Experimental Study on the Neurological Basis for Systemic Inflammatory Response Syndrome (SIRS) Pathophysiology

Granville G. de Oliveira¹,², Samer A. H. de Oliveira³, Paulo Henrique H. Botelho⁴, Marcos Aurélio Barboza de Oliveira⁵*, Alexander Kots², Ferid Murad²

¹Department of Internal Medicine, Faculty of Medicine, Catholic University of Brasilia. Brasilia, Brazil
²Department of Biochemistry and Molecular Biology, George Washington School of Medicine and Health Sciences, George Washington University, Eye St. NW; Washington, DC, USA
³Department of Cardiology, Division of Electrophysiology, University Hospitals Case Medical Center, Euclid Ave, Cleveland, OH, USA
⁴Department of Cardiovascular Surgery, Faculty of Medicine of S.José do Rio Preto, S. Paulo, Brazil
⁵Department of Cardiac Surgery, Hospital Santo Antônio and Femina Cuiabá, Sinop, Mato Grosso, Brazil

*Corresponding author: Granville G. de Oliveira, MD, PhD, FCP. Address: 204 Rollins Ave. Rockville Maryland, 20,852., USA. Home telephone: 240-6699958; Cell:301-755-3465; E-mail: granville.oliveira@gmail.com; granville@gwu.edu

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Abstract

Background and Objective: Sepsis, and infection-related inflammatory reactions have been, for decades, considered as SIRS pathophysiologic basis. However, only an average of 35% of all SIRS cases can be due, primarily, to such etiology. In early seventies, we proposed a different pathophysiological hypothesis based on the Theory of Systems(TS). This focused on a Central Nervous System(CNS) secondary imbalance provoked by post-trauma Alarm Reaction complex responses, as the core of the inducing process. The present study aims to experimentally verify the role of this possible CNS imbalance, secondarily provoked by any general trauma, as the main inducing-mechanism of SIRS.

Methods: a) Wistar male rats were anesthetized and submitted to bilateral anterior hypothalamus stereotaxic electrolytic lesions, as an effective neurological model for experimental SIRS development. Secondarily, they were anesthetized and submitted to the following procedures: b) Intracerebroventricular microinjections of: propranolol; lidocaine; cyproheptadine; pyrilamine; cimetidine; diazepam; haloperidol. c) After the sacrifice, the animals were submitted to organs removal and histological examination. Consolidated gravity scores utilizing the following organs: brain; lung; kidney; stomach; liver. The statistical analysis utilized Kruskall-Wallis and X² non-parametric tests.

Results: The intracerebroventricular microinjections provoked, potentiated or attenuated the pathologic picture of cerebral stereotaxically-induced SIRS, depending on their pharmacophysiologic characteristics.

Conclusion: The results of the histopathologic examinations showed that different drugs injected into CNS lateral ventricles induced different results suggesting that different neurologic systems would play a direct role in the potentiation or attenuation of cerebral stereotaxically-induced SIRS. These results reinforce the importance of the CNS in the induction and modulation of SIRS pathologic picture.
Keywords: ARDS; Alarm Reaction; Sepsis; SIRS; Theory of Systems

Introduction

Despite being officially recognized in 1983, when first appeared in the Index Medicus, with the designation of “Multiple Organ Failure”, an approximate description of Multiple Organ Failure Syndrome (MOFS) pathologic findings can be found in very remote descriptions. Especially that done by William Cumin, surgeon of the Royal Infirmary, and the Asylum of Lunatics of Glasgow, by Joseph Swan, physician of the Lincoln County Hospital, coincidentally, in the same number LXXXVI of the Edinburgh Medical and Surgical Journal, in 1823. Cumin, accurately, observed in the necropsy of an 8 year old burned girl: “…distant internal parts sympathized with the burned surface and suffer inflammation” [1,2]. In addition, it is interesting to be emphasized that similar descriptions were done by other authors, such as Cooper [3], in 1839; Long [4], in 1840 or Curling [5], in 1842, among others. These findings, however, were totally disregarded by their time scientific community. Throughout the XX Century, several other authors have described the development of this yet unknown pathology. Especially relevant, were the reports of Moon [6], in 1947, and Mallory [7], in 1950, which described the histopathologic findings in soldiers who suffered trauma during the World War II, dying after a varying period of survival. They reported the universal involvement of multiple organs not primarily damaged by different types of severe injuries.

