Review

Treatment of Ebola and other infectious diseases: melatonin "goes viral"

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ABSTRACT

This review summarizes published reports on the utility of melatonin as a treatment for virus-mediated diseases. Of special note are the data related to the role of melatonin in influencing Ebola virus disease. This infection and deadly condition has no effective treatment and the published works documenting the ability of melatonin to attenuate the severity of viral infections generally and Ebola infection specifically are considered. The capacity of melatonin to prevent one of the major complications of an Ebola infection, i.e., the hemorrhagic shock syndrome, which often contributes to the high mortality rate, is noteworthy. Considering the high safety profile of melatonin, the fact that it is easily produced, inexpensive and can be self-administered makes it an attractive potential treatment for Ebola virus pathology.

Key words: hemorrhagic shock, Rho/ROCK pathway, vascular disease, inflammation, oxidative stress, immunosuppression, viral infections

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1. INTRODUCTION

Melatonin is functionally an unusual molecule with highly divergent actions which depend on the specific environment where it is located. As one example, melatonin promotes growth of cells under normal circumstances while it inhibits proliferation of cancer cells, actions that are described as being context specific (1). These discretionary actions allow melatonin to benefit normal cells/tissues while attacking pathological cells/tissues. Such divergent actions are commonplace for melatonin and there are many other examples.

Another uncommon feature of melatonin is the breadth of its actions. There seem to be few cellular functions that are not impacted by this molecule (2-5). The recent findings documenting that it is in high concentrations and that it is both rapidly taken up and produced in the mitochondria and chloroplasts perhaps of every cell, animal and plant, surely underlies its varied functions (6-11). Also, the likelihood that melatonin evolved a couple billion years ago has allowed it time to develop a working relationship with numerous other molecules (12, 13).

This brief review summarizes a function carried out by melatonin that is probably not well known even by scientists who routinely work with melatonin, i.e., its ability to reduce virus-mediated diseases. Again, this has been shown to be valid in both plants and animals.

2. MELATONIN/VIRUS INTERACTIONS

The evidence that melatonin impedes the pathophysiological consequences of viral infections has a longer history than most realize. In 1988, Maestroni and co-workers (14, 15) published what is believed to be the first reports which showed that, in rodents, melatonin has significant efficacy in attenuating the effects associated with the inoculation of viruses, i.e., either the encephalomyocarditis virus (EMCV) or the Semliki Forest virus (SFV). EMCV is a highly pathogenic virus that induces, as the name implies, severe inflammation of the central nervous system and heart which commonly leads to death (15, 16). SFV is a typical arbovirus that promotes brain inflammatory reactions when it invades and replicates in neural tissue (17); as with EMCV, SFV is likewise commonly fatal (18, 19). For their studies, Maestroni et al. (14, 15) used both BALB/c mice (for the EMCV study) and outbred IRC mice (for the SFV studies). Mice inoculated with EMCV exhibited the characteristic pathogenic paralysis and death over the subsequent 10-day period. Giving melatonin daily over the same interval reduced both of the pathological parameters. In the studies using the SFV, melatonin was given for 3 days in advance of virus inoculation followed by a 10-day observation period. In this case, melatonin forestalled symptoms onset, lowered the viral load and limited death. While these experiments did not include detailed pathophysiological measurements of molecular mechanisms because of the lack of appropriate methodologies, the outcomes were obviously very telling in terms of documenting the efficacy of melatonin as an anti-viral agent. Despite their potential veterinary and clinical importance, the findings of Maestroni and colleagues (15, 16) did not generate much scientific traction.

The same group (15) reported that mice infected with an attenuated West Nile virus (WN-25) also responded positively to supplemental melatonin administration. This strain is not highly virulent, i.e., it *per se* does not cause encephalitis. When animals infected with WN-25 are exposed to stress, brain inflammation does occur and it may be sufficiently severe that it causes death (20). The administration of melatonin to stressed mice inoculated with WN-25 virus, reversed the immunosuppressive actions of the stress/virus combination and counteracted death of the animals (15).

