REVIEWS

Common Clinical Manifestations of Serotonin Deficiency and Intoxication Syndrome

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Clinical manifestations of serotonin deficiency, its genesis, diagnostics, and treatment are described. The contribution of free hemoglobin and myoglobin to the genesis of absolute serotonin deficiency — disseminated intravascular coagulation (DIC) syndrome — is shown. Evidence is presented suggesting that chronic serotonin deficiency underlies aged-related and diabetic angiopathies. It is demonstrated that the serotonin deficiency syndrome has common clinical manifestations with the intoxication syndrome.

Key Words: *serotonin; serotonin-ferroprotein receptors; serotonin deficiency syndrome; smooth muscle insufficiency; intoxication syndrome; DIC syndrome*

Normal functioning of the human body is associated with a wide range of biologically active substances. Some of them (hormones) circulate in the bloodstream in strictly defined concentrations, and an absolute or relative rise or fall in their concentration leads to pathological processes with specific clinical and laboratory manifestations. A disease accompanied by hyperserotoninemia has been described as the carcinoid syndrome; however, the symptoms of hyposerotoninemia have not been outlined, i.e., there is no clinical definition of the serotonin deficiency syndrome.

The role of serotonin in the body has been studied since 1948s [20], when serotonin was isolated from animal blood serum and its high biological activity was demonstrated. Subsequently, serotonin (5-hydroxytryptamine) was detected practically in all animal species, in man, and in many plants. Serotonin and its receptors are present in the brain and other organs. Eighty-ninety-five percent of serotonin in the body is synthesized and stored in enterochromaffin cells of the gastrointestinal tract. Blood levels of serotonin normally vary from 20 to 200 μg/liter, but can be as high as 5200 μg/liter in the carcinoid syndrome. Although serotonin has been the subject of numerous studies, its role in the body remains unclear [2-4,7,8,18-20,22].

The carcinoid syndrome is accompanied by diarrhea and hyperemia of the skin (due to elevated activity of smooth muscles in the gastrointestinal tract and the microcirculatory bed) and by thrombocytosis. It is logical to suppose that serotonin deficiency is manifested as impaired smooth muscle (SM) contractility and thrombocytopenia. Figure 1 illustrates the interactions between serotonin and serotonin receptors (SR) and general patterns of serotonin behavior in the body.

Normally, serotonin does not cross the blood-brain barrier which is permeable for its precursors, metabolites, and antagonists. This barrier can be regarded as a natural borderline separating circulating serotonin and SR of the body (general serotonin cycle) into two pools: serotonin and SR confined to the central nervous system (minor serotonin cycle) and to other organs and tissues (major serotonin cycle).

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The major serotonin cycle includes a) serotonin synthesis, storage, and release by enterochromaffin cells, b) serotonin adsorption, storage, transport, and release by platelets, c) serotonin interaction with SR in SM and other organs and systems, and d) elimination of serotonin metabolites from the body.

The minor serotonin cycle includes a) serotonin synthesis, storage, and release by specific cells of the central nervous system (CNS), b) transport of serotonin from the sites of its synthesis to the sites of its interaction with SR in the CNS, c) serotonin interaction with these SR, and d) release of serotonin metabolites from the minor into the major cycle. In the CNS, the transport function of platelets can be mediated by certain substances in the cerebrospinal fluid. The fundamental difference between the two cycles lies in the rates of serotonin metabolism. In fact, serotonin half-life in the CNS is 2-20 min, in enterochromaffin cells it is 11-17 h, and 33-48 h in platelets, i.e., serotonin half-life in the major cycle, where it ranges from 11 to 48 h, is hundreds to thousands times longer than in the CNS [4,7,8, 19,20,22].

Functional impairment of organs and systems containing SR may result both from a decrease in the total amount of serotonin in the body and the appearance of endo- and/or exogenous serotonin antagonists. Organ and system functions may also be impaired after relatively small changes in the serotonin cycle components (synthesis and transport of serotonin and its interaction with SR) or in the level of degradation of these receptors. In order to better understand the role of serotonin in the body and ensure targeted modeling of the processes leading to the serotonin deficiency syndrome, it is appropriate to consider first the conditions of impaired serotonin-receptor interactions. Our method of investigation is based on the working hypothesis of "serotonin cycles" with predictive identification of their most vulnerable components followed by modeling of particular pathological process or its component. The processes leading to serotonin deficiency inside and outside the CNS have both common and distinctive characteristics.