The consolidation of the multidisciplinary intensive care units concept, occurred around 1958, roughly at the same time, at the Baltimore City Hospital, at the Oxford University Hospital, at the Toronto General Hospital, at the Presbyterian Hospital of the University of Pittsburgh, at the University Hospital of Baltimore, among others. These units proposed to deal with severely ill patients with the most advanced multidisciplinary techniques, placed in the same geographic area in the hospitals. This concept resulted in an important reduction in the morbidity and mortality rates among these patients. However, the life prolongation of seriously ill patients who suffered all modalities of severe trauma, burns, infections, pulmonary aspiration, multiple transfusions, acute pancreatitis, extracorporeal circulation, among others highly dangerous conditions, gave rise to the emergence of an yet unknown, aberrant, and frequently fatal disease: the Multiple Organ Failure Syndrome (MOFS) [1]. To emphasize how much the scientific community was worried with the occurrence of such strange and fatal cases, Tilney et al. [8] in 1973, published a paper reporting the finding of multiorgan damage in the necropsy of 18 patients that died due to abdominal ruptured aneurysms. They speculate vaguely that “its etiology is probably mixed and possibly unknown...”.

While working in the Central Army Hospital ICU, in Rio de Janeiro, de Oliveira et al. [9] in 1972 proposed a hypothesis that the yet not described secondary post-traumatic syndrome would be provoked by Central Nervous System (CNS) cybernetic imbalances. However, the worldwide perception of the possibility of the existence of this post-traumatic syndrome resulted in an authority opinion through an editorial note signed by Baue [10], published in 1975. In this editorial, the author proposed the possibility of a septic pathophysiology basis as the responsible for the yet unknown syndrome development. Therefore, from that time on, the scientific community accepted that hypothetical explanation, without consider other pathophysiologic possibilities. This inflexible position was corroborated by the 1992 American College of Chest Physicians / Society of Critical Care Consensus Conference, when MOFS changed to other denomination: Systemic Inflammatory Response Syndrome(SIRS) [1].

SIRS can be defined as a complex clinical manifestation, with secondary sub-acute characteristics, that occurs following a severe and non-specified trauma. It develops, usually, after a gap of time of apparent stability, and is associated to high morbidity and mortality. It leads to universal and progressive organic deterioration, due, basically, to the development of generalized and confluent ischemia-reperfusion anatomic lesions, involving all organic systems. The typical SIRS mortality, in general, shows an average of 50% and may, frequently, reach levels above 80% [1,3,4]. Since sepsis and its corollaries theories are not, per se, sufficient to justify the occurrence of majority of SIRS cases, we decided, alternatively, to search another explanation, as, we have proposed in early seventies, utilizing our previous CNS-based working hypothesis supported by the model of the Theory of Systems logic [5], in conjunction with Selye’s Adaptation Syndrome mechanisms [6]. Our hypothesis was, indeed, supported by the previously mentioned theories [1,5-7] and resulted in the observation of the following clinical and pathological facts:

a. Peripheral Effector(PE) Functional Restrictions: Most endogenous Peripheral Effectors (PE) humoral systems, such as vasoactive amines, peptides, inflammatory and immunologic factors, hormones, nitric oxide, growing factors, cytokines, among others, have characteristically, short half-lives and are dependent of the existence of extrinsic triggering and modulating mechanisms [5-8].

b. Evolution Gap: There is an average lag of time, from 2 to 10 days, between the primary traumatic event and the clinical detection and evolution of different SIRS manifestations [1,8]. This behavior suggests the evolution of a CNS functioning system defect.

c. Evolution/Prognosis Mismatch: Many patients present, after a minimally severe trauma, a fair initial evolution, just to be detected, days after, a multi-organic functional deterioration.
Therefore, we concluded that the correlation of severity of trauma and the development of SIRS was not mandatory [1,11].

d. Etiological/Pathological Stereotypy: The pathologic SIRS pattern is, typically stereotyped, and qualitatively independent from different trauma etiologies [1,11].

e. Identity of SIRS Lesions in Exclusive CNS or Peripheral Trauma: The literature review have shown, extensively, the identity of pathological SIRS features in either exclusive CNS or exclusive peripheral trauma [1,11].

f. Sepsis-Induced CNS Stimulation: The association of sepsis and SIRS occurs, at most, in 35% of the cases. Therefore, it does not explain the majority of SIRS cases not associated with sepsis. Indeed, it is widely perceived that most part of sepsis pathophysiology and its corollaries-induced signs and symptoms are due to CNS stimulation, and consequent participation of CNS-activated peripheral effectors [1,8].

