



Animal Welfare and Resistance to Disease: Interaction of Affective States and the Immune System

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Good management and improved standards of animal welfare are discussed as important ways of reducing the risk of infection in farm animals without medication. Increasing evidence from both humans and animals suggests that environments that promote wellbeing over stress and positive over negative emotions can reduce susceptibility to disease and/or lead to milder symptoms. We point out, however, that the relationship between welfare, immunity, and disease is highly complex and we caution against claiming more than the current evidence shows. The accumulating but sometimes equivocal evidence of close links between the brain, the gut microbiome, immunity, and welfare are discussed in the context of the known links between mental and physical health in humans. This evidence not only provides empirical support for the importance of good welfare as preventative medicine in animals but also indicates a variety of mechanisms by which good welfare can directly influence disease resistance. Finally, we outline what still needs to be done to explore the potential preventative effects of good welfare.

Keywords: affective state, immunity, welfare, gut microbiome, wellbeing, antibiotic resistance

OPEN ACCESS

Edited by:

Keelin Katherine Mary O'Driscoll,
Teagasc, Ireland

Reviewed by:

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University of British Columbia, Canada

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equally to this work

Specialty section:

This article was submitted to
Animal Behavior and Welfare,
a section of the journal
Frontiers in Veterinary Science

Received: 27 April 2022

Accepted: 16 May 2022

Published: 14 June 2022

Citation:

Döpjan S and Dawkins MS (2022)
Animal Welfare and Resistance to
Disease: Interaction of Affective States
and the Immune System.
Front. Vet. Sci. 9:929805.
doi: 10.3389/fvets.2022.929805

INTRODUCTION

The spread of anti-microbial resistance (1, 2) and the devastating effects of diseases, such as influenza, covid, malaria, and TB, are grim reminders that even with the full resources of modern medicine at our disposal, we are only just keeping ahead in the arms race against current and emerging diseases. Furthermore, the current emphasis on the need to reduce the use of antibiotics e.g., (3, 4) removes an important means of safeguarding both human and animal health (5). There is thus an urgent need to find new ways of fighting disease, preferably ones that do not use medication.

In this study, we focus on the growing evidence that an important way of reducing the risk of infection may be through good management and improved standards of animal welfare. We draw on evidence from both humans and animals that environments that promote wellbeing over stress and positive over negative emotions can reduce susceptibility to disease or at least lead to milder symptoms and quicker recovery. However, the relationship between welfare, immunity, and disease is highly complex (6, 7), and there is no simple connection between “happiness” and resistance to infection. Therefore, we caution against claiming more than the evidence shows and outline what still needs to be done to explore the potential preventative effects of good welfare.

POSITIVE AND NEGATIVE WELLBEING

Historically, the majority of studies on wellbeing, affective states, and health have focused on negative wellbeing, such as the negative effects of acute or chronic distress on morbidity and mortality (8–10). However, human health has long been acknowledged to be more than just the absence of disease (11). Similarly, animal welfare is not just the absence of stress and negative states (12, 13). Approaches such as the Five Freedoms (14) and Welfare Quality (15) emphasize the importance of going beyond physical health and including mental health as well. Physical health is ensured by keeping animals in clean, safe, and comfortable conditions and making sure that they have adequate access to water and nutritious food. Mental health is achieved by keeping them in conditions in which they have predominantly positive emotions associated with having what they like and want (16, 17).

WELLBEING AND HEALTH—EVIDENCE IN HUMANS

In human medicine, the relatively new interdisciplinary field of Affective Immunology studies the links between emotion and the immune system. This covers both the way the immune system affects the emotional state and also the way that emotions alter the status of the immune status (7, 18). Studies investigating these links in humans use different approaches and constructs, making it difficult to interpret results and draw conclusions for non-human species. The term “wellbeing” includes eudaimonic wellbeing (whether someone sees their potential fulfilled or has a sense of purpose in life), hedonic wellbeing (having pleasurable experiences), and optimism (the expectation of positive results) (12, 13, 19). Health outcomes, on the other hand, are conceptualized as morbidity/recovery from disease, mortality/longevity, activation of certain parts of the immune system or associated systems (especially the cardiovascular system), or self-reported health. This diversity of concepts and measures, together with variation in sample sizes and potentially confounding variables (20), has led to controversial results and confusion about the direction of causation. However, systematic reviews and meta-analyses have helped to clarify the picture.