Subsequent studies, although not numerous, that used melatonin to interfere with viral infections were equally as effective in attenuating their pathologies. A group of South American scientists (21-23) tested the utility of melatonin as a preventative molecule against Venezuelan equine encephalitis virus (VEEV). This group had ample reason to examine this association since VEEV is a common mosquito-borne organism which is pathological to not only equine species but to humans as well (24) and it has infected thousands of humans and domestic equine species in northern South America especially (25). Using a mouse model of the disease, Bonilla and colleagues (21-23) found that melatonin, in three individual studies, delayed the development of VEEV disease, deferred the time of death, reduced the viral load in both the central nervous system and in the blood and lowered neural apoptosis and lipoperoxide concentrations as well as the mortality of the infected mice. Finally, the titers of the IgM antibody, mediated by the virus, were highly elevated (21). Despite the success of these studies, and the fact that VEEV continues to plague certain regions (24-26), no studies known to the present authors have been performed to determine whether melatonin would be an effective treatment of VEEV in equine or human species.

Although the number of endpoints measured was limited, the findings published by Ellis (27) suggest that the pathologies that accompany Aleutian mink virus disease (AMVD) are also

probably squelched by melatonin. When AMVD-infected minks were subcutaneously implanted with melatonin-containing silastic capsules, which release melatonin continuously, their death rate was reduced. A major pathogenic feature of AMVD is hypergammaglobulinemia which causes lesions in several visceral organs including the arteries (28). In the Ellis study, gamma globulin was not measured. It would have also been of interest to determine the fur quality in the melatonin-transplant mink given the data showing that melatonin generally is beneficial to fur quality (29).

Fulminant hepatic failure (FHF) is a serious syndrome that greatly compromises hepatic function and is often fatal (30). FHF can be a result of drug usage, toxin exposure or due to a viral infection. One example of a model of this condition is rabbit hemorrhagic disease (RHD) in which FHF is initiated and sustained. A series of elegant studies from one group has shown conclusively that RHD virus (RHDV)-mediated FHF is significantly attenuated when melatonin is used as a countermeasure (31-33). In these studies, multiple biochemical and molecular endpoints were measured and, universally, regardless of the outcome estimated, melatonin was beneficial and recovered normal liver function. For these tests, rabbits were treated with hemagglutination units of RHDV alone or in combination with melatonin. RHDV caused a strong inflammatory response as indicated when numerous inflammatory cytokines were measured and for each of these parameters, melatonin treatment alleviated the large increases (31, 32). Continuation studies documented that, in addition to controlling inflammation, melatonin also interfered with endoplasmic reticulum (ER) stress by altering aspects of unfolded protein response (UPR) signaling (33). Finally, the authors observed that melatonin reduced the negative molecular processes associated with RHD injection and prevented acute liver failure (ALF) (31-33). Collectively, the results provide ample evidence that melatonin, via multiple molecular mechanisms, abates FHF and ALF; the authors, as a result of their findings, urge that melatonin should be further tested and possibly used as a potential treatment agent against RHD-induced hepatic destruction.

Human papilloma virus (HPV) infections are associated with a host of genital cancers, particularly cancer of the cervix (34, 35). HPV DNA living in host cells markedly alters the transcriptome and proteasome profiles of the host cells presumably contributing to the oncogenic activity of the virus (34). The infected cells exhibit downstream signaling pathways which induce molecular changes conducive to cancer initiation and progression (36). While there are no studies specifically evaluating the ability of melatonin alone to forestall cervical cancer mediated by HPV, there is a single report showing that combining melatonin, which stimulates the immune system (37) with an inhibitor of indoleamine 2,3-dioxygenase-1 (IDO1), an enzyme associated with immunosuppression (38), improved vaccine-mediated protective immunity of tumor cells infected with HPV 16 (39). Given how common HPV-induced cervical and skin cancer is worldwide, along with the increasing HPV-mediated oral cancer, identifying molecules that directly or indirectly interfere with this cancer is essential. Melatonin may have some utility in this regard and has been found to be a potential inhibitor (40).