Non-specific brain trauma [1,8,10-13], as well as some subtle cerebral experimental manipulations [1,7,8,11,12], such as stereotaxic electrolytic lesion of the anterior hypothalamus nuclei [1,8,10-12]; lesion of the preoptic nuclei [1,10] lesion of the tractus solitarii nuclei [1,8] lesion of the ala cinerea [1,10] bilateral carotid ligation; intracranial hypertension provoked by injection of mineral oil into lateral ventricles; vagotomy; intracisternal injection of veratrine, thrombin or fibrinogen; intra-carotid hypertensive injection of physiologic solution (NaCl 0.9%); extracorporeal selective brain hypoxia; among others CNS manipulations, are well known methods to induce typical and generalized SIRS-like multiple organ damage [1,8,10-12]. In opposition, posterior hypothalamus nuclei electrolytic lesion [1,11] would act protectively against the syndrome development. Therefore, the existence of, even, minimal post-traumatic brain damage, would be a logic hypothetical premise for this research intentions. Briefly, under such proposal, the Center of System Control (CSC): the CNS, through its stress-adaptation nuclei, would output stereotyped orders to be run by a complex array of Peripheral Effectors (PE). This will, ultimately, result in the so-called Alarm Reaction (AR) [1,7,8]. The PE adaptation actions on the entire system would lead it, eventually, to the homeostatic equilibrium recovery and these effects could be assessed by the CSC through Peripheral Receptors (PR) input, through the feedback loop (FL) [1,7,8]. Conversely, the PE actions could be highly detrimental in some possible instances, such as: 1- Prolongation of the appropriate AR due to unresolved primary trauma imbalances or development of system secondary complications; 2- Prolongation of, either qualitative, or quantitatively inappropriate AR actions due to a cybernetic-defective CSC; 3- CSC defaulted translation process, or to damaged receptors/communication feedback systems; 4-Continuously-interfering and harming extrinsic systems: sepsis, detrimental iatrogenic actions; environment. This would be, therefore, the uniform theoretical basis to explain SIRS generalized and smoothly progressive organ anatomical damage and its eventual corresponding physiological failure [1,7,8]. Therefore, we have proposed, in this work, to, experimentally, verify, through microneurosurgical, pharmacological and morphological methods, an eventual CNS influence on the evolution of SIRS, as previously proposed by de Oliveira et al. [1].

Methods

The experiments protocol was approved by institutional experimental review committee and were performed on Wistar male rats weighing from 180 to 220g, that were kept separate cages placed in a thermally stable room (21 degree Celsius) with free access to water and balanced food. Each group was composed by 10 animals. These animals were submitted to the following procedures:

SIRS-Inducing Stereotaxic Electrolytic Lesions

For the SIRS pathology development, it was used the anterior hypotalamic stereotaxic electrolytic lesions model. The animals were submitted to ethyl ether anesthesia (average anesthesia time:15+9 minutes) before the neurosurgical procedure. They were adapted to the stereotaxic equipment (David Kopf 1404, Tujunga, CA), and after skin sterilization and skin incision at the level of inter-parietal bones suture, where bilateral drill holes of 0.5mm in the position established by the Konig & Klippel stereotaxic atlas. Stereotaxic electrolytic lesions (EL) were placed in the anterior (AH) hypothalamus nuclei by using an anodal constant current of 5mA for 20 seconds through a monopolar stainless-steel insulated electrode (0.3 mm diameter and 30u of tip diameter) previously calibrated in an optical microscope. Sham-operated(S) animals were submitted to the same procedures, except for the placement of hypotalamic lesions. The electrode was stained with methylene blue for further histological lesion placement evaluation.