The following pathological processes, events, and factors cause derangements in the general serotonin cycle components and lead to serotonin deficiency: 1) impaired production of serotonin precursors; 2) disorders occurring in serotonin-producing cells and impairing serotonin synthesis, storage, and release; 3) processes of various genesis interfering with serotonin transport in the cerebrospinal fluid and blood; 4) processes leading to the emergence in the cerebrospinal fluid and blood of exogenous or endogenous substances that modifying the rate of serotonin metabolism; 5) serotonin antagonists (drugs, abnormal metabolites, and other chemical agents) disturbing the serotonin-receptor interactions, including acute and chronic intoxication caused by these antagonists; 6) pathological changes in SR (degradation) caused by relatively low doses of endo- or exogenous serotonin antagonists and leading to chronic serotonin deficiency; and 7) a combination of two or more pathological factors resulting in acute or chronic serotonin deficiency in the CNS.

Impairments specific for the components of major serotonin cycle are those occurring in the platelets that transport serotonin to SR outside the CNS. They include 1) quantitative and qualitative changes in platelets in thrombocytopenia and thrombocytopathy of various origins resulting in hyposerotoninemia as a consequence of reduced serotonin adsorption, storage, transport, and/or release; 2) impaired serotonin transport, storage, and release by normal platelets reacting with viruses, bacteria, toxins, antibodies, etc.; 3) substances accelerating serotonin metabolism and impairing the serotonin-receptor interactions in platelets; 4) blockade of platelet SR and accelerated serotonin metabolism in platelets caused by various chemical or physical factors, including radiation.

Serotonin interaction with SR occurs continuously both inside and outside the CNS, but at different rates. Even a single change in the physiological time of serotonin interaction in a particular cycle can probably result in impairment of vital functions. It follows from the scheme of serotonin cycles that if the serotonin-receptor interaction is impaired at various stages, this eventually results in dysfunction of SM, platelets, CNS, and other systems.

Clinically, serotonin deficiency outside the CNS will arise through symptom complexes of functional intestinal obstruction and/or vascular insufficiency and microcirculatory disturbances caused by impaired SM contractility. Platelets play a key role in maintaining the integrity of the major serotonin cycle. Functional and morphological integrity of platelets is maintained by serotonin and SR (hyperserotoninemia leads to thrombocytosis, while hyposerotoninemia leads to thrombocytopenia) [3,9,11,14]. In the CNS, serotonin deficiency is manifested as consciousness disorders [7-9,11,14,17].

Based on the literature and our findings, we came to the conclusion that the contribution of serotonin to the maintenance of homeostasis can be assessed by studying its pharmacological effects. Experiments modeling acute serotonin deficiency in isolated intestinal segments showed that serotonin antagonists impair serotonin interaction with smooth muscle SR, modifying the contractility of SM. The

