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A Study on Consequences of Anthropogenic Stress in Bats: Emergence of Nipah Virus

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Abstract

Emerging infectious diseases are the concerning challenge in recent years. A large number of emerging zoonotic viruses like Marbug virus, Hendra virus, Ebola virus, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory coronavirus (MERS-CoV), SARS-CoV-2 and their corresponding natural reservoirs are identified during last decades. Among many infectious agents, Nipah virus (NiV) outbreaks have got much attention due to its extreme fatalities especially in South-East Asia. NiV is a significant bat-borne paramyxovirus that causes yearly outbreak of fatal encephalitis in one of the most populous region of the earth. A decades of research established that bats are the well identified reservoirs of Nipah virus, a bird's eye provides us a clear insight about several anthropogenic factors that are responsible for driving bats to spread out this specific virus as well as other fatal viruses. In this review, we have focused on the anthropogenic stress mediated disturbances of natural balanced state of host-parasite, which results in the seasonal outbreak of Nipah virus mediated diseases.

Keywords

Anthropogenic Stress, Glucocorticoid, Immune Suppression, Viral Load, Emergence

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1. Introduction

NiV is a zoonotic paramyxovirus, capable of causing infectious disease. It is a single stranded RNA virus containing six genes in its genome and are able to infect many mammalian species [1, 2]. Bats, the second largest mammals in this world, are the natural reservoir host for about more than 66 viruses including NiV [3-5]. Several studies showed that, many species of bats were found to carry NiV in a wide range of geographical distribution including Australia, Papua New Guinea, Malaysia, Cambodia, Indonesia, Thailand, Bangladesh, India, Ghana, and China [6-12]. Due to some special features, bats may carry the emerging zoonotic viruses through maintaining a mutual relationship.

Various anthropogenic factors including deforestation, urbanization, agricultural expansion, light pollution, global travel, military activities, trade in wild life, and wind turbines etc. favour the increased interactions among humans, domestic animals and wild life. These interactions facilitate the emergence of many infectious diseases [13, 14].

2. Bat Speciality

Bats are the second largest mammals which consists 20% of all mammalian population in the world [15-17]. The oldest fossil of bat was found around 52.5 million years ago [18]. Among all mammalian species bats are the only one that can fly, and fly hundreds of miles for their foraging and seasonal migration [4, 19], therefore they are able to exist in almost every terrestrial environment [15]. Bats have highly social roosting behaviour and reside in very large and dense colony [20, 21]. Bats are exceptional for their long life span and

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maintain around 25-35 years longevity [3, 22]. As they remain close contact in highly dense colonies it is easy for them to inter-species transmission of viruses. This inter-species transmission is also occurred by echolocation process through spill over secretion [21]. All these special features of bats offer the characteristics of an appropriate reservoir for emerging viruses.

3. Mutual Relationship Between Bat and NiV

Although bats are the natural reservoir of NiV but there are no evidences for NiV induced diseases in bats. The absences of diseases indicate the highly evolved mutual relationship between NiV and bat [4, 23, 24]. Rather than interacting as a threatening agent for bats, NiV serves as the defensive biological weapons of bats to protect them from others predators to maintain their ecological niche [20]. It's really a fight for survival. NiV is also benefited by using host replication machinery and biochemical pathways to maintain their replication frequency [4]. To perform this action, viruses must have to evade the host immune responses. Some commonly employed evasion strategies include virus-encoded immune-modulating cytokines, decoy soluble cytokine receptors, inhibitors of apoptosis and cellular signalling, inhibitors of antigen processing, T-cell antagonists [25-28], and evading the IFN-induced antiviral responses [29, 30]. Some paramyxoviruses including Nipah viruses, encode V, W, and P proteins that affect the signal transducer and activator of transcription 1 (STAT1) and STAT2 proteins of host cells to block interferon responses [31, 32]. Specifically, the p gene products inhibit both dsRNA signalling [33, 34] and IFN signalling [35] and the V and P proteins interact with STAT1 in the cytoplasm, whereas the W protein co-localizes with STAT1 in the nucleus [36].