Additional Microneurosurgical Procedures

The animals were anesthetized with ethyl ether (anesthesia wakening time of 12 minutes+ 3 minutes) and placed in a stereotaxic neurological frame (David Kopf 1404, Tujunga, CA). After appropriate antisepsis, the parietal bones were exposed and holes (0.5mm of diameter) were drilled bilaterally in specific places. Specific group of animals (n=10) was submitted to the following procedures:

Intracerebroventricular microinjections were performed with a 10ul microsyringe (701 - N Hamilton, Rockford, IL) with the needle tip stained with methylene blue for further histologic placement evaluation. Intracerebroventricular microinjection (ICV) volumes were of 1uL placed into the lateral cerebral ventricles. The drug doses were chosen based on literature and our own experience [1].
The drugs were diluted in Artificial Cerebrospinal Fluid (ACF) in order to avoid major physicochemical interferences in local drug action. Its composition: Na 140 mEq/L; K 3.5 mEq/L; Ca 2.5 mEq/L; Mg 2.5 mEq/L; Cl 105 mEq/L; glucose 65 mg/dL; pH:7.15. The sham-operated animals followed the same routine, but were injected only with ACF. The animals were allowed to recover for 30 minutes, as a general rule, before any additional procedures. The following drugs and doses were utilized as intracerebroventricular microinjections: a)- Cimetidine(Ci): 30ug(Smith, Kline & French, Philadelphia, PA); b)- Cyproheptadine(Cp): 10ug(Merck Darmstadt, Germany); c)- Diazepam(Di): 5ug( Roche Labs, Manati, PR); d)- Haloperidol(H):0.5ug(McNeil Lab, Spring House, PA); e)- Lidocaine(Li): 0.1ug(Astra USA, Westboro, MA); f)- Pyrilamine(Py):20ug(Rhodia, France).

Ancillary Procedures

The animals were sacrificed 24 hours after the last procedure, under ethyl ether anesthesia, by sectioning the abdominal vessels. In our laboratory experience, this period was sufficient to allow the development of intermediate-gravity SIRS pattern. In addition, intermediate levels of multi-organ involvement would make possible the evaluation of, either attenuation or potentiation of SIRS evolution. Aorta washing was not performed in order to preserve the already-formed micro-thrombosis. The following organs were removed fixed in neutral 10% formaldehyde solution and after embedded in paraffin and stained with hematoxylin-eosin for further histological examination: brain, lungs, heart, spleen, liver, kidneys (and adrenals), and stomach. Spleen, duodenum, heart and adrenals histology were not considered in this work due to its minimal SIRS-related deterioration. Animals with inappropriately placed cerebral lesions were discarded and replaced in the experimental series. SIRS evolution will be presented through histopathological assessment that was quantitated by reviewing ten microscopic fields, based on an arbitrary grading scale, basing on literature and on our previous experience.

The histopathologic examination was performed by a “blind” physician. The microscopic slides were identified only by a computer-generated randomized numbers, kept under a code that was broken after finished slide examination. The scores were attributed to every slide, basing on the sum of each grade of ten 64X microscopic neighbor fields. Therefore, the minimum slide score would be 00(zero) and the maximum would be 40 for each organ. The basic number of animals for each group was 10 animals per group. Therefore, the total minimum group score would be 000 and the maximum 400 for each organ. 250X magnifications were utilized only in order to detect specific qualitative Tissue Damage (TD) for grading classification.

Statistical Analysis

The results (mean+SD) were evaluated through the Gravity Consolidated Organ Damage Scores (GCODS) of all the organs scores: Lung Scores (LS); Stomach Scores (SS); Kidney Scores (KS); Brain Scores (BS); Liver Scores(LS), for each experimental setting of n=10 animals., being 0000 the baseline and 2000 the maximal gravity. We utilized the non-parametric method of Kruskall-Wallis for general inter-groups analysis. We utilized, also, the X² method for several comparisons between two groups. It were considered significant values of P<0.05, or of highly significant values of P<0.01.
Discussion

Local anatomic and physiologic damages may be induced by cerebral micro-thrombosis [1,7,8,10]. These lesions are quite similar to those provoked by micro-electrolytic lesions, not only during the ischemic period, but also in the reperfusion phase. It is accepted that post-traumatic AR would provide much of the hyper-coagulation, endothelial lesions and vasoconstriction/low blood flow and reperfusion inductive scenario necessary to micro-thrombosis development [1,8,13-15]. Tinoco and Barrucand [16], in 1968, were the first to show the development of cerebral micro-thrombi with surrounding edema in rabbits submitted to two-hour hemorrhagic shock. In fact, extensive literature reports the massive presence of cerebral brain micro-thrombosis in cases of nonspecific trauma [1,14,16,17].

