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Pain - its effects on immune function and growth in animals

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ABSTRACT

Pain, in both animals and humans, can induce wide-ranging biological consequences. In farmed livestock, two of the most important of these consequences are the potential impacts of pain on immune function and growth. In humans, the subjective experience of pain is correlated with decreases in immunocompetence and increases in the subsequent incidence of illness. In animals, procedures that can be readily assumed to be painful, and which produce behavioural and physiological stress responses, can cause immunosuppression and reductions in feed intake. Although transient pain may temporarily enhance immune function, chronic pain is immunosuppressive. The deleterious effects of pain on animal growth appear linked to the inflammatory response that accompanies tissue injury and to the direct impact of pain on feeding behaviour. The pro-inflammatory cytokines, (interleukin-1, interleukin-6 and tumour necrosis factor alpha) contribute to tissue catabolism, and act directly at the central nervous system to induce anorexia and lethargy. Although these behavioural and metabolic responses to painful conditions are adaptive in the short term, allowing the animal to rest its injury and mobilise body reserves to aid healing, ongoing pain responses have obvious negative consequences for animal productivity. Therefore, both animal welfare and productivity considerations suggest that the relief of any ongoing pain, as well as of acute pain, is important.

Keywords: pain; immune system; feed intake; growth.

INTRODUCTION

Pain in animals is undisputedly linked with suffering, and thus, has obvious implications for animal welfare. In animals, the presence of pain may be assessed by a range of physiological and behavioural responses (Mellor *et al.*, 2000). For example, animals that are in pain may exhibit behaviours that are assumed to be indicative of a depressed or adverse mental state. Such behaviours include reduced activity and response to stimuli, unusually submissive behaviour, or irritability and aggression (Morton & Griffiths, 1985; Dobromylskyj *et al.*, 2000). It is clear, therefore, that pain has consequences for animal behaviour. However, what we are now coming to understand is that pain has wide-ranging biological consequences for animals, and that pain is not just an end point in itself, but may act as a pathogen in its own right.

In animal agriculture, the avoidance, alleviation or minimisation of pain is a vital consideration for animal welfare, and is expressed in the "Five Freedoms" (Farm Animal Welfare Council, 1993). Additionally, it is important to appreciate that pain in farm animals may have consequences for a range of body systems, and that among the most important of these effects are those on the immune system and on animal growth.

PAIN AND IMMUNITY

Research interest in the effects of pain on the immune system has been driven largely within the field of human medicine (Page & Ben-Eliyahu, 1997), although many of the experimental studies have been conducted with animals, chiefly rodents. Research has expanded from the first published observations, thirty years ago, that surgery resulted in suppression of the immune system in human patients (Park *et al.*, 1971). However, it is now known that the effects of pain on immunity appear to depend on the duration and intensity of the painful experience, and whether it is associated with significant tissue disruption.

There is evidence that brief or mild pain is associated with enhancement of elements of the immune system. Pain induces the short-term secretion of natural opioids, such as β -endorphin within the body, and the administration of β -endorphin has been shown to enhance the production by lymphocytes of the cytokines interleukin-1 and interleukin-2 (Bessler *et al.*, 1990). Similarly, Hemmick & Bidlack (1990) showed that rat lymphocyte proliferation was enhanced by β -endorphin. More interestingly, in an *in vivo* study, Griesen *et al.* (1999) demonstrated that a 30-minute painful stimulus in humans caused an immediate enhancement in the cytotoxic capacity of natural killer (NK) cells of the immune system. When local anaesthetic was administered before the pain experience (blocking the conduction of pain signals along peripheral nerves to the central nervous system), this enhancement of NK cell cytotoxicity was abolished, indicating that it was pain alone that was modulating the changes in immunocompetence.

The adaptive value of any enhancement of immune function in response to a painful stimulus may be that the immune system is primed to respond to any challenges that may be associated with a painful event. For example, it would be advantageous for an animal to have its immune cells at a heightened state of readiness to deal with microbial pathogens that may enter the body via a skin wound. However, in contrast to the results of research examining transient or very mild pain, the overwhelming bulk of evidence indicates that severe or chronic pain is associated with reductions in immune system competence. This effect may have arisen because there is unlikely to have been any selection pressure for enhanced or maintained immunocompetence in the face of chronic and severe pain, because wild animals with persistent pain would be unlikely to survive and reproduce anyway.