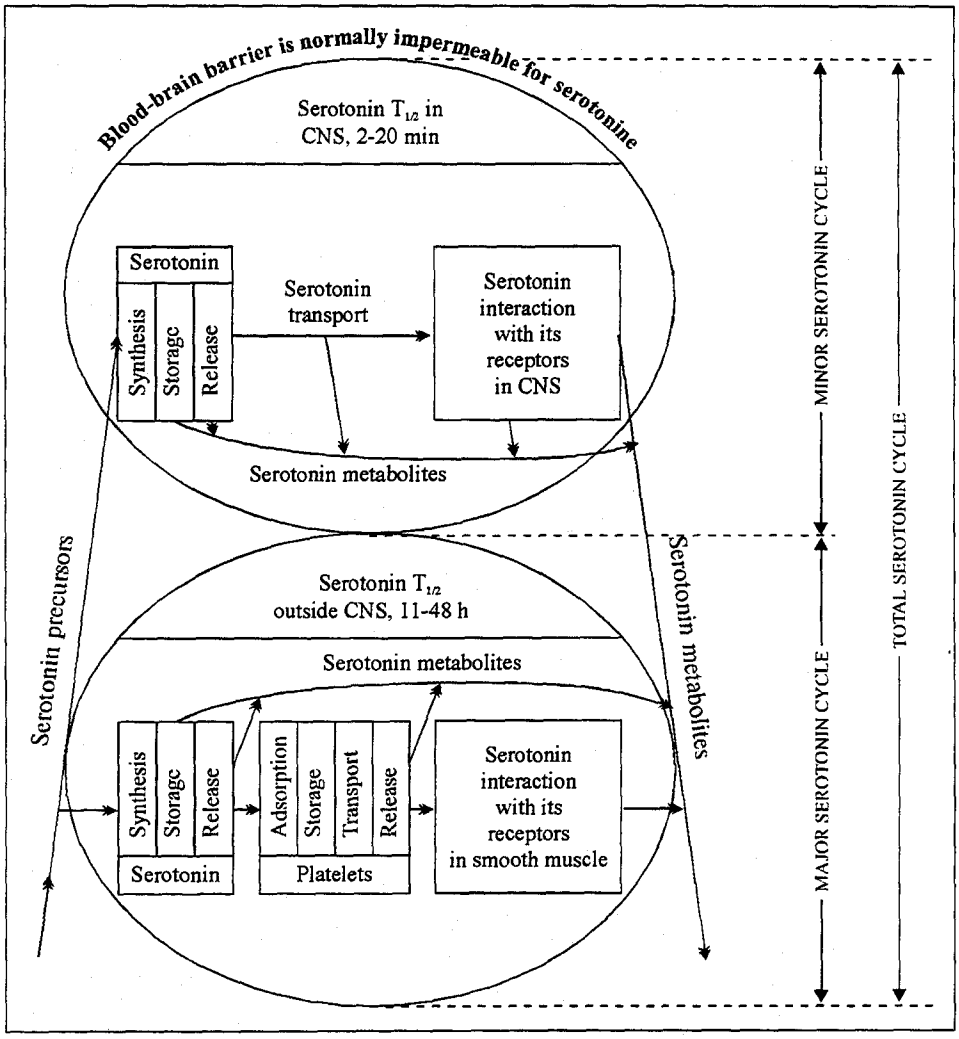

Fig. 1. Serotonin cycles. $T_{1/2}$ = half-life.

addition of serotonin to the preparations normalized SM contractility [9,10,12-14,16].

Pathological processes occurring in the body can be acute or chronic, depending on their duration. Analogously, serotonin deficiency can be acute or chronic. In clinical practice, acute serotonin deficiency is observed in intoxication caused by psychotropic drugs (serotonin antagonists). The following drugs: anesthetics, ampicillin, cocaine, dimedrol (diphenhydramine), gentamicin, hydrocortisone, isadrin (isoprenaline), ketanserine, morphine, procaine, exo- and endotoxins, physiological and pathological metabolites, and other chemical substances act as serotonin antagonists [3,4,7-14].

After crossing the blood-brain barrier, psychotropic drugs disrupt normal serotonin interactions with all SR, including those in the CNS, which impairs consciousness and SM contractility with the development of SM insufficiency manifested as functional intestinal obstruction and/or vascular insufficiency and microcirculatory disorders. Exogenous serotonin adipinate normalizes serotonin interaction with SR on smooth muscles and in the CNS, i.e., restores consciousness, eliminates functional intestinal obstruction, corrects vascular insufficiency, and improves microcirculation, reducing mortality fatality rates more than 2-fold compared with the control. In other words, the concentration of circulating serotonin in individuals poisoned with psychotropic drugs becomes too low for the maintenance of normal serotonin—SR interactions and, consequently, normal functioning of SR-containing organs. The binding of serotonin antagonists to SR is reversible, i.e., exogenous serotonin compensates serotonin deficiency and restores the serotonin interaction with its receptors, normalizing functions of SR-containing organs and systems.

When serotonin antagonists that cannot cross the blood-brain barrier appear in the body, acute serotonin deficiency may also occur, but without im-

pairment of CNS functioning. In this case exogenous serotonin normalizes motor function of the gastrointestinal tract, elevates arterial pressure, improves microcirculation, and reduces tissue hypoxia.

In clinical studies, 10 mg serotonin adipinate dissolved in 40-200 ml normal saline was infused intravenously at a rate ranging from 1-2 mg/h to 1-2 mg/min, depending on the patient's condition and the duration of action of this preparation. Its daily dose ranged from 10 to 500 mg (the LD_{50} of serotonin adipinate is 164 mg/kg). The infusion was started with a minimal dose, and the dose was then increased until first clinical manifestations of its action appeared, such as normalization or elevation (by 10-20 mm Hg) of arterial pressure, restoration of peristalsis, evacuation of accumulated gases and defecation, skin hyperemia, and tachypnea. If these clinical manifestations were pronounced, serotonin was discontinued, after which its action ceased immediately so additional therapeutic measures were unnecessary; in such cases, infusion was resumed in 10-15 min at a rate 2-3 times slower than initially. In some cases, selection and infusion of optimal dose of serotonin adipinate were controlled by SM electromyography, transcutaneous determination of Po_2, and some other procedures. Patients in a comatose state because of poisoning with psychotropic drugs showed clinical signs of regained consciousness concurrently with improvement of brain's electrical activity as evidenced by electroencephalography [9-14].