4. Emergence of NiV in Bats: The Complexity of Natural System Perturbation

NiV outbreak was first observed in 1998 [37] at Nipah village in Malaysia. Few years later, bats are identified as natural reservoir of Nipah virus. Since then NiV infection in human has become the concerning research issue in the field of infection and immunity. NiV infection associated with increased rate of fatality is attributed to encephalitis and central nervous system dysfunction [38, 39].

Disturbance in animal physiology and behaviour due to chronic stresses particularly anthropogenic stresses and the impact of these stressors have got the considerable attention in recent years [40, 41]. Human activities including urbanization, recreational activity, construction of roads, and noise from military activity can cause behavioural changes leading to altered density, dispersal, and home ranges of wildlife [42, 43] which ultimately result in physiological changes, such as reduced reproductive success and immune-competence in wildlife [44, 45]. Moreover, immune-suppression due to chronic anthropogenic stresses can lead them to become susceptible for various infections [46, 47].

Deforestation, the leading cause of habitat destruction is a threatening anthropogenic stress [48, 49]. In Africa, South East Asia and Amazonia the anthropogenic fire mediated deforestation has become the concerning issue [50, 51]. A large area was burnt in Borneo, Sumatra and east Kalimantan due to drought and poor land use management [52]. It has been observed that NiV infected bats migrated to Malaysia from Indonesia due to El Nino Southern Oscillation (ESNO) drought and anthropogenic forest fires. This series of events directed to an ultimate reduction in the availability of flowering and fruiting forest trees for foraging by flying-foxes in their previously lessening wildlife habitat [52, 53]. All of these evidences indicate that rapid urbanization results in drastically reduction of bats food availability and biodiversity.

Anthropogenic light pollution is a continually alarming problem, disturbing the ecological balance of bats in the context of foraging, communication and reproduction [54, 55]. Extensive exposure to artificial light causes disturbed vision and damaged retina of bats [56]. Experimental evidences suggested that, bats magnetic based orientation and echolocation is negatively correlated with artificial lightening [57, 58]. Under artificial lighting condition the normal flight trajectories [59] and commuting behaviours [55] of bats are altered, results an increased energetic cost. The increased rate of agitation in a maternity colony at cave [60] and decreased colony size in illuminated sites are highly correlated with anthropogenic light pollution. Studies revealed that, the artificial lighting shortens their feeding time [61, 62] and the time span responsible for insect prey [63] which results in food scarcity. Bats from illuminated sites are also subjected to shorten in size [64].

In recent years observation, the impact of wind turbine found to be highly correlated with the large number of bat fatalities notably in European countries including France, Germany, Portugal, UK [64, 65], and North America [66, 67]. One possible reason for bat fatalities could be the close proximity of wind turbines with bats foraging and migratory trajectory [68]. Other possible reasons to be considered that bats may be unaware of the presence of wind turbines, this cause could be correlated with bats low echolocation ability in recent years due to light pollution [69]. Bats are also attracted to

turbines believing its potential sites for roosting [68, 70].

5. Chronic Anthropogenic Stress Mediated Immune Suppression in Bat

When an animal experiences stress for prolonged period and continuously initiate stress responses, then the animal is called chronically stressed animal [71]. Stressors can be food shortage, dwelling in areas with high density of predator or parasite, introduced species, fluctuation from favourable condition etc. [72]. Anthropogenic changes like habitat alteration and urbanization have potential to alter stress responses in animals and cause diseases (Figure 1) [73]. A number of studies have suggested the connection between human activities and the emergence of various wildlife diseases. Normally urban animal populations experience more parasite prevalence than rural population [47]. Consequently, immune suppression in free living animals is a common event during chronic stressful situation. Glucocorticoid (GC) which is the most established stress hormone secreted through hypothalamic pituitary adrenal (HPA) axis during chronic stress. When stressful events sustain for prolonged time, the GC levels are increased and this elevated level of GCs suppress the immune system, thereby facilitating various infection [74, 75].

