



Post-radiation syndrome as a NO/ONOO⁻ cycle, chronic fatigue syndrome-like disease

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Summary Post-radiation syndrome is proposed to be chronic fatigue syndrome (CFS) or a chronic fatigue syndrome-like illness, initiated by exposure to ionizing radiation. This view is supported by the nitric oxide/peroxynitrite (NO/ONOO⁻) cycle mechanism, the putative etiologic mechanism for CFS and related illnesses. Ionizing radiation may initiate illness by increasing nitric oxide levels via increased activity of the transcription factor NF- κ B and consequent increased synthesis of the inducible nitric oxide synthase. Two types of components of the nitric oxide/peroxynitrite cycle have been studied in post-radiation syndrome patients and shown to be elevated. The symptoms and signs of post-radiation syndrome and its chronicity are similar or identical to those of chronic fatigue syndrome and can be explained as being a consequence of nitric oxide/peroxynitrite cycle etiology. While the data available to test this view are limited, it provides for the first time a comprehensive explanation for post-radiation syndrome.

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Properties of post-radiation syndrome

Post-radiation syndrome (PRS) is a chronic illness following exposure to ionizing radiation [1–7]. It has been most studied among those exposed to ionizing radiation after the Chernobyl nuclear accident with some additional studies of atom bomb survivors. The complex chronic symptoms have typically been found in persons both shortly after exposure and continuing for years after such exposure. Pastel [7] described the symptoms as including “fatigue, sleep and mood disturbances, impaired memory and concentration and muscle and/or joint pain”. Loganovsky [4] described them

as including persistent fatigue, odd skin sensations, bizarre feelings in bones, muscles and joints, irritability, headache, vertigo, pain in the chest area, emotional lability, lack of concentration and memory, cognitive deterioration, depression signs and sleep disorders. Kumerova et al [3] described the symptoms as including headache, dizziness, poor memory, prostration, lowered work ability, excessive nervousness, local pains in the bones and disorders of the digestive system.

These symptoms and the chronic nature of illness are quite similar to those described in a group of chronic multisystem illnesses including chronic fatigue syndrome (CFS) (also known as myalgic encephalomyelitis or ME), fibromyalgia (FM) and multiple chemical sensitivity (MCS) [8–14]. CFS, FM and MCS have been linked to each other because they share a set of common symptoms, symptoms

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similar to those of PRS. CFS, FM and MCS also have substantial comorbidity with each other, and they share a common pattern of case initiation. Cases of each of them are often immediately preceded by a short term stressor, such as infection, physical trauma, severe psychological stress or exposure to certain chemicals [11–13]. These similarities have led many investigators to suggest that these illnesses may share a common etiology. The proposal being explored here is whether PRS shares this same etiology and may simply be CFS or a CFS-like illness that is initiated by the stressor of exposure to ionizing radiation.

CFS, FM and MCS as NO/ONOO⁻ cycle diseases

At least 12 short-term stressors have been linked to the initiation of the multisystem illnesses CFS, MCS, FM and the related illness, post-traumatic stress disorder (PTSD) (summarized in Table 1). All 12 of these short term stressors can increase the levels of nitric oxide in the body [11–13,15,16]. They act to do so via several mechanisms, with infection acting by inducing the inducible nitric oxide synthase (iNOS) [11] and certain other stressors acting primarily by increasing activity of the NMDA receptors which act in turn to stimulate two other nitric oxide synthases, designated nNOS and eNOS. How can the increased nitric oxide lead, then, to the initiation of chronic illness? It is proposed that nitric oxide and its oxidant product peroxynitrite can act to initiate a biochemical vicious cycle which is responsible for the chronic illness [11–13,15–18]. This cycle has recently been called the NO/ONOO⁻ cycle [12,13] after the structure of nitric oxide (NO) and peroxynitrite (ONOO⁻) but pronounced no, oh no! This cycle mechanism is diagrammed in Fig. 1.

