Short communication

Animal welfare as preventative medicine

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Abstract

Antimicrobial resistance is a major threat to both human and animal health but reduction of use raises issues of how standards of animal health and welfare can be maintained without them. This turns the spotlight on the role of good management and higher standards of animal welfare as drug-free ways of improving immune function and increasing resistance to infection. Research is urgently needed into the relationship between animal welfare, immunity. gut microbiota and disease, and we are not yet in a position to claim that improving welfare will improve resistance to disease. 'Boosting' the immune system is not straightforward and an interdisciplinary approach is needed.

Introduction

Reduced immune function and greater susceptibility to disease are widely recognized as results of poor welfare (Gross & Siegel 1981; Moberg 1985; Broom & Johnson 1993; Cockram & Hughes 2011) and are routinely used as welfare ‘indicators’ (Gross & Siegel 1983; Shapiro, 2002; Bartomolomucci, 2007; Vermette et al. 2017). My aim here is to ask whether there is a case for viewing the relationship the other way round and seeing good welfare not just as a consequence but as a potentially major contributor to improved immune function and disease resistance.

Antimicrobial resistance is now recognized as a major threat to human health across the planet (Hudson et al. 2017; Aldara-Kane et al. 2018) and extensive use of antimicrobials given to farm animals has been a major contributor to this problem (Teuber 2001; McEwen & Fedorka-Cray 2002; Kemper 2008; Silbergeld et al. 2008). There are consequently international calls for reduced antibiotic use on farm animals (ECDC/EFSA/EMA 2017; DEFRA 2017; Ying et al. 2017) but because of concerns about how standards of animal health can be maintained without antimicrobials (Gimeno et al. 2016) and their veterinary use for livestock continues to rise across the world (Van Boeckel et al. 2015). A major step forward would be to avoid the use of antimicrobials as growth promoters or routine prophylactics altogether (Aidara-Kane et al. 2018) and to reserve certain types for agricultural use when they are really needed to treat actual infection. An even further step would be to find ways of reducing the risk of infection in the first place. In the context of reducing the need for antimicrobials, several different alternatives have been proposed (McEwen & Fedorka-Cray 2002), including improved management practices, wider use of vaccines, use of probiotics (Bailey & Cryan 2017; Gao et al. 2017) and drugs that boost the ability of the immune system to kill bacteria (e.g. Christiansen et al. 2017). Of these possibilities, vaccines may often not be available or expensive, it is often not clear how probiotics and antibiotics differ in the impact they have on immune function or gut flora (Angelakis 2017; Gao et al. 2017), and immune-boosting drugs are largely untested and may have unforeseen consequences. This turns the spotlight on the potential for improved management and in particular good welfare as a drug-free route to improved immune function. However, although the pressure for reduction in antibiotic use provides an unprecedented stimulus for research in this area, the relationship between welfare, immunity and disease resistance is more complex than is often realised (Berghman 2016). Animal welfare as preventative medicine is an attractive hypothesis with worldwide implications for both human and animal health but that hypothesis now needs to be rigorously tested.

Immunity: the biggest arms race of all time

For at least a billion years, an evolutionary battle has been raging between disease organisms and their hosts. The odds are stacked heavily against us and other animals by virtue of our large size and long generation times. For every anti-disease mechanism our bodies evolve, bacteria and viruses can reproduce much more rapidly, allowing them, in a few hours or days, to produce new mutations and combinations of mutations that give them a whole new set of possibilities for evading our defences. Faced with a never-ending horde of newly equipped enemies, vertebrates have evolved a truly extraordinary range of defence mechanisms, collectively called the immune system, which includes the skin, specialized cells circulating in the blood and lymphatic systems and molecular pathways for detecting and destroying pathogens in cells throughout the body. In addition, an ecosystem of bacteria in the gut also has a profound effect on health in general and immune function in particular (Bailey & Cryan 2017; Yeoman et al. 2017). Even behaviour such as grooming and avoidance of sick individuals (Zylberberg et al. 2013; Evans et al. 2017) can be seen as part of the body's barrage of defences against infection.

The immune system has two parts that operate together but have very different implications for animal welfare (Berghman, 2016). The initial response to infection or injury is mobilisation of responses known as the 'innate' or non-specific cellular immune response, such as production of bacteria-destroying granulocytes, release of cytokines, local inflammation and generalised sickness behaviour. This emergency response 'holds the fort' long enough for the second stage immune response – adaptive or acquired immunity – to develop specific antigens against particular pathogens, which may take several days. The two immune systems have been likened to an initial grenade that causes general destruction followed by a sniper with a single target (Berghman 2016).

