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Repurposing prolactin as a promising immunomodulator for the treatment of COVID-19: Are common Antiemetics the wonder drug to fight coronavirus?

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ABSTRACT

Prolactin (PRL), the well-known lactogenic hormone, plays a crucial role in immune function given the fact that long term hypoprolactinemia (serum prolactin level below normal) can even lead to death from opportunistic infection. High blood PRL level is known to provide an immunological advantage in many pathological conditions (with some exceptions like autoimmune diseases) and women, because of their higher blood PRL level, get an advantage in this regard. It has been reported that by controlled enhancement of blood PRL level (within the physiological limit and in some cases a little elevated above the normal to induce mild hyperprolactinemia) using dopamine antagonists such immune-stimulatory advantage can led to survival of the patients in many critical conditions. Here it is hypothesized that through controlled augmentation of blood PRL level using dopamine antagonists like domperidone/metoclopramide, which are commonly used drugs for the treatment of nausea and vomiting, both innate and adaptive immunity can be boosted to evade or tone down COVID-19. The hypothesis is strengthened from the fact that at least seven little-understood salient observations in coronavirus patients can apparently be explained by considering the role of enhanced PRL in line with the proposed hypothesis and hence, clinical trials (both therapeutic and prophylactic) on the role of enhanced PRL on the course and outcome of coronavirus patients should be conducted accordingly.

The world has been facing a significant threat from COVID-19 and there is a race to find out the cure of coronavirus-2, an enveloped, single-stranded RNA virus (SARS-CoV-2) with an alarming transmission rate (reproduction number (R_0) can be as high as 3.8). To date, no proven therapy to treat coronavirus exists, but the unprecedented challenge has fueled an extensive research across the globe leading to potential treatment options [1–3] like antivirals, repurposed drugs, immunotherapy and convalescent plasma therapy. Most COVID-19 patients are either asymptomatic or show mild symptoms. Around 15–20% patients need hospitalization and some of them succumb to hyperinflammation (cytokine storm), vasculitis, hypercoagulability and multiple organ failure [4–6]. Patients with severe symptoms show a significant decline of B cells, NK cells and CD4+ and CD8+ T cells and the surviving T cells appear functionally exhausted [5–8]. In addition, critically ill patients show dramatic upregulation of cytokines like TNFα, IL-2, IL-6 [4,5,8,9]. Since hyperactive immune system leads to lung injury and acute respiratory distress syndrome (ARDS) with consequent fatality in many ICU admitted patients, immunosuppressive therapies [10–12] have turned out to be prospective options to tackle ARDS and save the patients. Some of the immunotherapies [10–13] tried or under clinical trial (with mixed results and sometimes with unacceptable side effects) are chloroquine/hydroxychloroquine (immune suppression and interfering with the pH-dependent endosome-mediated viral entry), glucocorticoids (immune suppression), tocilizumab (blockade of IL6 receptor), stem cells (suppression of inflammation) and convalescent plasma (antibodies to eliminate the virus).

Surprisingly, children have been found to be less susceptible to COVID-19 and it has been proposed that their strong innate immunity helps them to keep the disease under restraint [14]. In contrast to adaptive (specific) immunity where primarily T and B lymphocytes are involved, innate immunity (nonspecific, and mediated by natural killer cells (NK), neutrophils, monocytes, dendritic cells (DC), macrophages, mast cells etc.) is of pivotal importance and is the body's frontline defence. For innate immunity, the pathogen associated molecular patterns (PAMPs) on the pathogen's surface bind with the pattern recognition receptors (PRRs, including TLRs, Toll-like receptors) on macrophages and dendritic cells and in the process interferons (IFNs) and interleukins (ILs) are released, dendritic cells are activated and cytotoxic T cells and NK cells are enhanced which help in getting rid of the viruses

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[14,15]. It has been suggested that trained immunity (memory in innate immunity from antigen challenge) in children may provide them a strong innate immunity [14–16]. Against this backdrop, immunotherapy in the form of immune boosting through BCG vaccination is also under clinical trial [14–16].