In human medicine, the immunosuppressive impact of pain is generally accepted, and the clinical implications

of the effects of pain on immunity are considered in continuing education material for professionals involved in caring for patients with pain (Page & Ben-Eliyahu, 1997; Kremer, 1999). One of the most compelling pieces of evidence for the adverse consequences of pain for immunity comes from a study with human patients at a dental clinic. Logan *et al.* (2001) examined NK-cell cytotoxicity in response to a potentially painful procedure—root-canal treatment. In comparison with control patients, root-canal patients exhibited a slight *increase* in NK-cell cytotoxicity in the 30 min immediately before treatment (possibly in association with the mild stress of anticipating the painful procedure), but then had a profound *decrease* in NK-cell cytotoxicity in the hours after treatment. Furthermore, the extent of the suppression in NK-cell function was negatively correlated with the patients' reporting of the level of pain they experienced. Logan *et al.* (2001) also found that the patients who had undergone the painful procedure had a higher incidence of illness during the 2-week period following treatment.

There is also evidence from animal studies that significant pain has adverse effects on the immune system. Page *et al.* (1993) investigated the effects of surgery on the likelihood of tumour metastasis in rats. The immune system plays the crucial role in the body's fight against cancer, particularly where tumour cells break away from the main cell mass, and lodge in other areas, thus potentially forming significant metastases. These few cells are vulnerable to attack from immune cells, such as NK cells, before rapid tumour cell proliferation can outstrip the ability of the immune system to cope. Page *et al.* (1993) showed that surgery without ongoing pain relief actually increased the likelihood of tumour metastasis in the rats, and that this effect was mediated through inhibition of the NK cells of the immune system. However, the permissive effect of surgery on tumour metastasis was blocked when the rats were administered the analgesic drug morphine. Other studies with laboratory animals have also demonstrated the suppressive effects of surgical procedures on immune cell function (Pollock *et al.*, 1987).

By comparison with the human and laboratory animal research fields, there have been relatively few studies examining the impact of painful procedures on immune function in farm animals. Experiments investigating the effects of surgical castration of calves (younger than the statutory age requiring anaesthesia), have shown that the procedure causes suppression of immune system function that persists for at least 1 to 3 days (Fisher *et al.*, 1997a; Fisher *et al.*, 1997b). Although immune function was assessed in these studies by measuring the capacity of lymphocytes to produce the cytokine interferon- γ , it is likely that the immunosuppression seen was similar to that measured in rodent and human studies. Research with humans has shown that exam stress in students causes concomitant decreases in lymphocyte interferon production and NK-cell activity (Glaser *et al.*, 1986).

What, then, are the mechanisms that are responsible for the suppression of immune system function by pain? The most popular theory over past years has been that painful procedures cause stress-associated increases in glucocorticoid hormones such as cortisol, and that these

hormones directly affect cells of the immune system, causing reduction in function and number (Roth, 1985). This has been supported by evidence showing that pharmacological administration of cortisol reduces immune cell activity, for example, in cattle (Blecha & Baker, 1986) and pigs (Salak-Johnson *et al.*, 1996). However, the results of studies in recent years have called into question the importance of cortisol as the sole or dominant mediator of immunosuppression induced by pain and other stressors. In sheep, although restraint and isolation caused reductions in lymphocyte proliferation and increases in plasma cortisol compared with control animals, the administration of similar concentrations of cortisol to a third group of animals did not result in immunosuppression (Minton *et al.*, 1995). Similarly, in pigs, restraint stress initially increased NK-cell cytotoxicity, but then caused suppression of NK cells, apparently independently of cortisol concentrations (Wrona *et al.*, 2001).

Using a pain model, Fisher *et al.* (1997a) found that although castration of calves both increased plasma cortisol and decreased immune function compared with control calves, the duration of the cortisol increase was much shorter (8 hrs) than the immunosuppression (3 days). In addition, the administration of cortisol to a third group of calves, in such a way as to mimic the castration-induced cortisol increase, did not result in suppression of immune function.

