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REVIEW ARTICLE

Ebola virus disease: potential use of melatonin as a treatment

Abstract: The purpose of this report is to emphasize the potential utility for the use of melatonin in the treatment of individuals who are infected with the Ebola virus. The pathological changes associated with an Ebola infection include, most notably, endothelial disruption, disseminated intravascular coagulation and multiple organ hemorrhage. Melatonin has been shown to target these alterations. Numerous similarities between Ebola virus infection and septic shock have been recognized for more than a decade. Moreover, melatonin has been successfully employed for the treatment of sepsis in many experimental and clinical studies. Based on these factors, as the number of treatments currently available is limited and the useable products are not abundant, the use of melatonin for the treatment of Ebola virus infection is encouraged. Additionally, melatonin has a high safety profile, is readily available and can be orally self-administered; thus, the use of melatonin is compatible with the large scale of this serious outbreak.

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Introduction

The Ebola outbreak in West Africa is the largest event of this type since the identification of this virus in 1976 [1]. Currently, this outbreak has infected the inhabitants of four countries including Guinea, Sierra Leone, Liberia, and Nigeria. Thousands of people have been infected and more than half of the patients have perished from this devastating disease. This epidemic has not shown any tendency to fade since its outbreak in December, 2013, and additional cases may well surface in other countries. Because of its highly contagious nature and extremely high death rate, the World Health Organization (WHO) has declared this epidemic as an international public health emergency. Moreover, there is now considerable concern that this Ebola outbreak will threaten world security [2]. There is no effective cure currently available for this disease and the treatment is palliative. WHO has given a green light to an experimental antibody (Zmapp) and allowed this potential remedy, which has not undergone clinical trials, to be used to treat a few select Ebola patients. The obvious shortcoming for this remedy is its very limited availability; thus, it cannot match the scale of this outbreak. The patient selection has also raised an ethical question as to who should be given priority for this highly experimental treatment. The vaccines for Ebola virus disease (EVD) are estimated to become available at the earliest in 2015.

To reduce the worldwide panic and possibly to save lives, it is urgent for medical researchers to propose some alternative remedies, which may have positive effects on this epidemic during the intervening period from now to when effective vaccines become available. Based on our extensive knowledge and experience with melatonin and the understanding of the pathology of EVD, we strongly believe that melatonin should have some practical utility as a treatment of this rapidly expanding EVD. We feel that, as medical researchers, we have an obligation to share our opinion with others in this critical period even though this opinion may be premature or may even prove to be ineffective after appropriate tests are performed.

Ebola infection

EVD is a disease of humans and other primates caused by an Ebola virus (*Zaire ebola*). Ebola virus in humans causes hemorrhagic fever with a case fatality rate of 50% to 90%. The main causes of death are disruption of vascular endothelium, disseminated intravascular coagulation (DIC), fibrinolysis, and followed by multi-organ hemorrhage [3]. The major pathological alterations caused by the Ebola virus are, more or less, associated with the destruction of the endothelial lining of blood vessels. It was reported that the endothelial injury is not the direct result of viral inoculation into the endothelial cells but rather due to a cascade of reactions of immune- and inflammatory responses involving monocytes, macrophages, and dendritic cells [4]. After infection with the Ebola virus, these cells are activated to release cytokines, chemokines, Ebola virus proteins, complement, microparticles and also excessive amounts of toxic reactive oxygen and nitrogen species (ROS and NOS, respectively) [4–6] (Fig. 1).

The cytokines and chemokines produced include TNF- α, IFN- α, IL6, IL8, TF, MCP-1. These factors and mediators trigger a host of downstream events in endothelial cells [4–6]. These include activation of the coagulation system, inflammatory reactions, and disruption of the vascular