Prolactin (PRL), the well-known lactogenic hormone, has been associated with more than three hundred different biological functions [17]. It is involved in restoring neuroendocrine, immune and hematopoietic homeostasis under conditions of impaired function and is produced not only from the anterior pituitary gland but also from various extra-pituitary sites such as immune cells, neurons, prostate, decidua, mammary epithelium, and skin [18,19]. PRL has three isoforms [20,21] and the most biologically active isoform is the monomeric free little PRL (molecular weight of 23 kDa) and the others are called big PRL (molecular weight between 40 and 60 kDa), which is a mixture of dimeric and trimeric forms of glycosylated little prolactin and big-big PRL also called macroprolactin (molecular weight ≥ 100 kDa), which is glycosylated prolactin coupled with immunoglobins and is the least bioactive amongst the three isoforms. As PRL is also synthesized and secreted from lymphocytes, it is considered as a cytokine and it signals through the same pathways as the immune cytokines [19]. PRL plays a significant role in adaptive immunity, both humoral (mediated primarily by B cells and helper T cells) and cellular (mediated primarily by T lymphocytes), through endocrine, paracrine, and autocrine mechanisms [20–24]. Normally, PRL elicits Th1 (T helper type 1)-mediated proinflammatory response [25,26] and high blood PRL (specifically hyperprolactinemia) is mostly recognized as a pathological state (excluding physiological hyperprolactinemia like pregnancy) responsible for autoimmune diseases like systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA) and are more prevalent in women (and more so during pregnancy), given the fact that women have higher blood PRL than men. It has been found that bromocriptine, a dopamine agonist which lowers the prolactin levels can suppress the disease [20,21,27–30]. It is interesting to note that immunostimulatory PRL can also exhibit immunosuppressive response in relatively higher doses under certain conditions [21,27–31].

Interestingly, in contrast to its adverse role in some autoimmune diseases, PRL is involved in many ways to safeguard our immune system. It stimulates B and T cells and there is a direct correlation between PRL levels and the number of B and T cells [20,21]. Indeed, prolonged suppression of PRL is associated with lymphocyte depletion and can lead to nosocomial infection and death [24]. A correlation between hypoprolactinemia and increased mortality in preterm infants has also been observed [32]. In case of trauma and severe haemorrhage, it has been found that female patients having higher blood PRL survive better than men and the role of higher PRL in female-biased survival is corroborated by clinical observations where administering metoclopramide, a dopamine antagonist which enhances blood PRL, the depressed immune system of severe trauma patients can be stimulated leading to favourable outcome in survival of the patients [33]. In case of patients with HIV/AIDS, raising blood PRL by using imipramine (dopamine antagonist) has been found to stimulate the immunity of the patients by increasing the CD4 cell count [34]. It has been suggested that in patients with HIV infection, dopaminergic adaptive mechanisms maintain their blood PRL at a high but physiological concentration, which stimulates CD4+ T lymphocyte proliferation and increases viral apoptosis [35]. Also, by enhancing PRL in appropriate amounts, and in even in some cases by inducing short-term mild hyperprolactinemia, intervertebral disc degeneration, graft-versus-host disease, asthma and allergic lung inflammation have been toned down [23,31,36,37]. In this context, it may be noted that mild hyperprolactinemia is normally harmless as many physiological causes like pregnancy, lactation, sleep, and stress [38] raise plasma PRL level. Though medication induced hyperprolactinemia [39] may be accompanied by galactorrhea, menstrual disturbance, impotence and low bone mass, it is of little consequence in low doses.

In addition to its role in augmenting adaptive immunity, PRL has a key function in enhancing innate immunity which is the early line of defence against the pathogens. PRL can boost innate immunity by stimulating NK cells, macrophages, neutrophils, and DCs (dendritic cells which can cross-talk with T lymphocytes and can act as messengers between innate and adaptive immune systems) and can also increase the expression of TLRs [21,40,41]. PRL has been reported to induce the phagocytosis of C albicans, S epidermidis, S. aureus, T gondii and A castellani [40]. Higher PRL serum level has also been found to improve the survival of patients with sepsis by activating both the innate and adaptive immunity [42]. Indeed, PRL insufficiency has been documented in more than fifty percent cases of neonatal sepsis [43].