The half-life of serotonin is 2-20 min in the CNS and 11-48 h in other systems. The appearance of free (unbound to proteins) hemoglobin or myoglobin in the blood (as a result of hemolysis or myolysis of any etiology) is associated with microcirculatory disturbances and thrombocytopenia whose mechanisms are not fully understood. We postulated that ferroproteins (free hemoglobin and myoglobin) replace serotonin on platelet SR, thus raising its metabolic rate to values characteristic of the CNS. Enhanced outflow of serotonin from platelets accelerates their destruction. Free hemoglobin and myoglobin also interact with SR in SM, inducing pathological contraction (spasm) of SM in microvessels, thus disrupting normal serotonin interaction with its receptors in the SM of the microcirculatory bed and gastrointestinal tract.

We first described this ability of free hemoglobin and myoglobin to destroy platelets and cause SM spasm and designated serotonin receptors specifically interacting with ferroproteins as serotonin-ferroprotein receptors (S-Fpr receptors). These properties of hemoglobin and myoglobin motivated our interest into numerous physiological and pathological processes involving these receptors [9,12,14].

The appearance of free hemoglobin and myoglobin in the circulation accelerates platelet destruction and leads to thrombocytopenia, which results in absolute serotonin deficiency, since platelets are responsible for serotonin transport to its receptors on SM. Impairment of SM contractility combines with hypoxia of serotonin-producing cells and, consequently, with impaired serotonin synthesis and release into the bloodstream. Laboratory diagnosis of absolute serotonin deficiency is difficult because serotonin occurs in platelets in two forms, labile and stabile. Labile serotonin amounts for 70-90% of platelet serotonin, and an increase in the rate of platelet destruction results in thrombocytopenia, while blood content of serotonin may remain normal, since serotonin is released from electron-dense platelet granules. Since thrombocytopenia is severe, serotonin cannot be transported to its receptors in SM, which accounts for local elevation of tissue serotonin levels in microcirculatory disorders [9,12,14].

Clinically, absolute serotonin deficiency manifests itself as disseminated intravascular coagulation (DIC syndrome). This syndrome is developed as a result pharmacological interactions between hemoglobin and myoglobin with SR on platelets and SM, which was confirmed by the laboratory triad used to diagnose the DIC syndrome: 1) presence of disintegrated erythrocyte fragments and of free hemoglobin in the blood, 2) thrombocytopenia resulting from accelerated platelet destruction, and 3) microcirculation disorders due to impaired SM contractility (Fig. 2).

The carcinoid syndrome is also accompanied by neutrophilia. The mean rate of the neutrophil pool motility (1 pool comprises 30-70 neutrophils) in healthy donors is 8.8 μ/min, and slow neutrophil motility has been associated with lowered nonspecific and general immunity. The motility of neutrophils from patients with wound infection and clinical manifestations of intoxication is markedly decreased and can be normalized by exogenous serotonin. This indicates that bacterial toxins act as serotonin antagonists and impair normal serotonin interaction with SR on neutrophils, which is reflected in reduced motility. Exogenous serotonin eliminates serotonin deficiency, thus normalizing neutrophil mobility and, consequently, the corresponding part of nonspecific immunity [11].

We distinguish between two forms of acute serotonin deficiency: relative and absolute (Fig. 3). In relative deficiency, serotonin production and transport remain virtually normal, and serotonin antagonists impair the serotonin—SR interactions, which leads to dysfunction of SR-containing organs and systems. In relative serotonin deficiency, serotonin