Some viral diseases are highly contagious when in their active phases whether melatonin impacts this aspect of viral conditions mentioned are uninvestigated. Moreover, there are many other viral diseases that should be tested as to their responsiveness to melatonin. An important example is herpes zoster, an acute viral condition that is caused by the chickenpox virus and is communicable. The serious and highly painful phase of this infection is referred to as shingles. A common feature of shingles and other viral infections is that they are often most severe in immunocompromised patients (40, 41), a condition that may be rectified by melatonin (42).

There is no evidence that melatonin is viricidal but rather it reduces the severity of these infections.

Collectively, the published reports related to the success of melatonin in reducing the negative sequelae of these serious viral infections using disease models indicate the indole is generally beneficial in protecting against viral infections including virus-related cancer. The observations have importance considering that no other drugs effectively combat these grave conditions and the economic losses from these pathologies are massive (25, 26, 30).

3. EBOLA VIRUS: AN UNWELCOMED GUEST

Perhaps the most notorious of the viral infections is Ebola virus (*Zaire ebola*) disease (EVD). It became worldwide news as a result of a far-reaching and devasting outbreak that occurred between 2014 and 2016, the epicenter of which was in several West African countries; this epidemic was massive in scale and an estimated 11,000 deaths were recorded that actually contributed to the destabilization of several countries (44, 45). EVD was initially described in 1976 in a settlement near the Ebola River in central Africa. Since then there have been repeated sporadic outbreaks but none as severe as that which occurred between 2014 and 2016. Since then, another Ebola epidemic has been growing which could be of greater magnitude than the earlier unprecedented version. Typically, in excess of 50% of the people infected with the Ebola virus die as a result of the infection. Another common means of acquiring an Ebola infection is by eating inadequately cooked flesh of infected animals. There are a variety of species that are carriers of the virus that are commonly eaten by the indigenous people; among these are fruit bats, monkeys, antelope, and others (46). Finally, Ebola is spread when healthy individuals come in contract with soiled personal items of an infected individual or contaminated medical waste (47).

Symptoms of an Ebola infection usually appear 8 to 10 days after infection but may become apparent up to 3 weeks. Some of the symptoms are common to other diseases, e.g., abdominal pain, fever, diarrhea, muscle pain, weakness, etc. (48). Hemorrhage at multiple sites and bruising are features of EVD which are symptoms that require immediate treatment; if treatment is not instituted quickly, up to 50% of the patients die. Individuals who are infected are not contagious until the symptoms of the disease appear (49).

Often the symptoms of EVD abate due to medical intervention; unfortunately, the virus may persist in some of these individuals (50). Immune-privileged locales where the virus may persist in a dormant state include the central nervous system, the eye, and the testes. As a consequence, the Ebola virus may be spread through the male ejaculate (51). Even after successful treatment, residual complications including vision problems and joint discomfort may persist.

4. MELATONIN AS A TREATMENT FOR EBOLA VIRUS DISEASE

Shortly after the Ebola outbreak became known, two groups independently soon published articles that provided a rationale as to why melatonin should be considered a treatment option for this deadly disease (52, 53). In the first of these reports, we argued that melatonin would be a sensible choice considering the multifunctional aspects of this endogenously-produced molecule that would likely impede pathologies that are associated with an Ebola infection (Figure. 1) (52). The Ebola virus disables the immune system, enhances blood coagulation, induces a marked inflammatory response that leads to the generation of massive numbers of damaging free radicals

that cause extensive oxidative damage and cellular and organ failure. In particular, the endothelium of blood vessels is damaged which contributes to hemorrhage shock, a prominent and life-threating feature of an Ebola infection (49, 54, 55). In contrast to Ebola, melatonin stimulates the immune system (56, 57), has anti-inflammatory actions (58, 59), is a powerful direct and indirect free radical scavenger (60, 61), and impacts platelet physiology and thrombin formation (62-64), all of which could aid in melatonin's ability to combat the consequences of Ebola infection.