The meta-analyses by Chida and Steptoe (9) provides evidence for the protective effects of psychological wellbeing on mortality, although they are more controversial for already diseased populations (8). A more recent meta-analysis by DuPont et al. (13) found that hedonic wellbeing is linked to better hemodynamic recovery after stress, which might reduce the risk of developing stress-related cardiovascular diseases. Furthermore, good immune function is closely related to peoples' subjective reports of being happy and satisfied with their lives (21, 22). Conversely, impaired immune function has been found in people distressed by circumstances such as homelessness (23), and mental illnesses such as schizophrenia and depression are associated with an increase in the cellular immune response (24, 25) and neuronal cell surface antibodies (26, 27). Chronic

stress can result in glucocorticoid receptor resistance that in turn leads to an inflammatory immune response that is pathologically out of control (28). On the other hand, conscientiousness has been linked to better health and more supportive social relationships (29), Tai Chi exercises can improve mental and physical health in persons with cardiovascular disease (30), and mindfulness-based training can improve emotional wellbeing as well as physical function and health (31). However, overall optimism does not seem to be linked to health as clearly as hedonic wellbeing (13) or not at all when controlling for other influencing factors in the statistical models (29). Even though optimistic patients might be more likely to persevere with therapy (29), optimistic judgements about health status might prevent someone from seeking timely medical advice (8). Indeed, Luo et al. (32) found that, during the COVID-19 pandemic, people worrying less about the disease showed less safety-seeking behavior, while perceived risk correlated negatively with wellbeing.

WELLBEING AND HEALTH—EVIDENCE IN ANIMALS

What is true for humans is now increasingly seen as applying to animals too (33). Human depression is associated both with chronic inflammation and compensatory responses to combat inflammation (34, 35), and there are clear parallels to stress responses in animals (36). For example, mice that are repeatedly subjected to stress such as being defeated in social encounters show an inflammation response throughout the body including enhanced neutrophil and cytokine activity (37). Social stress in pigs caused by fighting suppressed the immune response to a viral vaccine (38) while groups with low aggression social support can buffer acute stress responses in both humans (39) and other species (40, 41), with positive effects on the immune system (42, 43). It follows that providing stable social groups is a promising way of not only reducing injuries but also avoiding inflammation resulting from the stress of aggression. Giving animals the opportunity to feed undisturbed by conspecifics can have beneficial effects. In a cognitive enrichment experiment pigs had to learn their names and were then called to a feeding station, where they could then eat by themselves, and this had positive effects on health (44) and affective state (45–47).

The physical environment can also affect immune responses (48, 49). For example, enriching the environment of turkeys with “turkey trees” led to an increase in circulating white blood cells (50), and providing pigs with enrichments such as straw and branches resulted in a series of immunological changes including a higher percentage of T cells (51). Providing pigs with straw bedding can reduce the risk of gastric lesions (52), and young pigs with social and environmental enrichment were less susceptible to co-infection of PRRSV and *Actinobacillus pleuropneumoniae* and showed healthier lungs (53). Environmental enrichment early in life can also have positive effects on the development of the immune system and the establishment of gut microbiota in pigs (51).

WELLBEING AND HEALTH—WHAT WE STILL NEED TO KNOW

Although animal welfare as a way of controlling a disease is an attractive proposal with worldwide implications for both animal and human health, it is based on many ideas that are still largely untested (16, 33). The interactions between the brain, gut microbiome, and immune system are highly complex (36, 54, 55), and there is consequently no simple relationship between measures of immune activity and welfare. Evidence that improved animal welfare can lead to a reduction in infection may be true in some cases, but it is important not to claim more than the evidence shows.

One reason for caution is the complexity of the immune system itself. The vertebrate immune system consists of an extraordinary range of defense mechanisms, including the physical barrier of the skin that helps to prevent pathogens from entering the body as well as a whole range of specialized cells in the blood and lymphatic systems for detecting and destroying pathogens if they do get inside the body. In addition, an ecosystem of bacteria and other organisms living in the gut also has a profound effect on health in general and immune function in particular (54–56).

Immune responses occur in two stages which have very different implications for welfare. The innate or non-specific cellular immune system provides the first set of responses to infection or injury including the production of bacteria-destroying granulocytes, the release of cytokines, and local inflammation together with a whole range of sickness responses such as fever. It is an all-purpose emergency reaction, stimulated by a wide range of dangers and involving many different parts of the body. It needs such a high level of nutrients to keep it functioning that fighting disease may result in more resources being put into immune function and less into growth (57). Conversely, when animals become stressed, a cascade of hormonal responses including the release of corticosteroids or stress hormones shifts the entire metabolism away from immune responses and toward releasing readily available energy for taking some kind of action.

The second stage in the immune response is the more targeted “acquired” immunity stage which consists of the development of specific antibodies against particular diseases, in which the body “discovers” the correct antibody against a particular disease and then clones multiple copies. A relatively small number of specific antigens then provide long-lasting protection against infection.

Given the complexity of these immune reactions and their interactions with both the gut microbiome and the emotions, there are also many different ways in which immunity can affect and be affected by emotional state (10, 58). First, changes in the immune system, such as inflammation, may directly affect, and be affected by, the emotional state (7, 13, 59). Second, immunity and emotional state may be linked by more indirect routes, for example, via effects on the cardiovascular system (e.g., (8, 13, 60) and the gut microbiome (61). The gut microbiome is a complex community of viruses, bacteria, archaea, and eukaryotes, the composition of which is strongly influenced by factors such as diet and the neurological and endocrinological responses of the

body to stress (62). In turn, the microbiome affects how the body responds to stress and to disease challenges (61, 63, 64). Even more indirectly, the immune response can be influenced by behavioral changes such as dietary choice, rest or activity, and avoidance of other individuals, all of which can result in a reduced risk of disease and/or faster recovery from disease. Looking through the literature on the links between wellbeing and health in humans, despite known physiological pathways (8, 10), the most meaningful pathway between immunity and health seems to be via behavior (20). The happiest and most conscientious individuals tend to make less risky decisions and instead engage in behaviors that improve their health, such as a healthier diet and regular exercise (9, 29).

