SUMMARY REPORT

From mice to livestock: Exploring the potential of the gut-microbiome-brain axis regulation in animal production

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INTRODUCTION

Over the past decade, a growing body of literature has demonstrated that the gut-brain axis (the bidirectional communication between the microbiome within the digestive tract and the brain) plays a key role in the normal neurodevelopment and behaviour of rodent models and in human subjects (Cryan and Dinan, 2012; Mayer et al., 2014). Changes in the microbiota community structure have been associated with negative health outcomes, such as nutrition/metabolic related disorders (Turnbaugh et al., 2008) and immune-mediated diseases (Ott et al., 2004). Additionally, the microbiota and its metabolites are likely to be involved in modulating behaviours and brain processes, including stress responsiveness (Dinan and Cryan, 2012), pain modulation (Cryan and Dinan, 2012) and ingestive behaviour (Alcock et al., 2014). This raises the potential of targeting this system in other species, such as in livestock animals, in order to develop novel ways to modulate animal stress-susceptibility and feeding behaviour, and hence improving animal health, welfare and productivity (Jones, 1997; Von Borell, 2007; Freestone and Lyte, 2010), and therefore promoting the implementation of sustainable intensification and enhancement of livestock production systems.

The Sêr Cymru National Research Network for Low Carbon, Energy and Environment (NRN-LCEE) is a major pan-Wales initiative funded by the Welsh Government Sêr Cymru initiative and the Higher Education Funding Council for Wales. Through the MULTI-LAND cluster, the Network supports collaborative and interdisciplinary research that aims to improve our understanding of animal nutrition, behaviour metabolism and microbiology. Another important part of the Network is to generate innovative ideas and investigate new research areas. It was precisely with this purpose that a symposium was organised to share state-of-the art research on the microbiome-gut-brain axis, generate dialogue and facilitate greater research collaboration across disciplines and sectors, and strengthen the scientific rigor of the field of neurocognition of livestock animals, including concepts, frameworks, measures and methods.

On 24-25 April, Multi-Land Fellow Dr Diego Moya (Aberystwyth University) hosted a 2-day symposium exploring the potential of the gut-microbiome-brain axis regulation in animal production. Over 50 attendees from 27 Universities, research institutions and private companies contributed to the discussions around the implementation of current knowledge from rodent models and humans into livestock animal production. The symposium ended with a round-table discussion chaired by Prof Andy Smith (Multi-Land Cluster leader, Bangor University), where the complexity and cross-cutting characteristics of this research field were highlighted.

DAY 1: NEUROSCIENCE OF BEHAVIOUR, COGNITION AND MOOD

The mechanisms associated to preference and aversion learning, and the effects of stress on food preferences, by Prof Dwyer (Cardiff University): Rodent-based lab work has led to the development of techniques for using fine-grained analysis of consumption to investigate hedonic reactions. These have illustrated the mechanisms involved in flavour learning and the presence (and absence) of hedonic changes in response to external challenges. Preliminary results in pigs suggests similar methods might be developed for use in livestock species.

Affect and decision-making concepts and measurement of animal affect and welfare, by Prof Mendl (University of Bristol): New measures of animal affect can be developed based on empirical and theoretical links between affect and decision-making. A predictive framework allows translation across species, including livestock, and the measurement of long-term mood. Trait differences in judgement bias may predict stress coping ability. Can judgement bias tests detect the influence of (drug induced) gut microbiome changes on affect and welfare in livestock? Can gut microbiome changes enhance trait 'optimism' and decrease stress susceptibility? There still is work to be done in this regard.

The use of goats as a model to study emotions, cognition and personality in livestock, by Dr Alan McElligott (Queen Mary University of London): Goat emotions can potentially be monitored using a reduced set of parameters, which suggests potential for automated monitoring of animal welfare. Individual emotional states are perceived by other livestock (emotional contagion). Personality (sociability) affects heart rate and cognition during various behaviours.

Effects of early life experiences on stress responses, by Prof Cathy Dwyer (Scotland's Rural College): Chronic stress in pregnancy can induce profound changes in the stress reactivity and behaviour of offspring. This is clearly demonstrated in rodents, although some of the mechanisms now quite well described. Good evidence in pigs, some changes seen in other livestock species. Experiments with livestock species have typically used practical husbandry approaches, which may not be as severe as used in rodents. Limited studies using variable timings and outcomes. In altricial offspring, experiences in early postnatal period also affects stress reactivity. Some evidence also in precocial offspring.

Precision farming: measuring and managing the variability in biological resources at the individual animal level, by Prof Mark Rutter (Harper Adams University): Precision livestock farming can facilitate choice in several ways: i) automatic milking systems give cows the choice of when to be milked; ii) Automated feeding of partial mixed rations could give diet choice; iii) Environmental choice with 'adaptive' ventilation. By facilitating choice (a natural behaviour) we can improve the efficiency of production (through more efficient use of feed), and animal welfare (by helping animals make choices that "promote their own quality of life").

