

Chapter 7 General Discussion

7.1 Introduction

It is recognised that livestock temperament, defined here as an animal's inherent fearfulness is an important trait in the context of animal production and welfare. Currently, livestock breeders rely on practical behavioural tests to identify and select for animals with better temperament. These tests are largely based on assessing the degree of escape and/or avoidance behaviour. It is generally well accepted that there is significant variation between animals in their behavioural responses to fear-eliciting challenges. However, our understanding of the neurophysiological mechanisms regulating these responses is not clear. Further gains in our understanding may lead to an enhanced capacity to identify and select animals with the appropriate temperament for their production environments. Given this, this thesis examined specific neurophysiological pathways to quantify their involvement in the expression of temperament in a livestock species, sheep.

The research was undertaken in three stages commencing with dose response studies examining specific GABA and 5-HT receptor agonists and antagonists, respectively. In the second stage, a fear potentiation challenge model for sheep was developed. The model was based on the combination of two potent psychological stressors in sheep, namely isolation and the presence of a dog. In the final stage, this model was applied in sheep genetically divergent for temperament and the effects of the selected GABA and 5-HT receptor agonists on their responses were quantified. In addition, the role of glucocorticoid pathway in the development of the learned fear and potentiated fear responses was investigated.

7.2 Main findings

7.2.1 Dose response study using Diazepam and *m*-CPP

Diazepam (DZP), the GABA receptor agonist, and 1-(*m*-chlorophenyl)piperazine (*m*-CPP), the serotonin receptor agonist, were selected for investigation as they produced the most consistent behavioural and physiological effects in sheep during an acute stress challenge (chapter 3). Diazepam is a well-known anxiolytic and reduced the expression of fearful behaviour and serum cortisol levels in sheep. The 5-HT antagonist, *m*-CPP was highly effective in eliciting a marked anxiogenic effect based primarily on the increase in serum

cortisol. These outcomes from anxiety studies (Rodgers, 1992) are inconsistent in the absence of anxiolytic medication. In addition, after the administration of anxiolytic medication, the state as observed from the study is related to the variables of the treatments were administered.

Liebsch *et al.* (1998) showing that HPA reactivity and fear related behaviour can be regulated independently. Liebsch *et al.* (1998) proposed that the behavioural and neuroendocrinal responses to a psychological stressor may not be as tightly linked as generally thought. They showed that administration of DZP failed to elicit any line differences in coping strategy of rats selected for high anxious and low anxious behaviours. However, Liebsch *et al.* (1998) did observe differences in behaviours during the elevated plus maze test. These results and those found in this thesis suggest that fear related behaviour and the HPA axis may be regulated independently. It also highlights the value of using animals with divergent behavioural responses (such as the Merino temperament selection line used in the current research) in the investigation of fearfulness and temperament.

Although the above results hint at a disassociation between the key stress response pathways, an alternative explanation is that the behavioural response is the most effective primary response to cope with a challenge, and therefore more concerted responses (those of the HPA axis) are not always required. This point was highlighted by Moberg (2000), who stated that the behavioural response is typically the least-cost, first line of defense to a stressor challenge. Another possible factor as highlighted by Boissy (1995) is that an animal's primary response to a stressor may be dependent on how controllable or predictable the situation/event is. Specifically, whether or not the animal can, or perceives it can exert an influence on what occurs.

The typical fear potentiation model as used by Korte *et al.* (2003) has many advantageous factors that make it effective in assessing the fear state, particular in rodents. Korte *et al.* stated seven reasons as to why the FP model should be utilized more often in fear assessment studies. The reasons were that it: reflected an enhanced anxiety state, enhanced durability of the state, sensitivity to anxiolytics and anxiogenics, the ability to administer drugs in the absence of the original stressor, robustness, ability to study the neural mechanisms and the ability to measure fear in males and females. Several of these reasons are also pertinent in regards to the work carried out in this thesis, mainly in that the model was able to reflect an enhanced fearful state, which consisted of a longish duration, which hints at the robustness of the model. However, for it to be further considered in relation to further studying other aspects of animal welfare, more detailed work on the model needs to be investigated.