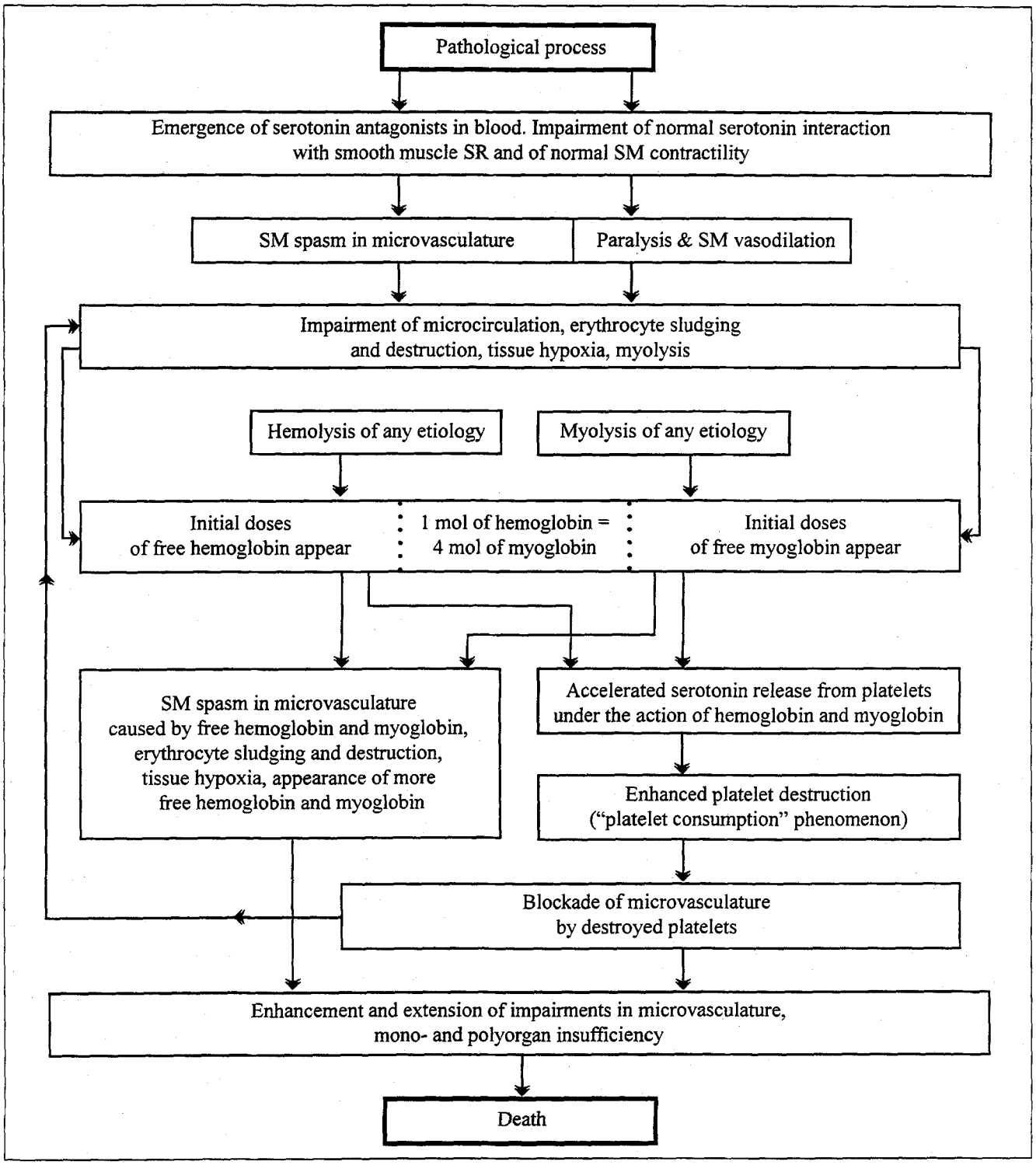

Fig. 2. Role and interrelationship of serotonin, platelets, smooth muscle, free hemoglobin, and free myoglobin in thanatogenesis (a scheme illustrating the development of the DIC syndrome). *SR*) serotonin receptors; *SM*) smooth muscle.

antagonists impair serotonin-receptor interaction reversibly, and exogenous serotonin corrects the functions of organs and systems with reversibly blocked SR by compensating serotonin deficiency. This accounts for the high effectiveness of exogenous serotonin, judging from the above-mentioned reduction in mortality among patients poisoned with psychotropic drugs [9-14].

The relative serotonin deficiency progresses to an absolute deficiency if impaired SM contractility per-