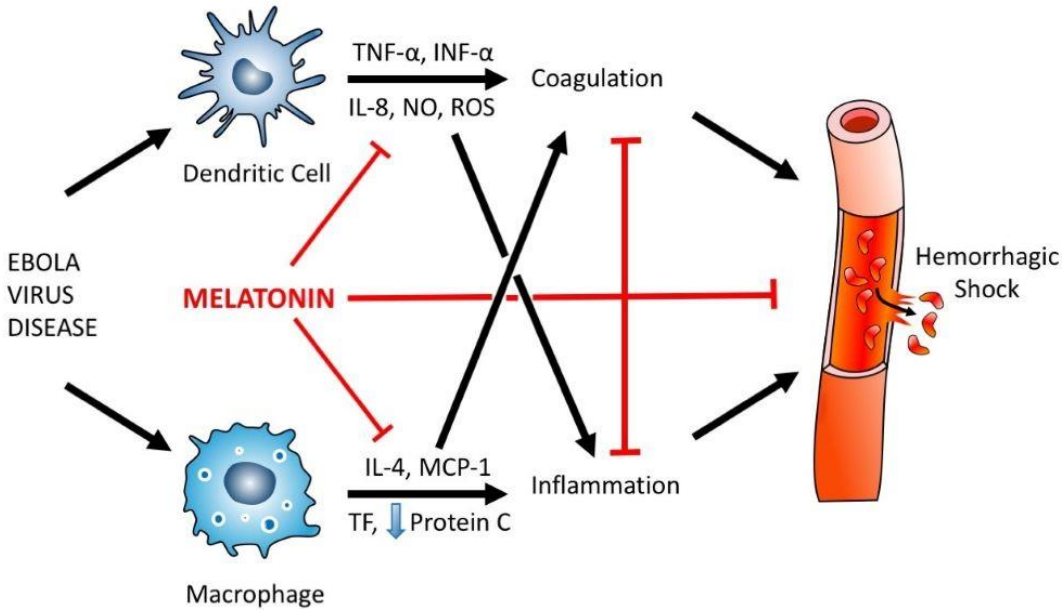

Fig. 1. Effects of melatonin on Ebola virus induced hemorrhagic injury.

This is a summary of the actions, as proposed in 2014, of melatonin that could lower the severity of an Ebola infection by interfering with the processes that promote blood coagulation, vascular inflammation and the subsequent hemorrhage shock. Melatonin strongly resists oxidative stress by directly scavenging free radicals and by stimulating antioxidant enzymes; free radicals contribute significantly to tissue damage that occurs during an Ebola infection. Moreover, melatonin has anti-inflammatory actions by reducing the production of pro-inflammatory cytokines which also stimulate the immune system. This combination of actions contributes to the ability of melatonin to prevent damage to the endothelium which reduces the extravasation of blood through the damaged capillary walls. Finally, melatonin's actions on platelet aggregation and thrombin production are instrumental in reducing blood coagulation,
IL-4, interleukin-4; IL-8, interleukin 8; INF-α, interferon alpha; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; NOS, nitric oxide synthase; TNF-α, tumor neurosis factor alpha; TF, tissue factors

Given that major damage occurs to the endothelial lining of blood vessels as a result of Ebola, it is particularly noteworthy that melatonin has repeatedly been shown to reduce endothelial damage and dysfunction thereby reducing the likelihood of multiple hemorrhagic sites as is observed in Ebola-infected individuals (65-67). As additional justification for the use of melatonin to treat Ebola infections, it is well known that similar vascular damage induced by bacterial lipopolysaccharide also is ameliorated by melatonin. This has been repeatedly

documented in experimental sepsis (68, 69) and has also been observed in human newborns suffering with septic shock (70).

The second report that acknowledged the potential value of melatonin as an antidote to Ebola infection was that of Andersen and colleagues (53). Their rationale for melatonin use is essentially the same as that used by Tan *et al*. (52). Again, front and center are the ability of melatonin to inhibit pro-inflammatory cytokines, reduce oxidative stress, and support the immune system which synergistically would afford protection against the complications induced by the Ebola virus. Additionally, Andersen and co-workers (53) reminded the reader that under similar pathological circumstances of bacterial lipopolysaccharide toxicity melatonin maintains more normal endothelial function and reduces fatality as mentioned above (68-70).