It appears likely, therefore, that there are other, or additional mechanisms, than increased glucocorticoids responsible for mediating pain-induced immunosuppression. Although these mechanisms remain to be fully elucidated, there is evidence for a role of peptides within the brain, particularly corticotrophin-releasing hormone, and activation of the sympathetic nervous system and resulting catecholamine secretion. Working with rats, Irwin *et al.* (1990) found that by blocking corticotrophin-releasing hormone within the brain, they abolished NK-cell suppression induced by a painful and aversive stimulus. In contrast, the peripheral administration of anti-corticotrophin-releasing hormone antibodies did not ameliorate the suppression of NK cells, but did attenuate increases in plasma corticosterone. Within the brain, corticotrophin-releasing hormone can act to stimulate the sympathetic nervous system (Minton, 1994), and there is evidence in rodents that stress-induced immunosuppression may be mediated peripherally by catecholamine hormones stimulated by the sympathetic nervous system (Ben-Eliyahu *et al.*, 2000). In pigs the administration of corticotrophin-releasing hormone into the cerebral ventricles of the brain resulted in suppression of lymphocytes collected from the general circulation (Johnson *et al.*, 1994).

Whatever mechanisms are responsible for pain-induced immunomodulation, it is becoming increasingly clear that such interactions are extremely complex, involve other systems within the body, and are likely to operate in more than one direction. For example, there is growing evidence that cells of the immune system can modulate pain perception (Cabot, 2001). Despite the underlying complexities, for producers and scientists involved in

animal agriculture, it is important to bear in mind that the main body of evidence indicates that ongoing pain has deleterious consequences for animal immunity.

PAIN AND GROWTH

The known effects of pain on growth in animals share a number of common features with the effects of pain on immunity- specifically, a generalised adverse impact of pain, together with some evidence that very brief pain may have a positive effect, and data suggesting that the relationship may be bi-directional. In general, pain-inducing tissue damage in animals is associated with deleterious effects on growth, through mechanisms incorporating both reductions in feed intake and alterations in body metabolism. However, there is some evidence in rodents for very transient and mild painful stimuli producing a sudden onset of feeding behaviour. There is also data from research with laboratory and farm animals indicating that eating in some circumstances can reduce sensitivity to pain.

In the laboratory rat, it is known that a very mild pinch of the tail often results in an immediate onset of consummatory behaviours, including licking and eating. This was investigated further by Levine & Morley (1982), who examined the effects of similarly transient and mild painful stimuli applied elsewhere on the body. The results indicated that it was the mildly noxious stimulus, and not the site, that induced the eating behaviour, with rats induced to eat after receiving similar stimuli to the neck, ears and paw. Such a response to a brief, painful stimulus may represent displacement behaviour.

However, there is overwhelming evidence from controlled studies in laboratory animals that significantly painful procedures result in decreases in feed intake and loss of body weight. In both rats and mice, various surgical procedures conducted under anaesthesia, but without post-operative analgesia, resulted in reductions in food consumption and body weight (Liles & Flecknell, 1991). When the same surgical procedures were conducted with the inclusion of post-operative analgesia through buprenorphine administration, the magnitude of these effects was substantially reduced (Liles & Flecknell, 1991). In a subsequent study with rats (Liles & Flecknell, 1993), surgical procedures graded in terms of invasiveness (skin incision only *vs.* laparotomy *vs.* complex laparotomy) resulted in similarly stepped reductions in feed intake and bodyweight, with the more invasive procedures causing the greater suppression. Once again, the administration of a pain-controlling drug substantially minimised these reductions in intake and weight.

Similarly painful procedures in farm animals have also been shown to reduce feed intake and weight gain. The surgical castration of 5-month-old calves by Fisher *et al.* (1996) resulted in reductions in feed intake for up to 10 days post-surgery, and a drop in body weight during the week following castration. Furthermore, the use of local anaesthesia for castration caused a bodyweight drop that was significantly less severe than that for calves castrated with no anaesthesia. Dehorning of cattle is another procedure for which pain-induced reductions in feeding and bodyweight have been demonstrated, although the

effects have been more short-lasting. McMeekan *et al.* (1999) recorded less grazing and ruminating during the following 4 hours among calves that had been dehorned with a scoop instrument. The use of local anaesthesia and the administration of a non-steroidal anti-inflammatory agent ameliorated these changes in behaviour. Faulkner & Weary (2000) used hot-iron dehorning in calves, and similarly found that the use of a non-steroidal anti-inflammatory agent improved weight gain in the 24 hours post surgery.