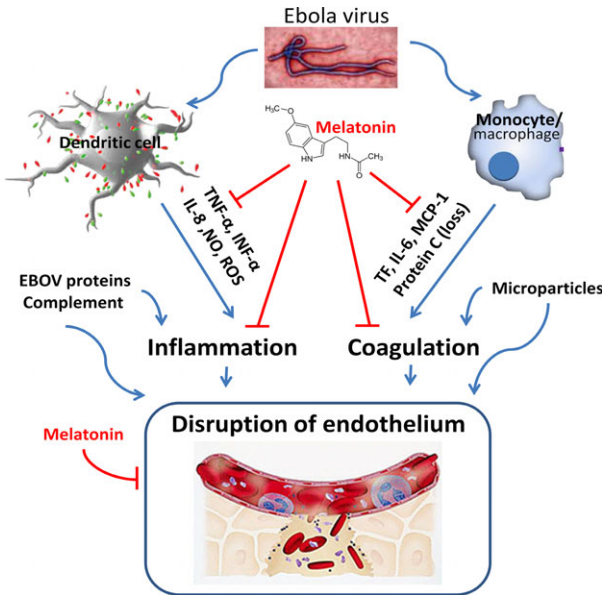

Fig. 1. The pathologies of Ebola virus infection and potential effects of melatonin. Monocytes, macrophages, and dendritic cells appear to be central to the development of this disease. Infection and/or interaction of these cells with EBOV stimulates the release of a variety of mediators and factors that trigger a host of downstream events including stimulation of the inflammatory response, activation of the coagulation system and disruption of the vascular endothelium. Melatonin application theoretically would act on each of the pathological alterations caused by the Ebola virus.

endothelium. Of importance is the activation of tissue factors (TF) which initiate blood coagulation. TF, thus, play a key role in triggering the coagulation abnormalities, an index of Ebola virus infection. When recombinant nematode anticoagulant protein c2 (rNAPc2), a potent inhibitor of TF, was given to the Ebola virus-infected rhesus monkeys, it significantly improved survival of the infected animals [7]. This was attributed to the reduced activation of coagulation, fibrinolysis, and also due to attenuation of the systemic pro-inflammatory response. Theoretically, if available treatments had the capacity to stop or reduce this excessive immuno-inflammatory cascade of reactions, it would provide some protection against the disruption of the endothelium and the coagulation abnormality caused by the Ebola virus; therefore, it would likely reduce the death rate.

Melatonin and its potential effects on Ebola pathology

On the basis of the published scientific research, melatonin is identified as such a molecule. Melatonin is a derivative of an essential amino acid, tryptophan. The particular and most important reason for melatonin being potentially useful for EVD is that this molecule seems to directly target all the immuno-inflammatory responsive events associated with the Ebola virus infection (Fig. 1). Melatonin is a potent free radical scavenger and an anti-inflammatory agent [8, 9]. It would predictably limit the oxidative stress and inflammatory injury that occurs in the infected endothelial cells and preserve their integrity. The ability of melatonin to protect the integrity of the endothelium of blood vessels was observed decades ago when melatonin reduced vascular permeability and inhibited the plasma leakage from capillaries caused by ischemia/reperfusion damage [10] (Fig. 2); this action has been re-affirmed many times subsequently [11, 12].

Recent studies have uncovered the potential mechanisms by which melatonin exhibits its beneficial effects on endothelial cells. These are, but not limited to, the fact that melatonin suppresses the levels of TNF- α, IFN- α, IL6, IL8, TF, MCP-1, VEGF, phosphorylation of JNK, and the degradation of the tight junctional proteins and it reduces endothelial apoptosis [13–15] Protecting against endothelial cell injury and preserving vascular structure and function are important to avoid the deadly hemorrhage in late stage EVD.

DIC is an important cause leading to the high mortality associated with EVD. In DIC, blood coagulation and fibrinolysis are dysregulated, and the result is widespread clotting followed by serve bleeding. The anticoagulation activities of melatonin have been tested in rats and human subjects and the results are clear [16–18]. Based on the findings, the authors of these reports have already claimed that melatonin may be useful in the prevention of DIC. Further studies indicate that melatonin exhibits dual effects by which it suppresses coagulation. It not only reduces the levels of TF, platelet activation and coagulation factor VIII but also stimulates vascular endothelial cells to secrete tissue factor pathway inhibitor (TPPI) [19]. The dual actions of melatonin make this molecule an effective anticoagulation agent.