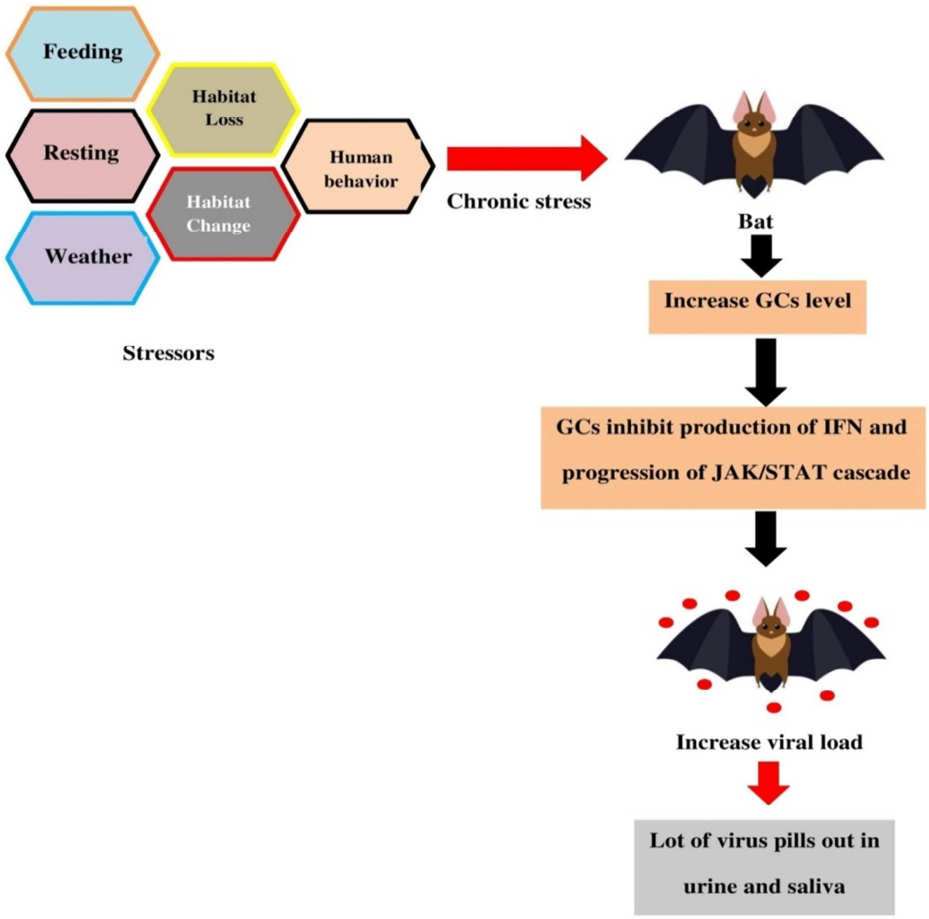

Figure 1. An overview of anthropogenic stress mediated outbreak of Nipah virus.

In recent studies, elevated levels of glucocorticoids are identified in bats from chronic anthropogenic stress affected sites**,** whereas bats from unaffected sites have lower GC level [76, 77]. So it is likely to be postulated that, chronic anthropogenic stress is highly correlated with GC levels in bats. Effect of GCs can be classified into five broad ranges: elevated levels of blood glucose concentrations; altered behavioural activity; inhibition of growth; inhibition of reproduction and modulation of immune system. When GCs persist at high levels it is seemed to suppress the bat immune system [78, 79]. Naturally immunosuppression induced by GC includes a series of events like: inhibition of cytokine expression; reduced MHC expression; reduction in lymphocyte chemotaxis; reduced T cells, B cells, macrophages activation and proliferation; death of immature T and B cells. All these events lead to immunosuppression of chronic stressed animal mediated by glucocorticoids. Chronic anthropogenic stresses modulate negatively the social status

of bats resulting in increased GC levels, thereby increase the parasitic load [80, 81].

Chronic anthropogenic stress might also responsible for virus persistence in reservoir hosts. Recent studies have suggested two mechanisms involved in virus persistence in host: resistance and tolerance [82]. Resistance refers to the mechanism that directly has negative effect on parasite prevalence which includes innate and adaptive immunity. On the other hand, tolerance is the mechanism that does not have direct negative effect on parasite, rather limit the damage by a given burden. Tolerance includes tissue repair and other immunological mechanisms which are directed to toxic substances produced by parasites. Glucocorticoid is responsible to reduce the resistance and thereby increase tolerance [72]. This clearly indicates the link between chronic anthropogenic stress and virus persistence in animal hosts.