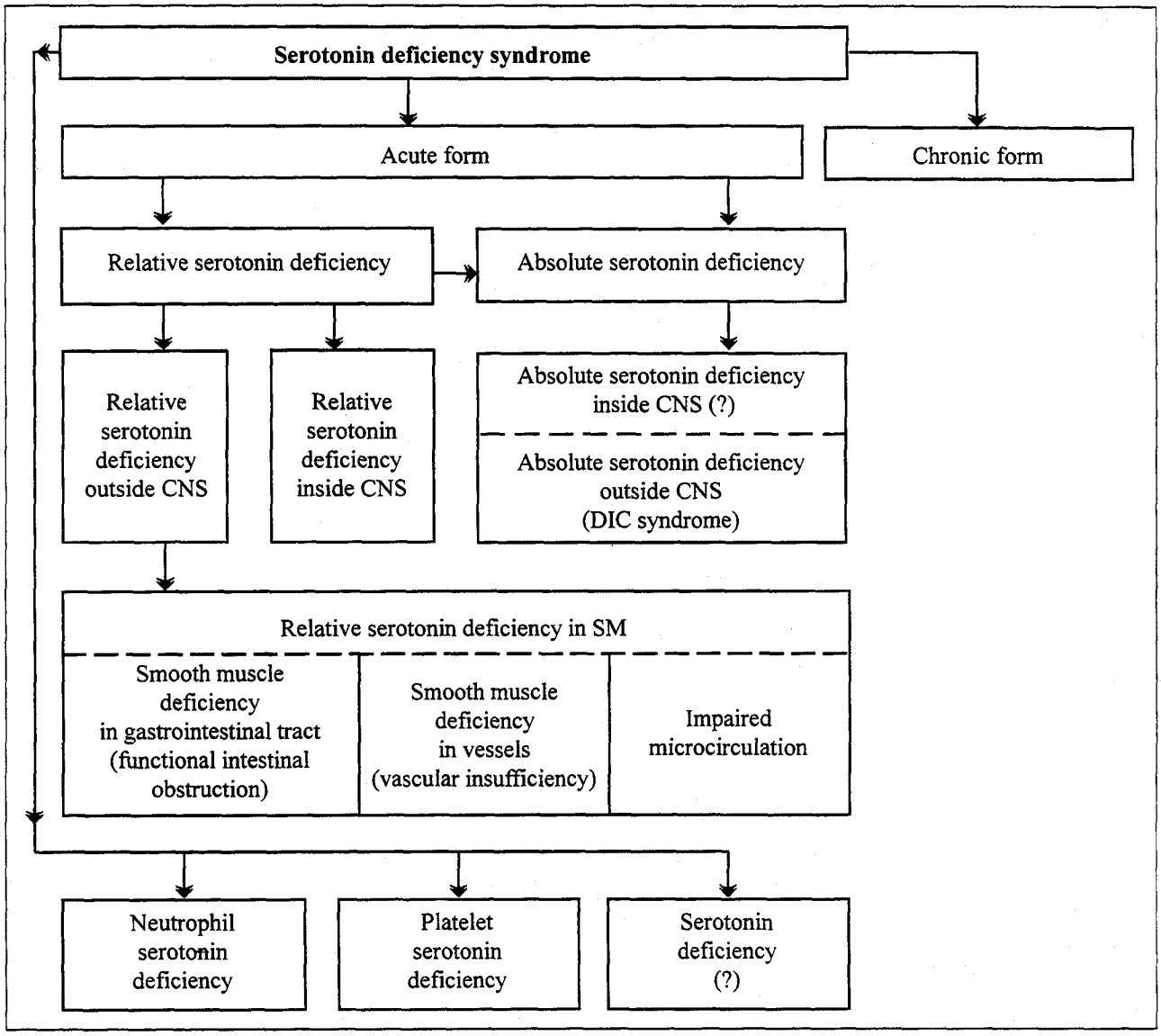

Fig. 3. Serotonin deficiency syndrome. *SM*) smooth muscle.

sists (i.e., microcirculation is not normalized), free hemoglobin and myoglobin appear in the circulation, and thrombocytopenia is developed. Thrombocytopenia aggravates microcirculatory abnormalities and leads to tissue hypoxia and low serotonin production. Eventually, major serotonin cycle is deranged, as well as the functions of all organs and systems with SR, i.e., a polyorgan insufficiency arises. In order to eliminate the absolute serotonin deficiency, serotonin infusion must be supplemented by removal of free hemoglobin and myoglobin from the blood or their binding to proteins, thereby preventing platelet destruction and preserving the transport system delivering serotonin to its receptors on SM and thus to preclude the development of tissue hypoxia in organs and systems, including those that contain serotonin-producing cells (Figs. 2 and 3).

Chronic serotonin deficiency is developed with age and in diseases accompanied by the appearance and long-lasting persistence of relatively small doses of serotonin antagonists in the body. We showed that serotonin infused at rates of 5 to 10 mg/h improves microcirculation with concurrent increase in electrical activity of SM and in tissue Po_2 (by >50% as measured transcutaneously) in elderly and old patients with a long history of diabetes mellitus and tissue necroses of hands and feet (diabetic and age-related angiopathy) [10].

During aging, pathological changes in the SR of SM develop under the action of physiological and pathological metabolites that act as serotonin antagonists, and the amount of circulating serotonin becomes too small to support the normal contractile activity of SM in the microcirculatory bed and, consequently, to maintain normal tissue metabolism.