Roseblum and El-Sabban [18] reported that minimal vascular injury, such as mice brain exposition to ultraviolet rays after pretreatment with a photosensitizing dye, may result in the development of platelet micro-thrombosis [15,17,18]. They reported predominant presence of micro-thrombi and micro-hemorrhages in vascular bifurcations of the floor of the 3rd and 4th ventricles in association to severe hypoxia or acute respiratory insufficiency [9,19]. Must be emphasized that most hypothalamic nuclei are located in these areas. Rowbotham & Little [20], in a double contrast study, had demonstrated the presence of intra-cerebral A-V shunts deviating blood from the ischemic regions, worsening the local oxidative metabolic deficit. Betz et al [21] referred to this as a "local-steal phenomenon". Obrist et al [22] demonstrated, in studies done with Xe 133, in patients with brain trauma, the occurrence of vasomotor paralysis, with intense vasodilation, calling this phenomenon as “luxury perfusion areas”. Majno et al [23] reporting the results of total cerebral ischemia that, from 5 minutes of brain hypoxia, rabbits developed the so-called “no-reflow phenomenon”, in which the dye carbon black failed to penetrate into the previously ischemic regions. They concluded that glial “hypoxic vacuoles” and edema were the responsible for the vascular luminal collapse and occlusion in this condition [21,24]. Cerebral anoxia for 2-3 minutes, in cats, provoked the arterial pH to fall to 6.96, with acid lactic elevation, fall in ATP stores and inorganic phosphate elevations [16,18,25-27].

Therefore, after trauma, factors such as micro-thrombosis, fall in arterial pressure, anemia, low blood glucose, low oxygen offer, among other damaging processes, may give rise to a disabled neuron population, resulting in areas characterized by low membrane potentials, irritation self-triggering neurons, in the disabled neuron population, resulting in areas characterized by consequent cell edema and membrane partial depolarization [25].

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Therefore, after trauma, factors such as micro-thrombosis, fall in arterial pressure, anemia, low blood glucose, low oxygen offer, among other damaging processes, may give rise to a disabled neuron population, resulting in areas characterized by low membrane potentials, irritation self-triggering neurons, in the so-called “ischemic penumbra layer” [18,20,25,28,29]. Neurons electrophysiologic functions cease at a local brain flow rate below 18mL/100g/minute [25]. Micro-thrombosis may induce neighbor cell death, when local reperfusion does not take place. Or, if neurons are not reached by collateral circulation diffusing oxygen [20,25,30] usually in a 50 micra radius tissue neighborhood [18,20,25]. The sudden fall in local O2 and nutrients offer will result in the initiation of a fully known chain of pathologic events resulting in cell damage or death. It will result in a depletion of ATP with consequent failure of all energy-dependent mechanisms [18,25], reflecting especially on mitosis, synthesis function and membrane ion transport [21-23]. This will result, initially, in an elevation of intracellular sodium (Na+) and potassium (K+) efflux, with consequent cell edema and membrane partial depolarization [25].
Extensive neurophysiologic studies have shown that, in this condition of energy depletion, occurs important fall in neuron membrane electrical potential, from a normal level of -90 millivolt, to a level around -45 millivolt [18,20,23,25,31], when starts to occur a process of spontaneous electrical firing of action potentials, without any stimulation. In this condition of extreme neuron irritability, occurs the outbreak of activation of reverberating circuits that initiates reactions typical of the affected area. To this explosion of inappropriate automatic firing of AR-like systems activation, we called “Parasothic Reaction” (from the Greek: Para: inappropriate; collateral; Sotha: salvation) [1,13,19,32]. This inappropriate reaction, acting for a prolonged period of time, can induce the activation of more than 100 factors, in several systems, such as cardiovascular-acting substances, hormones, cytokines, autacoids-related, coagulation/fibrinolysis factors, growth factors, among many others. This inappropriate AR-like reaction may provoke the development of the complete SIRS pathologic picture [1,13,19,32].

In addition, the important elevation of intracellular calcium will play a critical role in further ATP consumption, in the exocytosis processes of hormones, peptides, and neurotransmitters [18,20,23,25]. It activates, in addition, agents such as phospholipase A2, xanthine-oxidase, or nitric oxide synthase [23,33]. Conversely, in the reperfusion context, factors such as phospholipase A2, xanthine-oxidase, or nitric oxide synthase [23,33]. Conversely, in the reperfusion context, factors such as glutamate [23,25], toxic oxygen radicals [26], nitric oxide [1,13], nitric oxide synthase [23,31] or neurotrophins [23,29,30], among other factors, can play either, beneficial, or harmful effects over neurons. Neuron cytoskeleton depolymerisation will be one of the important neurotoxic calcium-mediated actions. In fact, calcium antagonists have been utilized as protecting agents against this ion harmful neurologic effects [34,35].