More profound and enduring reductions in livestock weight gain result from procedures that involve more extensive tissue damage and which cause wounds that take longer to heal. The surgical or banding castration of 14-month-old bulls by Knight *et al.* (2000) caused animal bodyweight gain over 108 days to fall behind that of control animals, and resulted in the body weights of the castrates tending to be less than that of long-term steers (castrated at 6 months). Although the removal of testosterone is likely to be at least partly responsible for the lower growth of castrates compared with the control animals, the growth rate of the castrates was worse than that of the long-term steers over the entire experiment, suggesting that the pain and stress of the late castration procedure had a significant impact. In addition, the banding castration method, which produced longer-lasting wounds, resulted in a tendency for those animals to have lower bodyweights than surgical castrates (Knight *et al.*, 2000).

Although the fact that pain can suppress feed intake in animals may appear fairly obvious, the precise mechanisms by which pain alters feeding behaviour and weight gain in animals are not fully understood. Recently, using techniques to map nerve cell activity in the rat brain, Malick *et al.* (2001) showed that a noxious stimulus induced a 3- to 4-fold increase in activity in neurones in the medullary dorsal horn area that processes nociceptive signals, as well as in hypothalamic neurones that are positioned to suppress feeding behaviour. There was also some evidence for cholecystokinin playing a role in activation of these appetite-suppressing neurones (Malick *et al.*, 2001). There is also evidence that the inflammatory response associated with painful conditions can induce suppression of feeding behaviour and changes in body metabolism. Pain-associated tissue damage leads to the production of inflammatory cytokines, including tumour necrosis factor- α , interleukin-1 and interleukin-6, which, in turn, can alter the metabolism of carbohydrate, fat and protein, and act at a central level to reduce appetite (Johnson, 1997). For example, the administration of interleukin-1 into the hypothalamus of rats by Kent *et al.* (1994) produced a dose-dependent suppression of feed intake and of bodyweight. Correspondingly, the administration of interleukin-1 receptor antagonist into the brain of rats suffering from colitis blocked the anorexia that was otherwise present (McHugh *et al.*, 1994). In common with one of the putative mechanisms of pain-induced immunosuppression, at least a part of the catabolic effects of inflammatory cytokines is thought to be mediated by their action within the central nervous system to increase activity of the sympathetic nervous

system, and thus catecholamine secretion (Johnson, 1997). Catecholamine hormones are profoundly lipolytic, and signs of sympathetic activation, such as increased heart rate, are a common finding in animals suffering from post-operative pain (Morton & Griffiths, 1985).

It should be noted that the act of eating has been shown experimentally to confer some analgesic benefits for animals. This effect appears to be mediated through the feeding-induced secretion of β -endorphin. Wylie & Gentle (1998) found that hens that had been feed deprived overnight and then fed, exhibited complete or marked analgesia to the effects of arthritis. The analgesic effect of feeding was blocked by administration of the opioid antagonist naloxone. Similarly, in pigs, the pain sensitivity of sows was reduced after feeding, but was unchanged if naloxone was administered just before the meal (Rushen *et al.*, 1990).

Biologically, the general effects of pain on feed intake and metabolism may be considered to be adaptive in the short term, in that they allow the animal to rest its injury, and mobilise body reserves to aid healing. However, for the animal in severe or ongoing pain, anorexia and catabolism of body tissues represent a potentially vicious cycle of debilitation, and, for animals under human control, a significant welfare problem.

CONCLUSIONS

Pain of any sort in animals under human care may be considered undesirable, but the adverse impacts of pain grow exponentially as its duration and intensity increase. This is because increased pain does not just cause increased suffering directly, but also induces a wide range of adverse biological sequelae, including suppression of immunity, feed intake and growth. For procedures or states that may cause pain for farm animals, both animal welfare and productivity considerations suggest that the relief of any ongoing pain, as well as of acute pain, is important.

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