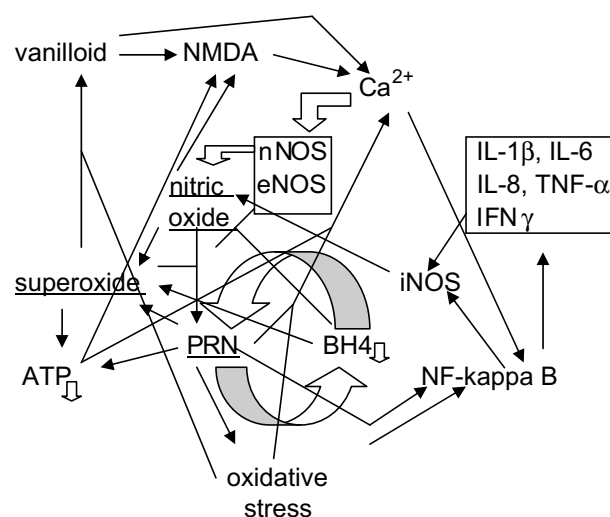


Figure 1 NO/ONOO⁻ cycle mechanism. The arrows in the figure each represent one or more mechanisms by which one component of the cycle elevates the levels of another component of the cycle. The cyclical nature of these interactions act as positive feedback loops, producing a complex vicious cycle. This figure is derived from the author's web site and is reproduced with permission.

The NO/ONOO⁻ cycle explanatory model of these illnesses is based on five distinct principles [12,13], the first two of which have already been discussed:

1. Short-term stressors that initiate cases of multi-system illnesses act by raising nitric oxide synthesis and/or other cycle elements, leading to consequent increased levels of nitric oxide and its oxidant product peroxynitrite.
2. Initiation is converted into a chronic illness through the action of vicious cycle mechanisms, through which chronic elevation of nitric oxide and peroxynitrite and other cycle components is produced and maintained.

Table 1 Short-term stressors initiating illnesses

Illness	Initiating stressors
Chronic fatigue syndrome	Viral infection, bacterial infection, toxoplasmosis (protozoan) infection, carbon monoxide exposure, organophosphorus pesticide exposure, ciguatoxin exposure, severe psychological stress, physical trauma
Fibromyalgia	Physical trauma, viral infection, bacterial infection, severe psychological stress
Multiple chemical sensitivity	Organic solvent exposure; organophosphorus/carbamate pesticide exposure; pyrethroid exposure; organochlorine pesticide exposure
Post-traumatic stress disorder	Severe psychological stress; physical (head) trauma

Each of the 12 stressors listed are known to trigger a response which is known, in turn, to lead to increased nitric oxide levels. In most cases, they have been shown experimentally to increase nitric oxide levels. The underlined stressors are implicated most frequently in the initiation of the illness on the left.

3. Symptoms and signs of these illnesses are generated by elevated levels of nitric oxide and/or other important consequences of the proposed mechanism, i.e. elevated levels of peroxynitrite or inflammatory cytokines, oxidative stress and elevated NMDA and vanilloid receptor activity.
4. Because the compounds involved, nitric oxide, superoxide and peroxynitrite have quite limited diffusion distances in biological tissues and because the mechanisms involved in the cycle act at the level of individual cells, the fundamental mechanisms are local.
5. Therapy should focus on down-regulating NO/ONOO⁻ cycle biochemistry.

There is substantial evidence supporting these five principles for CFS, FM, MCS and PTSD [12,13,16]. PRS has been reported to be similar to CFS, FM and MCS, with the most similarities to CFS [2–4,7]. The symptoms of PRS can be explained as being a consequence of NO/ONOO⁻ cycle components [12,13,15]. The question raised here, then, is whether PRS is simply CFS or a CFS-like illness that is initiated by exposure to ionizing radiation, rather than being initiated by the other stressors listed in Table 1?

Can ionizing radiation lead to nitric oxide increases?