The most complete documentation illustrating the efficacy of melatonin to thwart Ebola virulence is the recent detailed study of Junaid et al (71). This group specifically tested melatonin against Ebola-mediated hemorrhagic shock, which is the most prominent and deadly feature of an infection of this type. They developed and used a chip-based model; these models have become important tools in biomedical research (72, 73). Researchers in vascular medicine have especially exploited in vitro engineered chip models as experimental tools (74, 75).

Junaid and coworkers initially grew microvessels using human endothelial cells (HUVECs) adjacent to a collagen type I network (71). To ensure the endothelial cells exhibited the physiological barrier function of *in vivo* capillaries, the authors examined the potential transport of albumin through the endothelial wall into the collagen matrix and found no albumin leaked from the experimental vessel. When the vessels were challenged with the infusion of Ebola viral-like particles (VLP), however, albumin leakage occurred. The escape of the albumin was associated with the remodeling of the endothelial cell cytoskeleton and the endothelial cell-to-endothelial cell connections with the changes involving the upregulation of the intracellular Rho/ROCK pathway, which is normally involved with cytoskeleton maintenance and microfilament stabilization; albumin ooze out of the vessels was also viral load-dependent. These studies confirmed Ebola VLP do in fact disrupt the physical association of endothelial cells by interfering with cadherin, adhesion molecules which bind adjacent cells to one another as adherens junctions (Figure. 2).

The involvement of the endothelial Rho/ROCK pathway was supported by the finding that melatonin-mediated inhibition of this pathway prevented the Ebola VLP destruction of the cellular junctions.

There is evidence that glycoprotein $GP_{1,2}$, components of the Ebola virus envelope, are responsible for the pathological changes in endothelial cell adhesion when exposed to the Ebola virus (76). When the engineered vessels were exposed to $GP_{1,2}$, the endothelial cells responded with an increased permeability just as the vessels treated with Ebola VLP.

Subsequently, two drugs (melatonin and FX06) were compared as to their ability to arrest the damage to the engineered vessels treated with Ebola VLP. Since Ebola upregulates Rho/ROCK intracellularly, melatonin, which readily enters cells (77-80), was used to inhibit this pathway (81-83) and the associated vasculopathy. In contrast, FX06 works extracellularly where it binds to cadherin thereby preventing the loosening of adjacent endothelial cells (84, 85). Both FX06 and melatonin reduced vascular permeability via different mechanisms as described. The findings regarding melatonin also confirm the speculation that this indole will likely be useful as a drug to resist Ebola infection (52, 53, 86).

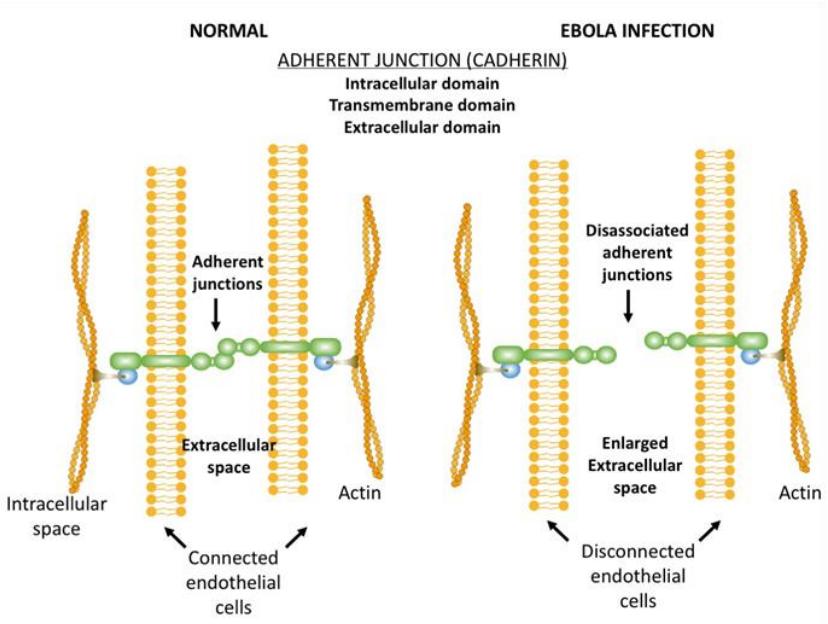

Fig. 2. Illustration how Ebola VLP disrupts the physical association of endothelial cells.