Initial pathological changes in the SR of SM are reversible, which accounts for the high effectiveness of exogenous serotonin in chronic serotonin deficiency. Age-related angiopathy and diabetic angiopathy are accompanied by degradation of SR on SM and development of serotonin deficiency. In health, in the constant presence of only one natural metabolite (free hemoglobin) throughout lifetime, conditions are created favoring pathological changes in SR of SM and the entire vascular system. Degradation of SR is accelerated when pathological metabolites acting as serotonin antagonists emerge in diabetes mellitus. These changes lead to impaired function of vascular SM, degenerative changes in tissues (their aging) in all organs and systems, and, eventually, to polyorgan insufficiency and death [10]. This concept is confirmed by atrophy revealed upon autopsy of individuals died from old age [6]. Chronic serotonin deficiency is a combination of relative and absolute serotonin deficiencies which cannot be differentiated at the present time due to the lack of procedures by which the quantities of serotonin required by the body in the presence of normal or pathologically altered SR could be determined.

Analysis of the literature and our findings showed that the symptoms of serotonin deficiency are identical to those of the intoxication syndrome (Fig. 4).

In various types of shock, including that caused by intoxication, vasomotor changes occur in the microcirculatory bed, therefore, endogenous vasomotility observed in shock is referred to as shock-specific. During the first phase of shock, pre- and postcapillary vessels strongly contract, while the arterial part of the microvasculature dilates in the second phase. During the third phase, the vasculature is completely paralyzed, and postcapillary vessels undergo further dilatation. This phase corresponds to the terminal stage of shock [5,15,21].

In the presence of microcirculatory disorders, three factors responsible for the development of tissue hypoxia can be identified: anemia, impaired protein and water-electrolyte metabolism, and dysfunction of microvascular SM. For correction of the first two factors, highly effective methods have been developed and used, targeted at replenishing circulating erythrocytes, proteins, and other blood components which are present in insufficient amounts. In addition, various vasopressors are used to restore SM contractility in the microvasculature, but their effectiveness is very limited.

In health, the microvasculature exhibits rhythmic variations in the caliber of its vessels, referred to as endogenous vasomotility, vasomotion, or myogenic regulation of microvessels. Endogenous vasomotility is determined by the automatism of smooth muscle fibers and does not depend directly on vegetative (autonomic) neural influences. Its mechanism is normally as follows. Serotonin, which is produced by

