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COMMENTARY

Urgent search for safe and effective treatments of severe acute respiratory syndrome: is melatonin a promising candidate drug?

Since the end of February of this year, global health is being threatened by the emergence of a new infectious disease, severe acute respiratory syndrome (SARS), caused by a novel coronavirus [1–3]. The disease was believed to have originated in the Guangdong province of China and has now spread throughout the world with a cumulative total of 5050 cases (321 deaths) from 26 countries as of April 28. It is noteworthy that the majority of deaths have been reported in Hong Kong and mainland China, in which the outbreak is still spreading and apparently not yet under control, despite intensive efforts by the governments concerned.

Without doubt, the rapid identification of the new coronavirus as the cause of SARS by the international network of laboratories, coordinated by the World Health Organization, in a relatively short time (about 6 wk) after the syndrome was first recognized in Hanoi, Vietnam, is a major scientific achievement in the history of mankind. The molecular and virological data will hopefully enable the international research community to develop effective and specific diagnostic tests, antiviral agents and preventive vaccines against this emerging disease. However, the most immediate concerns to the health authorities of Hong Kong and mainland China are to contain the spread of the disease and to reduce the mortality of those SARS patients who succumb to acute respiratory failure. Besides reducing the public concern associated with the disease, having methods to control it would reduce the negative impact on the economy.

While health officials are working hard to contain the spread of the disease in the hard-hit places such as China, Hong Kong [4], Singapore and Canada [5], clinicians are racing against time to find effective drugs to rescue SARS patients from serious illness and death. Not all patients are responsive to supportive management or to a combination of high dose steroids and ribavirin, which have been used widely as the first-line treatment in Hong Kong [6, 7]. Although it remains unknown whether the broad spectrum antiviral agent ribavirin is effective in inhibiting the growth of the SARS virus, many of the patients have apparently benefited from the use of high dose steroids as indicated by initial clinical reports. Steroids are mainly used to reduce the severe viral-induced inflammatory damage to the lungs of the patients. The lungs show histological changes comparable to acute respiratory distress syndrome (RDS) in those with severe disease [6, 7]. Apart from the well-known side effects associated with steroid use, e.g., gastrointestinal bleeding as well as metabolic and psychologic disturbances, high dose steroids as an immunomodulator in the current therapy against SARS could be a double-edged sword. It is highly possible that suppression of immune defenses by steroids in individual patients who do not respond to steroids and ribavirin may do more harm than good, by putting these patients at higher risk of developing superimposed infections with other microbial pathogens; also, it subjects them to a reduced coronavirus-specific antibody production and to uncontrolled cytolytic lung damage by the SARS virus if its growth is ultimately shown to be refractory to ribavirin.

Like many other acute and chronic inflammatory diseases, oxygen-derived free radicals play an important role in the pathogenesis of the acute RDS [8] triggered by the SARS virus. Reactive oxygen species can modulate a wide range of toxic oxidative reactions such as initiation of lipid peroxidation, direct inhibition of mitochondrial respiratory chain enzymes, inactivation of glyceraldehyde-3-phosphate dehydrogenase, inhibition of membrane sodium/potassium ATPase activity, inactivation of membrane sodium channels and other oxidative modifications of proteins. They are also potential reactants capable of initiating DNA single strand breaks, with subsequent activation of the nuclear enzyme poly (ADP ribose) synthetase (PARS), leading to eventual severe energy depletion and cell necrosis. Specifically in lungs, oxidative stress increases the surfactant peroxidation [9] and edema [10] and decreases the oxygen exchange function of alveoli [11]. Bernard et al. [12] reported that repletion of antioxidant levels with N-acetylcysteine and/or L-2-oxothiazolidine-4-carboxylate treatment shortened the duration of lung injury in patients with acute lung injury/acute RDS. The need for appropriate treatment with anti- inflammatory and/or antioxidative drugs in SARS patients is apparent.

Melatonin is a naturally occurring, endogenously produced and diet-contained molecule [13]. It is a potent antioxidant [14] with a significant anti-inflammatory activity as well [15]. This indoleamine also moderately stimulates the immune system which would decrease the likelihood that SARS patients would develop secondary viral or other microbiological infections. The protective effects of melatonin against viral encephalities in mice [16, 17] and viral infections in mink [18] have been documented. Moreover, the treatment of 40 newborn human infants suffering with RDS given intravenously administered melatonin (80 mg over 3 days) improved their clinical status and no death was observed; however, in another 36 RDS infants with conventional treatment only, 11% of them died and the clinical manifestations were more severe than in their melatonin-treated counterparts (E. Gitto, I. Barberi et al., unpublished observations). Animal studies have

demonstrated that melatonin reduces lung lipid proxidation and myeloproxidase activity which is the index of polymorphonuclear leukocyte infiltration which is induced by non-specific inflammation [19]. Melatonin also protects against the breakdown of lung surfactant, edema, and increases the oxygen exchange across alveoli [9–11]. Clinical studies have shown that melatonin treatment significantly reduces the levels of lipid peroxidation products in the blood of newborns as a result of asphyxia [20] and septic shock [21] and markedly increases the survival rates of these infants. In addition, melatonin also counteracts the side effects of steroids including metabolic disturbances [22] and cytotoxicity [23].

Given these positive effects in clinical conditions which have similarities to SARS, it would seem worthwhile to use melatonin, in conjunction with current therapies, to treat SARS patients with the intention of increasing the efficiency of conventional drugs [24] and lowering the death rate. Melatonin is inexpensive and has a very high margin of safety and could have significant benefit in improving the clinical status and reducing death of people with SARS.

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