereas today it is closer to 5% [122]. The prevalence of MH during general anesthesia varies from 1:15,000 in children to 1:50,000 in adults [123].

Clinical symptoms of MH are the consequences of uncontrolled calcium release in skeletal muscle and the subsequent uncoupling of oxidative phosphorylation and excess cellular metabolism. Exaggerated jaw rigidity after succinylcholine and excess carbon dioxide production are often the earliest signs [122]. As symptoms progress, skeletal muscle rigidity, tachycardia, and hyperthermia develop. As ATP depletion occurs, anaerobic metabolism with metabolic acidosis and lactate production occurs, followed ultimately by skeletal muscle breakdown with elevations in serum creatine kinase and hyperkalemic cardiac arrest. As with other causes of drug-related hyperthermia, consumptive coagulopathy, pulmonary edema, and cerebral edema can develop as late and potentially fatal complications [124].

Agents inciting MH include many inhalational volatile anesthetics (ether, halothane, enflurane, isoflurane, sevoflurane, desflurane) and depolarizing muscle relaxants such as succinylcholine and decamethonium [125]. Some patients have developed an MH reaction after undergoing previous general anesthesia with known triggering agents without problems. Although MH is typically associated with anesthetics, persons genetically susceptible to it may develop symptoms after excess exertion in warm environments [126,127].

MH occurs in persons with genetic defects at one of several receptors controlling the release of sarcoplasmic calcium in skeletal muscle [128]. When they are exposed to triggering agents, sudden increases in intracellular calcium result in a cascade of events, ultimately leading to the uncoupling of oxidative phosphorylation in the mitochondria with excess metabolic breakdown. The sympathetic nervous system plays an important role in mediating symptoms of MH such as significant elevations in circulating norepinephrine [129,130], and increased survival with therapeutic α -blockade has been demonstrated in animal models [131,132]. Nonetheless, norepinephrine does not appear to induce MH [133]. Activation of the hypothalamic-pituitary-adrenal axis is also believed to occur in MH, because pigs undergoing adrenalectomy appear more resistant to the lethal effects of a halothane challenge [132]. Elevated levels of serotonin have also been demonstrated in MH [134], with serotonergic drug agonists causing exaggerated responses in MH-susceptible pigs [135–137]. Serotonin antagonists, however, have not been shown to be effective in preventing MH in susceptible swine [138]. In summary, MH occurs secondary to unregulated calcium release with excess metabolic breakdown and uncoupling of oxidative phosphorylations, which likely contributes to the activation of the sympathetic nervous system and release of catecholamines.

Dantrolene sodium is an effective antidote for MH. Dantrolene causes complete and sustained relaxation of skeletal muscle contractures *in vitro* in MH-susceptible muscle and *in vivo* in both human and porcine MH [139]. Dantrolene inhibits intracellular calcium release in the myocyte by direct action on calcium release channels, with two separate binding sites proposed [140]. At low doses, dantrolene may actually release calcium, which could explain the recrudescence of symptoms in MH [140,141]. Side effects include muscle weakness, dizziness, and hepatic dysfunction [142]. Dosing of dantrolene is 1 to 3 mg/kg intravenously, repeated every 15 minutes as needed to a maximum dose of 10 mg/kg in the setting of acute MH. Recurrence is prevented by administration of dantrolene 1 mg/kg intravenously (or as much as 2 mg/kg orally) four times a day for 24 to 72 hours post-operatively. Those patients thought to have MH should be referred to an approved MH testing facility to arrange for genetic and muscle testing.

Summary

Toxin-induced hyperthermic syndromes are important to consider in the differential diagnosis of patients presenting with fever and muscle rigidity. If untreated, toxin-induced hyperthermia may result in fatal hyperthermia with multisystem organ failure. All of these syndromes have at their center the disruption of normal thermogenic mechanisms, resulting in the activation of the hypothalamus and sympathetic nervous systems. The result of this thermogenic dysregulation is excess heat generation

combined with impaired heat dissipation. Although many similarities exist among the clinical presentations and pathophysiologies of toxin-induced hyperthermic syndromes, important differences exist among their triggers and treatments.

Serotonin syndrome typically occurs within hours of the addition of a new serotonergic agent or the abuse of stimulants such as MDMA or methamphetamine. Treatment involves discontinuing the offending agent and administering either a central serotonergic antagonist, such as cyproheptadine or chlorpromazine, a benzodiazepine, or a combination of the two. NMS typically occurs over hours to days in a patient taking a neuroleptic agent; its recommended treatment is generally the combination of a central dopamine agonist, bromocriptine or L-dopa, and dantrolene. In those patients in whom it is difficult to differentiate between serotonin and neuroleptic malignant syndromes, the physical examination may be helpful: clonus and hyperreflexia are more suggestive of serotonin syndrome, whereas lead-pipe rigidity is suggestive of NMS. In patients in whom serotonin syndrome and NMS cannot be differentiated, benzodiazepines represent the safest therapeutic option.

MH presents rapidly with jaw rigidity, hyperthermia, and hypercarbia. Although it almost always occurs in the setting of surgical anesthesia, cases have occurred in susceptible individuals during exertion. The treatment of MH involves the use of dantrolene. Future improvements in understanding the pathophysiology and clinical presentations of these syndromes will undoubtedly result in earlier recognition and better treatment strategies.

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