This figure illustrates how normal endothelial cells form tight junctions with an adjacent endothelial cell thereby preventing the extravasation of blood cells from capillaries. A major component of these physical connections are cadherin-based adhesion proteins. Cadherins ("calcium dependent adhesion" molecules) have an intercellular domain, a transmembrane domain and an extracellular domain. The intracellular domain links to cytoskeletal proteins such as actin. The joining of intercellular domains of nearby cells anchors adjacent cells via what are identified as adherent junctions. When the intercellular proteins of adjacent cells are no longer in contact, the endothelial cells separate allowing blood cells to escape between them. EVD causes a breakdown of the cell-to-cell connections by altering the intracellular cadherin connections to cytoskeletal proteins and also by destroying the adherent junctions extracellularly. Both processes contribute to the resulting endothelial cell damage that leads to the widespread hemorrhage in multiple organs, a characteristic feature of an Ebola infection.

The vasculopathy that accompanies an Ebola virus infection is clearly a very serious process that contributes to hemorrhagic shock syndrome and often causes death (87, 88). Currently, no reliable treatments are available which seriously impact the course or outcome of such infections. Defining some of the molecular processes, as identified by Junaid and co-workers (71), is a much-needed advance in seeking a treatment for this ravaging disease. While neither FX06 nor melatonin are virucidal agents, they do significantly alter the course of hemorrhagic shock syndrome via different means under experimental conditions as shown by Junaid *et al*. (71) and as summarized in figure 3.

As a conclusion, Junaid and colleagues (71) identified melatonin as a useful agent that is both inexpensive and safe as a treatment for Ebola. They also noted that the dose of melatonin in translational studies must be defined with current doses used for sleep promotion (1-5 mg daily) probably being insufficient to seriously challenge a severe Ebola infection. Finally, these workers point out that a combination of melatonin and FX06 treatment of Ebola should also be considered.

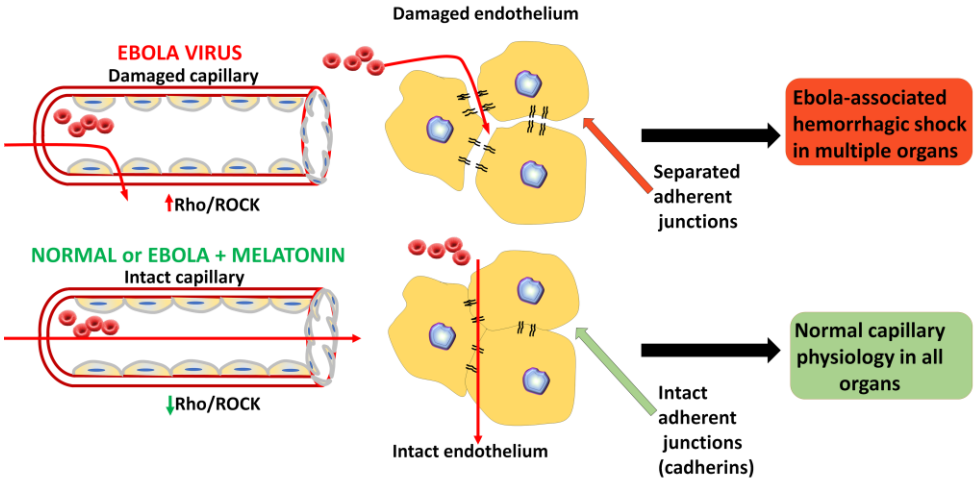

Fig. 3. Effects of melatonin on vasculopathy induced by Ebola virus.