Similarity of Ebola infection and septic shock

After the examination of the published literature, we noticed the obvious similarities between an Ebola virus infection and septic shock; both of these conditions

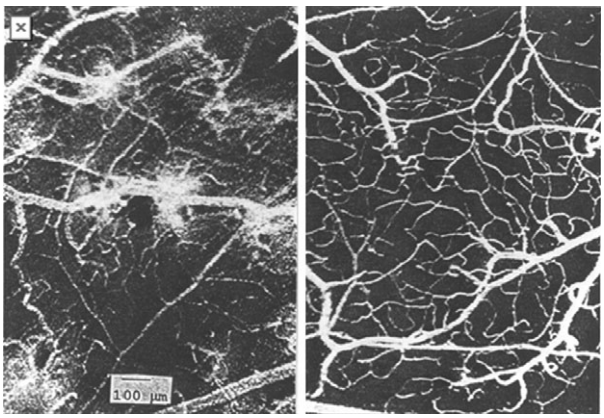

Fig. 2. Effects of melatonin on vascular permeability and integrity under oxidative stress. Left panel is the microvascular network after ischemia/reperfusion in a hamster cheek pouch. An increase in vascular permeability with obvious edema is evident indicating endothelial disruption. Right panel is the microvascular network after ischemia/reperfusion in a melatonin-treated hamster cheek pouch. Melatonin prevents the increased permeability of the capillaries induced by ischemia/reperfusion and the vessels appear intact and capillary perfusion is preserved. From Bertuglia et al. [10].

involve an infection by a pathological foreign agent. Whereas viral and bacterial infections are clearly fundamentally different, it is also obvious that the interactions of pathogens or their toxic components with pattern-recognition receptors associated with macrophages and related cells do cause relatively similar types of innate immune responses; including in these are uncommonly high levels of circulating pro-inflammatory cytokines and lymphocyte apoptosis [20]. Some scientists have ready mentioned these similarities and have proposed that examination of the similarities of Ebola hemorrhagic fever with septic shock may lead to an understanding of the pathogenesis and to improved therapies [21]. Interestingly, melatonin has already been successfully used in treatment of septic human newborns [22]. In this case, melatonin therapy significantly reduced the death rate in this small-scale clinical trial. Another clinical trial was recently proposed to test the efficacy of melatonin in the treatment of sepsis in adult humans [23].

Treatment rationale

It should be pointed out that melatonin is likely not *per se* an antiviral molecule. Therefore, the use melatonin in EVD is not for the purpose to eradicating the Ebola virus or even curbing its proliferation (although it may have this effect [24]). The strategy for melatonin application is for the purpose of retarding the body's excessive immuno-inflammatory responses caused by Ebola virus invasion. As a result, the severity of the lethal DIC and hemorrhage, which result from the excessive immuno-inflammatory responses, would potentially be suppressed with the use of melatonin. Therefore, melatonin administration may enhance the resistance of individuals to the Ebola virus infection and provide additional survival time for these patients. Due to the potentially prolonged survival period resulting from melatonin application, the immune system of some patients may have sufficient time to recover and finally eradicate the Ebola virus. For decades, melatonin has been known to be an especially potent immune system regulator [25]; particularly relevant are melatonin's actions on innate immune system responses [26]. If our prediction is correct, the death rate of EVD may be significantly reduced as a result of melatonin administration.

Key issues related to the use of melatonin probably include early intervention with a large dose (20 mg or more for a single dose; as there is no precedent for an effective melatonin dose, some upward adjustment of the dose may have greater efficacy); this dose should be given several times per day for a prolonged period. The treatment should be initiated as soon as possible after the infection is diagnosed; presumably it would never be too late to begin treatment (orally or i.v.). Considering the current lack of effective treatments for this devastating disease and with no vaccine available for EVD, the use of melatonin would be worth consideration.

Conclusions

Melatonin is a phylogenic old molecule. Its origin can be traced to 2.5–3.9 billion years ago. So far as is known, melatonin is present in all living organisms from primitive bacteria to human [27]. Due to its wide distribution in plant, plant products and natural diets, melatonin in the USA and several other countries is classified as a food supplement. Its availability is unlimited and it is inexpensive in pure form. The safety of melatonin has been extensively investigated in animal studies as well as in human clinical trials over a wide range of doses. Melatonin has very high safety profile and no deaths or serious toxicity related to melatonin usage has been reported. In addition, melatonin can be orally self-administered. These additional advantages make the use of melatonin practical in large-scale situations, such as the current Ebola outbreak.

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