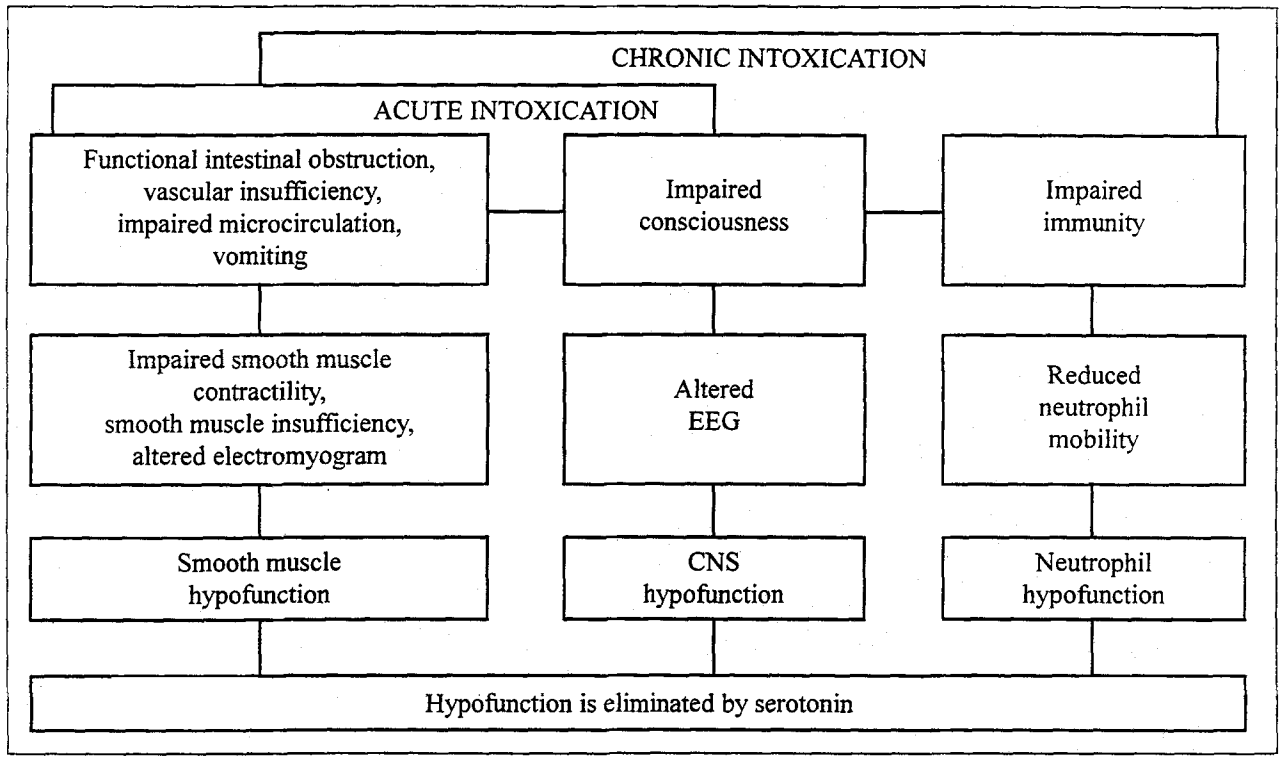

Fig. 4. Common signs of intoxication and serotonin deficiency syndromes.

enterochromaffin cells of the gastrointestinal tract, is continuously adsorbed by platelets; as the serotonin-containing platelets pass through microvessels, where they contact with the vessel walls, they release serotonin at each cardiac contraction under the pressure of erythrocytes, and the serotonin interacts with its receptors in SM of the microvasculature causing the SM to contract, which produces characteristic appearances, clinical and electromyographic (contraction, relaxation, contraction, etc.). Clinically, it is reflected in return to normal of SM contractility in the microcirculatory bed under the action of exogenous serotonin, while various vasopressors are ineffective. This normalization results in elevated vascular tone and stabilizes hemodynamics. Moreover, serotonin was found to restore SM contractility by normalizing motor function of the gastrointestinal tract during the first day after surgery for vagotomy or traumatic rupture of the spinal cord, i.e., in situations where neural regulation is obviously deranged. Serotonin improves endogenous vasomotility and mitigated tissue hypoxia in patients with age-related and/or diabetic angiopathy [10,12].

The findings presented above indicate that serotonin, which is responsible for the maintenance of normal tissue metabolism under physiological conditions, should be an essential component of measures aimed at preventing or treating disease states involving tissue hypoxia. Tissue hypoxia is particularly severe in shock, regardless of its etiology, and serotonin adipinate should therefore be included in the list of drugs essential for the prevention and treatment of shock.

Clinical manifestations of serotonin deficiency and intoxication syndromes, whether acute or chronic, should be compared not only in order to demonstrate their common features, but also to gain new information on the pathogenesis of the intoxication syndrome. A better understanding of its pathogenesis will be helpful in the development of effective approaches to prevention and treatment of various diseases accompanied by intoxication (Fig. 4).

Vomiting caused by cytostatics is a clinical manifestation of their toxicity. In an attempt to clarify the mechanism of this vomiting we carried out a study based on the principles underlying the development of serotonin deficiency and on the evidence that serotonin causes vomiting. Isolated segments of dog ileum 35-40-cm long (n=5) and the proximal and distal branches of the artery supplying this segment were cannulated outside the abdominal cavity. Infusion of serotonin into the proximal branch enhanced peristalsic of the segment, while its infusion into the distal branch induced antiperistalsis (vomiting) [1].

Acute or chronic intoxication, like serotonin deficiency, occurs when endo- or exogenous serotonin antagonists, whether natural or artificial, impair individually or in combination the normal interaction of serotonin with its receptors and thus lead to serotonin deficiency with functional impairment of the organs and systems where SR are located. Clinical manifestations of the intoxication syndrome, as well as of the serotonin deficiency syndrome, can be eliminated by exogenous serotonin regardless of the origin(s) of serotonin antagonists. This indicates that impaired serotonin—receptor interactions underlie both syndromes. We have successfully used serotonin to control various clinical manifestations of serotonin deficiency and intoxication syndromes in more than 400 patients treated in Moscow and other cities of Russia [9-14].

The above-mentioned facts indicate that such a vague concept as the intoxication syndrome starts acquiring concrete features of the serotonin deficiency syndrome. In fact, SR act as the "receptors of toxicity" that so far have not been identified.

Further confirmation of the important role serotonin and SR in maintaining homeostasis is provided by the observation that both serotonin and its receptors are responsible for the initial contractions of the heart and SM and for the emergence of initial electrical activity in the brain during ontogeny [13].

In our view, the toxicity of new drugs and other chemical substances, including physiological and pathological metabolites, and to determine their antagonist activity (direct and indirect) towards SR should be further investigated. Presumably, their toxicity is due at least partially to their adverse effects on SR. The reviewed data are consistent with established facts.

The first report on the serotonin deficiency syndrome and the ability of hemoglobin and myoglobin to induce SM spasm and accelerate platelet destruction was presented February 11, 1993 at the meeting of the Department of Clinical Medicine of the Russian Academy of Medical Sciences.

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