6. Transmission Routes of Nipah Virus to Human

In previous section we have discussed the interspecies transmission of NiV in bats, now we will discuss about the routes of transmission from bat to human. Various factors are seemed to facilitate this transmission includes indirect contact with infected bat, close contact with intermediate host or exposure to their body secretions [83].

In Malaysia, most encephalitis cases occurred among pig farmers, whereas cases reported in Singapore were mostly among abattoir workers, those who involved in slaughtering infected pigs imported from Malaysia. No human-human transmission was reported both in Malaysia and Singapore [6].

In Bangladesh, first case of encephalitis with death was reported in 2001 at Meherpur District. As pigs are infrequent in Bangladesh, *P. giganteus* is the only identified reservoir of NiV and there is no intermediate host in Bangladesh for transmission. NiV strain isolated from Bangladesh has 95% homology with Malaysian strain [83]. Case studies suggest that, date palm sap act as a vehicle for transmission [84]. When infected bats come to drink the juice, virus spread in juice which further consumed by people. Some people also affected by taking fruits from foraging areas of bats those located in urban areas [85]. Some differences are observed in routes of transmission between Malaysia, Singapore and Bangladesh. Human-human transmission is observed in some cases of Bangladesh which was absent in Malaysia and Singapore. Nosocomial infection and direct exposure to respiratory secretion of already infected patient are identified responsible for human-human transmission [86]. This could be due to poor health care management of Bangladesh in contrast to Malaysia and Singapore.

Outbreaks in Bangladesh occur in the same regions at the same time. Evidence suggests that the seasonal outbreak of NiV in Bangladesh results from interaction between fruit bats and human activity. *P. giganteus* attracted to specific foods available at specific season in these specific urban areas, which bring them close proximity to human for transmission [84]. Increased food abundance could also increase pathogen transmission for urban adapted species [47].

7. Antiviral Immunity of Bats: New Insights of Seasonal Outbreaks of NiV

NiV expressed the P gene products namely P, V, W, and C proteins [87] which can exert immunosuppressive effects in bats. Upon infection in bat all viruses are subjected to face challenge by IFN mediated innate immunity [29, 88]. IFNs facilitate antiviral state in bats through activating JAK-STAT signalling pathway [89]. In case of Nipah virus, all of those P gene products are identified as IFN antagonist. STAT1 and STAT2 signaling pathways are blocked by V and W protein [90] whereas W protein alone can inhibit TLR3 pathway [31, 91]. Although all of these IFN antagonist proteins are seemed as virulence factors [92, 93], V and C proteins play the crucial role in this context [94]. We have already discussed the immune suppressive role of GCs in the previous section. Surprisingly chronic anthropogenic stress mediated GCs also responsible in suppressing the IFN production and JAK-STAT signalling pathway, thereby facilitating the NiV mediated persistent infection in bats [95].

To explore the pathogenesis of Nipah virus, understanding the bat immunology is of major concern, which is little explored yet. Being mammals, bats share some common features with human immune system. The immune cells like macrophages, B cells, T cells, and follicular dendritic cells (FDCs) have already being identified from bats [96]. Moreover lymphocytes, nutrophils, eosinophils, and basophils are also found in Brazilian free tailed bats [97]. Unlike other mammals, bats are shown to delay the immune response during infection [98]. Complement activities in pteropoid bats are found to be decreased at lower temperature [5]. Immunoglobulin like IgM, IgE, IgA, and IgG are isolated from bats [99], whereas IgM, IgG, and IgA are homologous to corresponding human immuneglobulins [100]. Experimented evidences suggested that, during prolonged period of cold condition as like hibernation, bats fail to develop antibody mediated responses and this response may revert within one week with the increasing of temperature

from 8^0 to 24^0 C [101]. Immune competence of bats is seemed to be lower during early pregnancy at the time onset of September [5].