According to the NO/ONOO⁻ cycle model, for ionizing radiation to initiate a NO/ONOO⁻ cycle illness, it should be able to increase nitric oxide levels or other cycle elements. Ionizing radiation is known to increase the activity of the transcription factor NF-κB [19–27]. It is well-established that NF-κB activity produces increased synthesis of the inducible nitric oxide synthase (iNOS) which increases, in turn, nitric oxide levels [11,28]. This entire sequence appears to be involved when ionizing radiation produces nitric oxide increases [29,30]. While some of the studies showing NF-κB activation in response to ionizing radiation have used very high doses of ionizing radiation, others have demonstrated such activation at much lower doses [22,24–27], well within the range of doses implicated in the Chernobyl disaster exposures [3]. It is known that NF-κB activation by free radicals and oxidants that are the presumed intermediates in the process of activation by ionizing radiation, is quite variable among different tissues [31–33] so the levels of ionizing radiation needed for NF-κB activation and subsequent iNOS induction will be expected to be variable among different tissues. As diagrammed in Fig. 2, ionizing radiation can

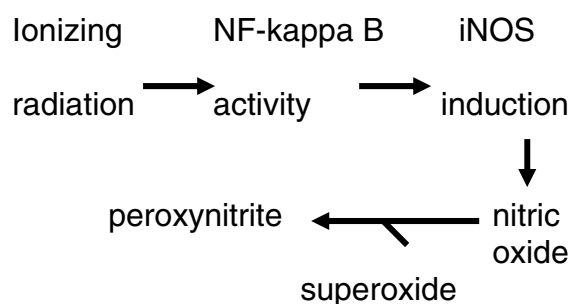


Figure 2 Sequence by which ionizing radiation can increase the levels of nitric oxide.

increase levels of nitric oxide, which will be expected, in turn, to increase levels of its oxidant product peroxynitrite.

Are there any chronic phase properties of PRS consistent with a NO/ONOO⁻ cycle etiology?

Principle 2 of the NO/ONOO⁻ cycle explanatory model predicts that components involved in the cycle should be elevated in the chronic phase of illness. While most of these components have not been studied in PRS sufferers, two of them have been. Oxidative stress has been reported to be elevated among PRS patients [3,6,34] and in some radiation-exposed animal models [30,35,36]. The Taysi et al. study [30] also showed elevated nitric oxide levels. Some of the inflammatory cytokines (upper right corner of Fig. 1) have been reported to be elevated in PRS patients [37,38]. Thus years after the initiating ionizing radiation exposure, some components of the NO/ONOO⁻ cycle are found to be elevated, consistent with a vicious cycle type mechanism. Other chronic phase properties such as changes in brain function in PRS [38–41] and changes in immune function including low NK cell function [1,42–45] are similar to those reported in chronic fatigue syndrome and related multisystem illnesses and may also be produced by a NO/ONOO⁻ cycle etiology [12,13].

Summary of the proposal

There has not been any previous, detailed proposed mechanism for PRS in the scientific literature. The only proposed “mechanism” that the author is aware of is some speculation that PRS may be of strictly psychological origin, a view that is inconsistent with the reported chronic oxidative stress, elevation of inflammatory cytokine levels, changes

in brain functions and changes in immune system function. The proposal that PRS is simply CFS initiated by ionizing radiation exposure is supported by three important types of evidence:

1. Ionizing radiation is capable of producing increased nitric oxide levels, as predicted of an initiator of the NO/ONOO⁻ vicious cycle.
2. Elevated oxidative stress and elevated inflammatory cytokine levels are found in the chronic phase of PRS, both predictions of the NO/ONOO⁻ cycle mechanism of CFS and related illnesses.
3. The symptoms of PRS are very similar to those of CFS and related illnesses and those complex symptoms can be explained as being due to elevated components of the NO/ONOO⁻ cycle.

While it should be noted that the types of evidence testing this view are distinctly limited, the most important consideration supporting this view is its comprehensiveness. The linkage of PRS to CFS and the NO/ONOO⁻ cycle, provides explanations for all of the features reported for PRS. It is important therefore, to determine whether other features predicted from a NO/ONOO⁻ cycle etiology can be confirmed in PRS. It is also important to determine whether the approaches that appear to be effective in the treatment of CFS and related illnesses, approaches predicted to down-regulate NO/ONOO⁻ cycle etiology [12, 13] show similar efficacy in the treatment or prevention of PRS.

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