The emergency response of the innate immune system mobilizes many different parts of the body and needs so many nutrients to keep it functioning that it may compete with other vital processes such as reproduction, growth rate and tissue repair. For example, leukocytes may compete for the same amino acids as are needed by liver cells (Kogut & Klasing 2009) or bone cells (Humphrey & Klasing, 2004). Animals have therefore been seen as having to allocate scarce resources optimally between a nutrient-hungry immune system and other systems in competition with it (Houston et al. 2007: McKean et al. 2008). For example, wild animals that are at high risk of predation or have to deal with unpredictability of food supply are less able to combat infection (Best & Hoyle 2013; Boots et al. 2013; Stephenson et al. 2015) and males that put resources into elaborate ornaments and displays may be more susceptible to disease than females (Zuk & Stoehr, 2010). Conversely, major disease challenge may result in more resources being put into immune function and less into growth (Brock et al. 2013). In response to changing risk of disease leads animals to change where and how much they forage (Houston et al. 2007) and how likely they are to explore new places (Zylberberg et al. 2013).

The later acting acquired immunity, by contrast, comes at very little nutritional cost (Iseri & Klasing, 2013) and so is very much less in competition with other systems. A relatively small number of specific antigens provide long lasting protection against infection but selecting and cloning the right ones takes time, which is why the initial holding response by the innate system is so important. It is quite clear, then, that very different approaches are needed to 'boosting' immunity depending whether innate or acquired immunity is being considered (Berghman, 2016).

'Boosting' the immune system(s)?

For farm animals, the concept of a resource-hungry (innate) immune system competing, sometimes unsuccessfully, for resources has led to the practice of adding extra nutrients to the diet to boost immune function (Kidd 2004; Klasing 2007; Ingvarten & Moyes 2013), in particular, amino acids such as arginine, glutamine and cysteine (Li et al. 2007). However, adding single nutrients to a diet, particularly if given in excess, can upset the balance of the immune system and gut flora and actually make the body more vulnerable to infection by opportunistic pathogens (Kogut & Klasing, 2009). Nevertheless, the idea that the body can switch resources away from or towards the immune system depending on circumstances is a powerful one and has led to the view that a more holistic approach to management such as reducing stress and positively improving welfare could free up much-needed resources for the immune system (Broom & Johnson 1993; Ekkel et al. 1995; Hoerr 2010).

Support for this idea comes from studies on humans, where good immune function is closely related to peoples' subjective reports of being happy and satisfied with their lives (Nakata et al., 2010; Takao et al. 2018), while conversely, impaired immune function has been found in people distressed by circumstances such as homelessness (Arranz et al. 2009). But it is not clear exactly how being happier is related to better immunity and there is every reason to be cautious about the interpretation of an increase in 'immune function'. Much research is still needed but there is now increasing evidence that mental illnesses such schizophrenia and depression are also associated with an increase in the cellular immune response (Maes 2011; Horsdal et al, 2017) and neuronal cell surface antibodies (Steiner et al. 2012, Lennox et al. 2017). Depression is associated both with chronic inflammation and compensatory responses to combat inflammation (Berk et al., 2013) and there are clear parallels to stress responses in non-human animals (Dantzer et al. 2008). 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 (Lafuse et al. 2017). To follow the military analogy, just because there are many grenades exploding does not mean that all is well. On the contrary it could indicate a situation that is pathologically out of control.

Implications for animal welfare

The interactions between brain, gut microbiome and immune system are highly complex (Dantzer et al 2008; Bailey & Cryan, 2017; Leonard 2018) and there is consequently no simple relationship between measures of immune activity and welfare (Boissy et al. 2007). Improving the ability of the acquired immune system to produce specific antigens through vaccination has obviously been one of the most important steps forward in the battle against disease, but even vaccines can trigger an unwanted innate inflammatory response (‘vaccine reaction’) especially with live attenuated vaccines so that there is still much work to be done (Kaiser 2010). However, it is the essential but volatile innate immune responses that we understand least and where we need to be particularly careful in our interpretations or desire to ‘boost’ it. Emergency innate immune responses such as inflammation are essential because they provide the first defence against infection and without them we could not survive. But the constant battle between host and pathogen, with viruses and bacteria evolving ever better ways of evading host defences can lead to unwanted side effects such as autoimmune diseases including rheumatoid arthritis and multiple sclerosis in which the innate immune system turns on its own body as the enemy. As mentioned above, even depression is now seen as a inflammatory disease arising through an over-active innate immune system (Maes, 2011: Berk et al. 2013).

The interactions between welfare, immune responses and disease resistance represent an immensely exciting area of research, given extra urgency by the need to reduce dependence on antimicrobials and the growing acknowledgement that animal health and human health are inextricably bound together (Murtaugh et al. 2017). Animal welfare scientists have much to contribute by way of how to assess good welfare and in particular how to use behaviour to put ‘valence’ on mood and emotion (Boissy et al. 2007. Dawkins 2008; Mendl et al. 2010). However, animal welfare is now an interdisciplinary science ((Veissier & Miele 2015) and cooperation with immunologists, physiologists and microbiologists is essential for the best research. We need to keep a clear separation between innate and acquired immunity because the implications for welfare are very different

(Berghman, 2016) and to be mindful of ethical and economic implications for the findings to be widely adopted Errikson

The evidence is not yet in that improving animal welfare would improve disease resistance and we cannot yet claim it is an important part of preventative medicine. But there are many pointers in this direction and if confirmed, this hypothesis would have major implications for living without antimicrobials but also for the priority that the world is prepared to give to improving animal welfare. The path is not easy but it is one well worth following.

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