Bats which are already in chronic anthropogenic stressed condition shows elevated level of glucocorticoids (GCs). When exposed to viral challenge, GCs acts as immunosuppressive agent which inhibits the anti-viral immunity of bats. GC suppresses both the production of IFN and progression of JAK-STAT cascade and ultimately bats become more immune suppressed than normal condition. Thus viral load of bat goes high. In September-March in time of early pregnancy and hibernation bat almost failed to show any immune response. This ultimately results in spill over incidents of Nipah virus.

Considering these observations, we are likely to postulate that NiV outbreak in South-East Asia in winter season is highly correlated with lower immune incompetence of bats during hibernation period. So we can hypothesize that, in normal condition with the absence of anthropogenic stress bats maintain a static viral load, which may not transfer through spillover. When bats are exposed with chronic anthropogenic stress this balanced viral loads are disrupted and tolerance increased which results in persistent infection. These immune suppressed bats exhibit high viral titter during hibernation periods (September-March) and availability of favourable food during this period which ultimately facilitates the spill over transmission of Nipah virus.

8. Future Implication: Urge for a Multidisciplinary Holistic Approach

Last few decades were marked for the emergence and re-emergence of several Emerging Infectious Diseases (EIDs) [102], when it was thought that the war against infectious disease is about to end. Almost three forth of all EIDs of human are of zoonotic disease [103], which are characterized by shift in new host population, increased incidence and change in host-parasite ecology [104]. The re-emergence and emergence of newly evolved infectious diseases highlighted the urgency of an effective management system. As we already discussed, anthropogenic stresses facilitated by rapid and unplanned urbanization, are the major key factors behind the emergence of NiV. This stress can also facilitate the emergence and re-emergence of other EIDs incidents, which can alter the biology of host, pathogen and vector biology, increased interspecies interactions and loss of biodiversity [104, 105]. We have also focused how stress and pollution make the hosts susceptible for infection and how unplanned urbanization could bring close contact of human and wild animals.

For long time, when dealing with infectious diseases, researchers focused mainly on disease pathogenesis of viruses in human model. However, this could give us only a partial view of the complex biological system. In recent years, the suppressive effect of stress response in human is well established but we should not have forgotten that, the animal kingdom has also been affected by stressors for long times. Our negligence and poor management in this issue is the key factor for most of EIDs. Human, animal, and nature are all inter-linked in a complex network system like a spider's web. Therefore, future researches must focus on systemic and holistic approach that will consider the molecular pathogenesis, virulence activity, ecology, biodiversity, host-pathogen interactions simultaneously. Without a systemic holistic approach, partial insights from our conventional way of research will not bring a sustainable result in the war with infectious diseases. In that case, in near future more new diseases will emerge ranging from more geographic area to more new animal hosts. Our present article is mainly focused on describing the issues responsible for the emergence of NiV, and urges a multidisciplinary systemic holistic approach for future implication with possible directions.

9. Conclusion

Being an emerging infectious disease, NiV has drawn much attention in recent years. To find the key factors of emergence i.e. how these virus could appear in bats or which drives bats to spread out the newly unfolding diseases. We have found some special and alarming reasons responsible for NiV outbreaks, which are our focus points in this review.

Anthropogenic stresses which are increasing in an alarming rate in recent years play key roles in the disturbance of bats activity. The host-parasite balance between bat and NiV are distorted through experiencing these disturbances**.** Upon stress, the viral load rapidly goes up in immune suppressed bats. During hibernation period, in the presence of anthropogenic stress the antiviral response of bats reduce dramatically and a lots of virus spill over occurs in saliva, urine and faeces of bats, which ultimately facilitate the NiV mediated disease in humans, pigs, and other animals.

We have already discussed the viral proteins responsible for virulence activity. Interestingly, in the presence of these viral proteins, the absence of disease in bats leads a crucial question: how they maintain these viruses in a pathogenic condition through host-parasite mutual relationship? From this interesting point, it could be fairly suggested that, these hidden relationship should be focused for future research to reveal the therapeutic approach as well as reducing anthropogenic stresses to establish a sustainable remediation

for many infectious diseases, which may achieve a milestone in coming era.

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