There are thus many different ways in which improving standards of animal welfare might influence immunity because there are so many different ways in which the immune system is influenced by, and exerts influence on, so many other systems of the body. There is much that we still do not understand and much we still have to learn. It is also important to remember that, even if a particular practice, such as an improvement in welfare management, affects immune responses, this is only the first step toward the much stronger claim that improved welfare protects against disease.

Many studies on the effects of welfare on disease, including most of those cited in this article, have been conducted by comparing the body’s immune response in different conditions and then drawing conclusions about the potential effect this might have on the ability to resist actual infection. From such evidence, it is often concluded that keeping animals in the higher welfare conditions would improve their ability to resist disease. Now while this is a plausible inference from the evidence presented, it is by no means certain that this would be the case out there in the real world. A disease may be so severe that the immune system, although making a valiant attempt to protect, will be ineffective at resisting infection.

While tests of immune response under controlled conditions are an essential preliminary, we also need on-farm studies to demonstrate that farm animals can actually realize the full potential of their immune function under real-world conditions. The ultimate test of the protective effect of good animal welfare must therefore be evidence that, under commercial farm conditions, animals kept in high welfare conditions are less likely to fall victim to disease or more likely to recover quickly, along with guidance about the limitations of what improved welfare can achieve. To exaggerate the effects of good management on disease resistance could be as counter-productive as ignoring the effects of good welfare altogether. There is an urgent need for research in this area and it needs to be based on evidence collected in the real world.

THE PATH TO BETTER WELFARE

Even knowing more about the relationship between disease resistance and welfare will not, however, resolve fundamental issues about how to implement them in practice. Indeed, there may be conflicts about how best to reduce the risks of different

diseases. In dairy cattle, access to pasture can reduce the risk of mastitis, claw health, and other health issues, but this can come with a higher risk for parasitism and malnutrition (65).

For some people “improving welfare” means moving toward free-range systems and away from intensive indoor methods of production altogether, despite these extra risks. There is a widespread assumption that animals are more likely to be healthy and to have positive emotions if they can show more “natural behaviour” (66–68) and the health risk of reduced biosecurity is judged as less important than the positive welfare benefits of a more “natural” life (69). In complete contrast, other people see the route to better welfare being through the increased use of technology that allows not only improved biosecurity but the provision of optimal environmental conditions that allow the immune system to function more effectively. For example, heat stress is a major form of poor welfare, leading to a variety of pathologies, including making animals more susceptible to infection (51, 70). Amongst other effects, heat stress damages the intestinal mucosa of poultry, making it more likely that endotoxins and even bacteria will enter the bloodstream (71). The controlled indoor conditions achievable by smart farming can do a great deal to reduce heat and other stressors (72). On the other hand, there may be adverse consequences for resistance to other diseases caused by high stocking densities or other features of intensive systems (73).

These two opposite views of how to improve welfare—more extensive outside “natural” living versus more intensive indoor technology-led living—clearly have very different implications for disease risk, both for the chances of animals encountering infective organisms in the first place and also for how their bodies might later react to being infected. There are no simple answers and future developments will need to find a balance between the costs and benefits of different systems. Animal welfare is only one of many weapons we have in the fight against infection, one that has perhaps not yet been fully appreciated but one where our knowledge is still very incomplete.

CONCLUSIONS

The hypothesis that good animal welfare optimizes the conditions in which the body's own natural defenses operate

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most effectively and can therefore be an effective weapon against infectious disease is a potential of major significance to both animal and human health. However, it currently lacks good supporting evidence, and it is important not to oversell the idea or exaggerate the ability of good animal welfare to substitute for medication. To test the hypothesis, it will be necessary to demonstrate that high welfare conditions (carefully defined) actually do protect against disease, not just in theory, in the lab, or in experimental conditions but in real-world commercial conditions. There may have to be many caveats, such as that good welfare can offer protection with some diseases but not others or that some aspects of “good welfare”, such as avoiding diseases associated with overheating, may be in conflict with what is meant by “good welfare” in some other respect such as allowing animals to range outdoors. With two things as complex as disease prevention and animal welfare, we should not expect simple solutions.

However, the accumulating evidence of close links between the brain, the gut microbiome, immunity, and welfare as well as the known links between mental and physical health in humans not only provides empirical support for the importance of good welfare as preventative medicine but also indicates a variety of mechanisms by which good welfare can directly influence disease resistance.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

The publication of this article was funded by the Open Access Fund of the FBN.

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