7.2.3 Modulation of the fear response in sheep divergent for temperament using GABA and 5-HT receptor agonists

The results from the pharmacological studies (chapter 5) did not reveal differential responses to DZP and *m*-CPP between the two temperament selection lines. Furthermore, the results confirmed that the primary difference in fear responses between the two temperament selection lines are largely behavioural, rather than autonomic or neuroendocrinal in expression. This perhaps was not completely unexpected given that the selection lines were generated based on specific behavioural responses. However, it also suggests that behavioural selection for fear-related behaviours may not necessarily convey a correlated neuroendocrinal response. Although no, or minimal differences in the responses were observed between the temperament selection lines following the pharmacological treatments, this is not conclusive evidence that the GABAergic and serotonergic pathways are not involved in the expression of temperament. Further testing is needed to clarify these associations and methodologies will need to be refined to allow identification of potentially subtle associations.

There are several possible reasons for the lack of conclusive answers with regard to the role of these pathways in the regulation of fearfulness and temperament in this study. These include: 1) the fear potentiation challenge may have been too complex, 2) the neurotransmitter pathways investigated may not have a prominent role or the neuro-regulatory mechanisms are much more complex, or 3) the use of the temperament selection lines were not an appropriate choice to identify neurophysiological mechanisms. These issues are discussed in more detail in the following sections.

There is no question the fear potentiation challenge evoked a fear response, but the relative contribution of learning, memory, perception, anticipation and lack of control are unknown and maybe a reason for the large variability in physiological responses. It would be difficult to reduce the complexity of the test unless a one step challenge was used, and this is unlikely to potentiate the fear response. However, learning capacity of humans and animals is variable and can be affected by stress. Additionally, Fisher *et al.* (2006) suggested a genetic basis for some stress and learning responses in sheep when exposed to a maze challenge, whilst Lee *et al.* (2006) showed that sheep with high behavioural agitation (tested in a box, arena and corridor tests), considered to be those with poor temperament (more fearful) had a reduced capacity for learning in the maze test. Therefore, the relative proportion that learning

contributes to the ability of sheep to cope with the stressor is called into question, as temperament of the animal contributes, in part, to the ability of the animal to learn from the challenge.

Another key feature of the challenge model is the general lack of control the sheep have when presented with the challenge. It is generally recognised that controllability or perception of control of a situation is an effective way of attenuating an emotional response in livestock (Boissy 1995; Désiré *et al.* 2002). Similar results have also been observed in rodents. Drugan *et al.* (2005) exposed rats to escapable and inescapable swim stress paradigms and observed an increase in immobility behaviour in those rats unable to escape from the challenge. Therefore it is recommended that there would be value in modifying the design of the fear potentiation model to introduce a degree of controllability into the challenge to ascertain how the level of control interacts with the response. This may provide a more effective model to examine the differential expression of fearfulness in the two temperament selection lines.

The temperament selection lines were originally selected based on the response to 1 minute of isolation in a box and other measures conducted in the arena test. However, it was hypothesised that selection for fearful behaviour in these tests would also bring about a corresponding divergence in other non-behavioural stress response pathways. This hypothesis was not confirmed as the differences in the HPA response between the lines were not clearly apparent. These results align with those of Beausoleil *et al.* (2005) who showed that there were no cortisol differences when the sheep were exposed to a conflict situation (arena test). However, they contrast with very recent results by Bickell *et al.* (in preparation) who applied the same challenge model, but replaced the dog with a loud fan blowing a moving plastic tube. They showed significant differences in cortisol responses between the selection lines where the cortisol response was higher in the nervous selection line. It seems that we do not know enough about the neurophysiological differences between the two temperament selection lines and further research is recommended particularly using more targeted methodologies (eg. in situ measurement of neurotransmitters *via* immunosensors or microdialysis). Although, the suggested dissociation of the behavioural and physiological responses to the challenge model observed here is an interesting outcome and worthy of further validation.