The vasculopathy, as shown in this figure, is a major feature that contributes to the severity of Ebola infections. The damage to endothelial cells by the Ebola virus (top images) allow the endothelial cells to separate which permits blood cell leakage. Since capillaries throughout the body are damaged, hemorrhage occurs in multiple organs leading to their failure and to death of the individual. Capillary endothelium of normal cells or cells exposed to Ebola virus plus melatonin maintain their physical connections thereby preventing the leakage of blood cells (bottom figures). Under the latter conditions, blood cells and serum merely pass through the capillaries without escaping into the subendothelial space and, as a result, the widespread hemorrhage characteristic of an Ebola infection is avoided. In Ebola-infected cells, Rho/ROCK is upregulated loosening the connections between cadherin and intracellular cytoskeletal proteins (see figure 2). Melatonin downregulates Rho/ROCK protecting endothelial cells from Ebola-mediated damage. Melatonin also markedly reduced vascular permeability in Ebola-exposed capillaries indicating that they not only prevent the interendothelial cell damage to the cadherin-cytoskeletal junctions, but also works extracellularly to protect the adherent junctions.

Heretofore, only one Ebola patient has been treated with FX06 (89) and no Ebola virus-infected subject has been treated with melatonin. Based on current experimental findings, it seems, at a minimum, a clinical trial, although there is significant urgency to this problem, using melatonin alone or in combination with FX06 should be urgently performed. Alternatively, melatonin could be made available to individuals already diagnosed with the disease or given as a preventative to patients at high risk of exposure to Ebola virus. Totally depriving these patients of melatonin would seem to pass on a real opportunity to potentially reduce the severity of the disease or to prevent the death of some patients.

A combination treatment that utilizes both melatonin and FX06 may be particularly beneficial. Their mechanisms are different with some overlap. Melatonin works primarily intracellularly to reduce the production of molecule-damaging cytokines that contribute to endothelial cell dysfunction. In contrast, FX06 functions extracellularly to strengthen adhesions between cells (an action that is shared by melatonin), These supportive therapies may reduce the severe hemorrhagic shock that Ebola patients endure and prevent death until the body is able to amount an antibody response capable of killing the virus. Melatonin also tweaks the immune

system which could be helpful in allowing for a more rapid upregulation of the immune response.

The advantages of melatonin are several. It is easily synthesized, is environmentally friendly, is inexpensive, has a long shelf life at ambient temperature, can be self-administered via any route (orally, sublingually, intranasally, etc.), comes in several forms (rapid release, slow release, etc.) and has a very high safety profile with essentially no toxic dose having been identified in either animals or humans (70, 71, 90, 91). The conventional sleep-promoting dose, i.e., 1-5 mg daily, however, would likely be inadequate to ward off the pathologies related to an Ebola infection, which are always serious (92).

5. MELATONIN: ITS TIME HAS COME

The reports summarized in this brief review show conclusively that melatonin reduces the consequences of a variety of different viral agents in several mammalian species and disease models (93). Certainly, the findings documenting the high likelihood that melatonin would lessen the severity of Ebola infections cannot be ignored. Considering the extreme severity of an Ebola infection, the data summarized herein should be more than adequate justification to use melatonin as a potential treatment in at least Ebola patients. Additionally, trials should be initiated in regard to other virus-related diseases and under circumstances where hemorrhagic shock is a prominent feature, e.g., bacterial sepsis. To illustrate the wide-ranging efficacy of melatonin against viral agents, the reader is reminded that in plants as well, melatonin has been used to attenuate virus-mediated diseases (94-96).

The high efficacy of melatonin as an agent to reduce viral infections likely stems from its wide ranging effects as a potent antioxidant (60, 61, 97, 98), as a substantial anti-inflammatory agent (58,59,99), its high immunoenhancing capabilities (56, 57) in addition to its direct modulation of intracellular and extracellular processes as summarized herein and which rendered exposed cells more resistant to the Ebola virus.

Just as this review was ready for submission, the deadly coronavirus (2019-nCoV) emerged in China and has already spread to other countries. It would behoove health care professionals to at least suggest the use of melatonin to possibly control the spread of the disease caused by this virus. A daily dose of 40 mg or more would seem judicious. Other preventative/treatment options are essentially zero.

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AUTHORSHIP

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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