Considering the present work experimental data, such as the ICV microinjections of the beta-adrenergic blocking agent-propranolol-in opposition to our previous results in a systemically-injected protocol, showed to induce a protective effect of 59.61% (P<0.01) against SIRS evolution [1,13], possibly due to its local anesthetic action, since ICV lidocaine has shown, equally, to exert a protective action of 48.29% (P<0.01). On the other hand, the muscarinic receptor antagonist-atropine- IC microinjections in the AH has shown to potentiate SIRS evolution, whereas IC cholinergic agonist- carbachol- injected in the AH, provoked its attenuation [1,13,23,29,34]. These findings were against our expectations, since the complex stress-related cholinergic system, especially at the lateral hypothalamic nuclei and amygdala, is considered to be directly related to positive AR output, being interconnected to catecholaminergic tracts [1,13,32]. However, the AH, a functionally AR-negative area, has a predominantly cholinergic system, that could explain the results [1,2,13,23,27,28]. Therefore, the AH seems to have a protective cholinergic function against SIRS evolution.

The results presented in this work shows some of the following characteristics can be detected: CNS histaminergic systems seem to play a modulating role on the cardiovascular system, interfering in stress-induced reactions [12,19,32]. Actually, the highest concentration of histamine in CNS in found in hypothalamic stress-adaptation nuclei [1,13,19,32]. In this context, ICV diphenhydramine, a H1-receptor antagonist, has shown to reduce arterial pressure and peripheral vascular resistance induced by ICV norepinephrine microinjection (Morgan Soares, personal communication). Our results suggest that histaminergic tracts might have an excitatory AR role. Anti-histaminic drugs administered through ICV microinjections were able to attenuate SIRS development. Both H-1 antagonist-pyrilamine-(reduction of 63.88% of SIRS evolution) (P<0.01) and H2-blocker-cimetidine (reduction of 57.90% of SIRS evolution) (P<0.01) proved to be protective [19,32]. In addition, serotonergic interneurons are known to play an inhibitory action over a variety of cerebral tracts, including stress-related dopaminergic, noradrenergic and cholinergic systems [1,2,13,17,23,26,27]. Lowering central serotonin levels enhances both vascular resistance and aggressive behavior [35]. ICV microinjections of a serotonin antagonist-cyproheptadine- had resulted in a potentiation of the SIRS pathologic picture in the range of 24.57% (P<0.01).

Gamma-aminobutyric acid (GABAergic ) neurons are expected, also, to induce depressant actions over excitatory neurological systems [1,13,17,23,35]. The ICV microinjections of the GABAergic agonist -diazepam- has shown, coherently, to play such a protective role of about 38.26% against SIRS development. Dopaminergic systems are considered among these directly related to a positive-output AR [2,13]. ICV dopaminergic agonists are known to produce a picture of behavioral and cardiovascular excitation [1,2,13,17,19,32]. Here, the ICV microinjection of a dopamine antagonist-haloperidol- has shown a reduction of 51.48% (P<0.01) in SIRS pathologic picture [13,19].

Stress-adaptation neurons are fully activated during trauma, with a high energy consumption rate and elevated electrical firing [1,2,13]. De Oliveira et al [32] has demonstrated the protective role against SIRS development of various types of systemically-injected neuro-depressant drugs such as: propofol, pentobarbital, chlorpromazine, urethane, haloperidol, diazepam and morphine [19,32]. Therefore, long-term maintenance of stress-adaptation system full activation, as seen above during AR, or PR, might have a deleterious cellular effect. Several authors [1,13,20,24,36] had reported during stereotoxic stimulatory procedures, the occurrence of prolonged neuron discharges, even after the suspension of the stimulation. Therefore, as we mentioned above, the “penumbra layer” of partially damaged neurons, peripheral to focal ischemia-reperfusion suppressed area, may provoke automatic and inappropriate brain electrical discharges, resulting in a self-
triggering, reverberating circuit-based, prolonged AR-like activity [19,32].

Conclusion

Despite the generalized acceptance of sepsis as the main SIRS pathophysiologic basis, this work suggests that, indeed, CNS might play a predominant role in the induction of this syndrome, through the modulation of a typical post-traumatic AR, or through the activation of multiple inflammatory systems as part of a post-traumatic inappropriate AR-like reaction (PR), primarily developed by AR-induced neuronal damage.

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