There is also the possibility that the fear potentiation model was not sensitive enough to effectively identify the behavioural and physiological responses between the temperament selection lines following treatment with the GABAergic and serotonergic receptor agonists. The use of the specific neurotransmitter ligands to identify neurophysiological mechanisms in the context of the expression of fear is always “risky” as, many different factors, including dose rate, timing and route of administration can have an influence on the effect they have on an animal (see review by Clement *et al.* 2002). Whilst it is plausible these pathways may not play a prominent role, other factors need to be considered, such as ligand specificity and assessment methods. The neuroregulation of fearfulness is clearly a complex process and perhaps the approach applied here may have been too simplistic.

The value of being able to select or use animals with divergent behavioural responses (such as the Merino temperament selection line used in the current research) are several with regard to animal welfare the ability in being able to physically select farm animals with a calm temperament is positive with regard to the type of handling that occur in intensive animal agriculture. Benefits of animals, having a calm temperament may include a higher daily average weight gain, improved handler safety, decreased wear on farming equipment, ease of handling, increased milk production, reduced animal injury, improved meat quality, improved maternal behaviour. These benefits have important considerations in regards to studying animal temperament, additionally because temperament is also heritable.

However, it may also be just as important to conserve the full range of temperaments in that selection on just one aspect, temperament, may then likely affect other traits, which may take a negative turn. The selection of animals that are more able to adapt to confining or challenging situations may also be of importance for areas such as zoos or wildlife parks, where it is of benefit for those handling the animals and for the animal themselves to be calmer to be able to negate difference in the environment. McDougall *et al.* (2005) {McDougall, Røale, *et al.* 2005 #12010} suggests that highly active or aggressive animals that are held in situations such as those mentioned above, are less able to adapt.

7.2.4 The use of a glucocorticoid (GC) receptor antagonist to modulate the fear response of sheep divergently selected for temperament

The expression of fearfulness is dependent on a large number of neural pathways involved in learning, memory, anticipation and reaction. In addition to their role in the negative feedback loop of the HPA axis, the GC receptors are involved in most of these functions (Aguilar-Valles *et al.* 2005; Erikson *et al.* 2003). We hypothesized that the use of a GC antagonist to block these receptors would elicit a divergent response between the calm and nervous selection lines when responding to the challenge model. Possible factors contributing to the divergence in behaviour may be that the regulatory mechanisms of the HPA axis themselves may be divergent or an imbalance may exist, causing differing responses during exposure to stress. A dramatic increase in the cortisol response on administration of the mifepristone (RU-486) was associated with all animals treated; however no observable divergence of cortisol response between the selection lines was evident. This may imply that genetic selection for temperament (at least in the case of these sheep) has had a small or negligible effect on HPA responsiveness and confirms the observations of chapter 5.

7.3 Future research

The fear potentiation model is complex and fear potentiation did occur but there are many different factors which were involved in testing; manipulation of the animals before being placed into the test, attachment of HR monitor and opening of the door are several parameters from which the sheep may have taken clues about being placed into the test. Therefore simplification of the test might be the next stage of the FP test. A simplified test may allow more targeted use of the pharmacological agents

Using the dog within the test is a psychologically relevant stress stimulus for the sheep, however assessing this in relation to a non-biologically relevant test would also be of interest. For example, Beausoleil *et al.* (2005) {Beausoleil, Stafford, *et al.* 2005 #9650} showed that a dog was far more aversive than a human in the arena test and alternative stimuli may be useful.

The ability to control a situation could also of great importance and Boissy (1995) {Boissy 1995 #100} suggested that actual or apparent controllability of a situation can markedly affect an animal's neuroendocrine response, of which this was first demonstrated by Weiss in

1972 {Weiss 1972 #12200} on yoked rats and using electrodes to shock the rats dependent on which animal had the ability to control shocks. This then is a particularly relevant means to attenuate emotional reactivity in sheep. One way to change the FP model would be to give the animals a way to escape from the box, away from actual isolation only, or the presentation of the dog, thereby giving control of the situation to the animal being tested. We would then expect the cortisol data (physiological data) to be significantly different between those that could 'control' aspects of the test as opposed to those of which that control was removed. Alternately, behavioural responses may be similar between the two groups, as taking action, or gaining 'control' of the model, would cause an increase in movement within the box, similar to the other group.