DAY 2: EFFECTS OF DIET AND GUT MICROBIOME ON BRAIN FUNCTION

The potential role of probiotics and phytobiotics in future clinical and metaphylactic treatments in ruminants, by Prof Jamie Newbold (Aberystwyth University): In the last 60 years there has been a real effort to manipulate rumen fermentation in terms of stimulating fibre digestion trying to get more energy out of the feeds, reducing methane production, making a better use of the dietary protein to increase productivity, and changing the fatty acids compositions of milk and meat to obtain functional foods for humans. In the literature there are many approaches to manipulate rumen fermentation, including dietary, antibiotics, fats, buffers, immunological strategies, probiotics and plant extracts. There is a significant market of probiotics in young ruminants to avoid pathogen overgrowth and stimulate rumen development. The most successful economic market for probiotics in ruminants are yeast (*Saccharomyces cerevisiae*). The second strategy that is coming through in contribution are plant extracts, or phytobiotics. In summary, there are methods to manipulate rumen fermentation, and we can target those to be specific to specific groups of bacteria or protozoa. Similarly, as suggested earlier, early life nutrition can program the rumen in the long term, in a way that makes it more or less efficient in fermenting nutrients. If these effects reach out to the behaviour of the animal, it's still an area to be explored.

Neurophysiological consequences of highly palatable feeds and how it affects neural mechanism of motivation in domesticated ungulates, by Dr Sebastian McBride (Aberystwyth University): The microbiome is one among several factors that regulate animal cognition, including both internal, such as the endocrine or immune systems; and external elements, such as the characteristics of the feed offered to the animals (palatability). How strong are each of these factors relative to the other is unknown. Using the horse as the model, the restriction of specific needs such as eating, locomotion or social contact, induces chronic stress, which is a highly aversive stimulus that is known to cause a permanent shift in the dopamine physiology. On the other hand, palatable substrates have a similar effect to psychostimulants on releasing dopamine, which serve as a rewarding stimulus that also causes a permanent shift in the dopamine physiology. There might be species differences in terms of how different animals are responding to the level of reward or aversion from each stimulus. In summary, we need to know how palatability of the substrates overlays or interacts with any sort of manipulation of gut microbiome.

Gut bacteria and mind control, by Prof Simon Carding (Institute of Food Research/University of East Anglia): When talking about gut bacteria and mind control, our research experience is fully based on humans and rodent models, but there are distinct parallels and overlaps with livestock animals. As mentioned before, the perinatal stage of an individual has a clear impact on the gut microbiota. In adult life things continue shaping the gut microbiota, with diet being a daily and dominant factor in influencing the structure and function of the gut microbiome. However, the effects of any food are not predictably universal for everyone, which reinforce the concept that nutrition recommendations need to be personalised. This could also be applied to livestock animals, as we enter in an era where precision feeding strategies are becoming more available. Gut bacteria can influence eating behaviour directly, with peptide mimics of hormones, or indirectly, by stimulating antibody production that block appetite regulation. Moreover, there is evidence showing that emotions can actually be transferred with faecal transplantations models. This is explained by the availability of microbes to produce a whole array of neurotransmitters, such as GABA, noradrenaline, serotonin, dopamine, and even androgens

Gut Microbiota Regulates Stress, Anxiety and Cognition: Mechanisms and Therapeutic Potential, by Dr Eoin Sherwin (University College Cork): As mentioned earlier, the human gut microbiota is heavily influenced by both dietary and environmental factors. The combination of both factors can actually be the cause of the behavioural deficits that we see in aged animals, such as deficits in cognition, increase anxiety and deficiencies in sociability. Gut defaunation or disbiosis could lead to deficits in the amygdala-dependant behaviours, as fear recall and social behaviours. There is evidence supporting that potentially we can use probiotics on neurodevelopmental disorders. Although promising, there still is work that needs to be done to confirm these trends, including larger clinical trials. The mechanisms of action by which modulating microbiota can have an effect on brain and behaviour are related to the numerous ways in which microbiota can signal to the brain: through the metabolism of tryptophan, cytokines, SCFA and the vagus nerve. It is important, however, to determine whether these alterations that we see in the microbiota are causative of the condition or merely a consequence.

Microbial endocrinology, by Dr Primrose Freestone (University of Leicester): Residents of gut microbiome can sense the emotional state of their host. Animal emotional & physical stress affects gut microbiota. Gut microbes can influence emotions & appetite of their host, and therefore, stress has to be considered holistically. Future: consider cross-communication between host microflora in livestock welfare.

CONCLUSIONS

The study of the gut-microbiome-brain axis is a research field in its infancy, but the research done to date on rodent and human models positions the gut microbiota as a master regulator of this axis. The work done with defaunated mice shows that there are key developmental time windows where microbiome disturbances cause long-lasting changes in brain health and behaviour, as demonstrated through changes in neurotransmitter levels, anxiety behaviours, exaggerated stress responses, and impaired social and cognitive skills. There is early evidence showing that this could also be the case in other species, suggesting that new opportunities will arise to manipulate the microbiome to modulate some of the animal behavioural traits that are closely related to stress-related diseases, gut health and growth performance. Given the complex and multidisciplinary nature of this approach, it is essential to improve our understanding of the interactions between animal physiology, gut microbiology, hormones, and brain function. This article is a summary of the emerging topics covered in a symposium about the potential of regulating the gut-microbiome-brain axis in livestock animals.

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