From the above discussion, it is evident that controlled enhancement of blood PRL level (within the physiological limit and in some cases a little elevated above the normal to induce mild hyperprolactinemia) using dopamine antagonists can boost both the innate and adaptive immunity and can tilt the balance in favour of survival for many critically ill patients. Hence, it is worthwhile to consider whether such immunomodulation by tweaking blood PRL level can be a beneficial intervention in the treatment of SARS-CoV-2 patients. Incidentally, some noteworthy observations on the modalities of COVID-19, which defy explanation, can be understood considering the importance of blood PRL level of coronavirus patients in conformity with our hypothesis as given below.

First, gender difference in the severity of COVID-19, where men (independent of age) are more at risk for worse outcome and death [44]. Any role of female hormones is ruled out as postmenopausal women also show higher survival rate. Incidentally, females have higher blood PRL than males and the levels do not fall after menopause [45]. Hence, higher PRL levels of women can explain the gender-bias of COVID-19.

Second, though pregnant women are susceptible to many diseases, COVID-19 normally does not pose any extra danger to pregnant women and the symptoms are found to be mostly mild for them [46]. Higher PRL level in pregnancy may have provided the pregnant women an advantage in tackling COVID-19.

Third, obesity is a major risk factor for COVID-19 and higher oxygen demand, more weight on lungs, more adipose tissue etc. have been proposed as possible reasons to explain the added risk [47]. An alternative explanation can be the lower blood PRL level [48] in obese patients.

Fourth, surprisingly, cigarette smokers have been found to be more resistant to coronavirus and the reason for such unusual behaviour is still unknown though it has been suggested that nicotine may lower cytokine storm [49]. Incidentally, nicotine enhances serum PRL [50] and thus can explain the observation.

Fifth, chlorpromazine has been suggested as a drug for clinical trial based on the observation that in a psychiatric hospital in France, the healthcare staff have been much more affected by coronavirus than the patients [51]. Possible antiviral and immunomodulatory effects have been suggested as the mechanisms for the effectiveness of chlorpromazine, a common drug used for psychiatric patients. However, in psychiatric hospitals, not all the patients take antipsychotics like chlorpromazine during their courses of the treatment and depending on the symptoms, some patients take tricyclic antidepressants and SSRIs and hence, any explanation based solely on chlorpromazine or related antipsychotics may not satisfactorily explain the observation. Incidentally, in addition to antipsychotics like chlorpromazine, which is a dopamine antagonist and enhances blood PRL, tricyclic antidepressants and SSRIs too augment PRL level [52] and therefore, the high PRL advantage can provide a comprehensive explanation irrespective of the type of medicines used by the patients in the psychiatric hospital.

Sixth, famotidine, a H2 blocker, has been found to ameliorate the symptoms (through unknown mechanism) of COVID-19 patients [53]. It is interesting to note that like dopamine antagonists, H2 blockers too enhance blood PRL level [52] and hence, can explain the observation.

Seventh, children in general have been found to show mild symptoms [14] towards COVID-19. Incidentally, the blood PRL levels of adults and children do not differ significantly except during the first year of life when blood PRL level of children remains high [54]. However, children have much higher plasma growth hormone (GH) than that of adults and GH like PRL shows immune stimulatory effects. It is known that PRL may compensate GH deficiency as GH can bind on PRL receptors and thus an action of PRL may partially be mediated by GH [55,56]. Hence, in case of children the combined effect of GH and PRL can effectively provide the high PRL advantage and consequently provide resistance to coronavirus.

In conclusion, given the pivotal role of prolactin (PRL) in stimulating both the innate and adaptive immunity in humans and the advantage of controlled enhancement of blood PRL level (within the physiological limit and in some cases a little elevated above the normal to induce mild hyperprolactinemia) in fighting many diseases, it is proposed that a controlled boost in blood PRL should help COVID-19 patients in getting around the disease or at least, in alleviation of their symptoms. Interestingly, the enhanced PRL advantage, as proposed in the hypothesis, gains strength by providing explanation of many significant but little-understood observations in the coronavirus patients as delineated above. Hence, clinical trials should be conducted in coronavirus patients to assess the role of immune modulation on the course and outcome of the disease by enhancing their blood PRL level using dopamine antagonists like domperidone/metoclopramide. Such dopamine antagonists should also be used as prophylactics and to that end, clinical trials should also be initiated.

Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110208.

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