Other specific ideas, as opposed to changing the specificity of the FP model include the potential to measure GABA directly in the blood of the sheep selection line, as Petty (1995) {Petty 1995 #8990} suggested that mean levels of plasma GABA in patients with depression or mania were between 10 and 15% lower than control patients. Additionally, GABA plasma levels were relatively stable even with changes in age, exercise and diet. Therefore the possibility that the nervous line of sheep have differing levels of plasma GABA is of interest sake and that low plasma GABA identifies a variety of mood disorders, may potentially indicate a measurable difference between the calm and nervous sheep.

The prevalence of specific receptors in the temperament selection line sheep would be an interesting area of research particularly those within the serotonergic system. For example, assessing where and in what amounts the 5-HT_{1A} and 5-HT_{1B} receptors were expressed. Fisher *et al.*, (2006) stated a genetic component for some stress and learning responses in sheep. The area of identifying genes which show changes in expression during stress would be of benefit, particular in the temperament selection line where behavioural changes to particular stressors are already evident.

A further in-depth assessment of the heart rate of the sheep, specifically during the isolation period in the box would be interest, as Désiré *et al.*, (2004) {Désiré, Veissier, et al. 2004 #11700} found the heart rate response by lambs to a sudden event increases rapidly, and was not linked to the movement of the lambs during testing, but it was also seen to be a very transient measure, so would require careful measurement. This would be a very applicable

methodology for the **Iso+Dog** challenge, as the primary behavioural response was that of freezing. Additionally, the variability of heart rate would also be more detailed and allow a more focused analysis of that measure, as many different authors have indicated its value as a physiological measure of stress {Mohr, Langbein, et al. 2002 #370}{Stauss 2003 #12640}{Malik & Camm 1995 #13270}. In the experimental chapters within this thesis, the heart rate values were averaged across the period when the sheep were within the box. Additionally, the same was done for HR variability, however there were very limited significant results found. Therefore the possibility exists that varying transient measures were missed. For example, the change from the door being closed during the first minute, to being open and presenting the dog. Freezing was the primary response, which rules out the heart rate changes being due to the physicality of the behaviour. Additionally, on subsequent exposures to the **Iso+Dog** challenge, was the heart rate response increased/decreased due to anticipation of the dog being present?

7.4 Summary

Overall, the thesis has provided new insights into the differences between the temperament selection lines in response to a potent psychological challenge. The results showed that there was a very pronounced behavioural divergence in response to the fear potentiation challenge. However, the differences in HPA responses between the selection lines were much less evident. This could suggest that selection on the basis of a behavioural trait to a fear eliciting challenge does not always convey a commensurate effect with regard to other stress related pathways such as the HPA axis. The lack of a HPA response is also suggestive of dissociation between the activation of the behavioural and neuroendocrinal responses to a fear-eliciting challenge and this issue warrants further investigation given that this is somewhat contrary to the dogma.

The aim of this research was to develop an improved understanding of the neurophysiological regulation of temperament in livestock. This thesis has highlighted the complexity of identifying mechanisms that contribute to differences in the temperament of animals and whilst the results were not conclusive, the findings have reinforced the need to undertake further research into this important issue. However, there is enough evidence presented to suggest that further studies are warranted into the underlying regulation of temperament and that the use of selected lines is an attractive model to use to assist in identifying selection traits

other than behaviours. Whilst pharmacological approaches, such as those used here are informative, other strategies may be required to better elucidate these underlying neuroregulatory mechanisms. For example, applying immunohistochemical techniques and gene expression tools to quantify receptor profiles in key brain regions may be a more fruitful strategy. Likewise identifying genes which show changes in expression during exposure to stress might also be an informative approach .

The use of a fear potentiated challenge model designed for sheep has demonstrated that fear can be potentiated in sheep and that this should be a consideration for the management of flocks. Evidence for dissociation between behaviour and the HPA response has also been presented and this has implications in assessing welfare of livestock. It would seem that assessment should involve both behavioural and HPA responses if a valid assessment of a stressful situation are to be made.

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