Can we feed cattle for enhanced immune response?

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Take home message

- The process of weaning, marketing, comingling, and transportation can increase the risk of sickness in calves upon arrival at a feedlot.
- The immune system can interact with the central nervous system and GI tract to reduce dry-matter intake.
- During an immune response, demands for energy and protein increase.
- Increasing dietary energy does not appear to improve health outcomes.
- Increasing dietary protein improves N balance, but little is known how it effects health outcomes.
- Nutrition may be more critical for recovery than the actual response.

Introduction

Nutritional challenges arise when calves mount an immune response to foreign antigens. The process of weaning, comingling, transportation, and entering a new environment represent a short period of time when calves are stressed and exposed to foreign antigens. Cytokines and stress hormones increase when calves are weaned (Hickey et al., 2003). Morbidity and mortality increased 73.5% and 80.6%, respectively, for calves purchased through a livestock market compared to ones from a single source (Step et al., 2008). As a result, calves are often sorted by different levels of risk (high, medium, and low; Wilson et al., 2012). Low and medium risk calves are often more desirable and generally easier to manage. Nonetheless, high risk calves are still commonly marketed in the U.S. and provide an opportunity for some producers to purchase these calves at a discounted price.

Dry-matter intake

The nutritional challenge posed by high-risk and sick calves starts with dry-matter intake (DMI). Holland et al. (2010) reported DMI of calves during preconditioning (65 d) decreased linearly as the number of treatments for BRD increased. Dry-matter intake was approximately 25% lower for chronically ill compared to calves receiving no treatment for BRD (Holland et al., 2010). Those authors noted that reductions in DMI can persist through the finishing phase as well. Burciaga-Robles et al. (2010 b) noted that steer inoculated with *Mannheima haemolytica* and persistently infected with bovine viral diarrhea virus (BVDV) ate approximately 5% percent less feed during finishing than their healthy cohorts.

The exact mechanisms by which the immune system regulates the immune system is not well established in cattle. It is likely many different interactions exist given the number of organs and biological systems involved with the GI tract and immune system. Research pertaining to these interactions has been described in other species. Johnson (1998) briefly outlines two key routes by which the immune system may regulate DMI (Fig 1). Cytokines have been shown to act directly and indirectly on the central nervous system. Rodents infused with IL-1ate less and subsequently grew slower (Johnson, 1998). In swine, feed intake was also reduced when animals were infused with TNF-α (Johnson, 1998). Greater cytokine concentrations for steers exposed to both *Mannheima haemolytica* and BVDV were reported by Burciaga-Robles et al. (2010 a), potentially explaining lower DMI observed by Burciaga-Robles et al (2010 b).

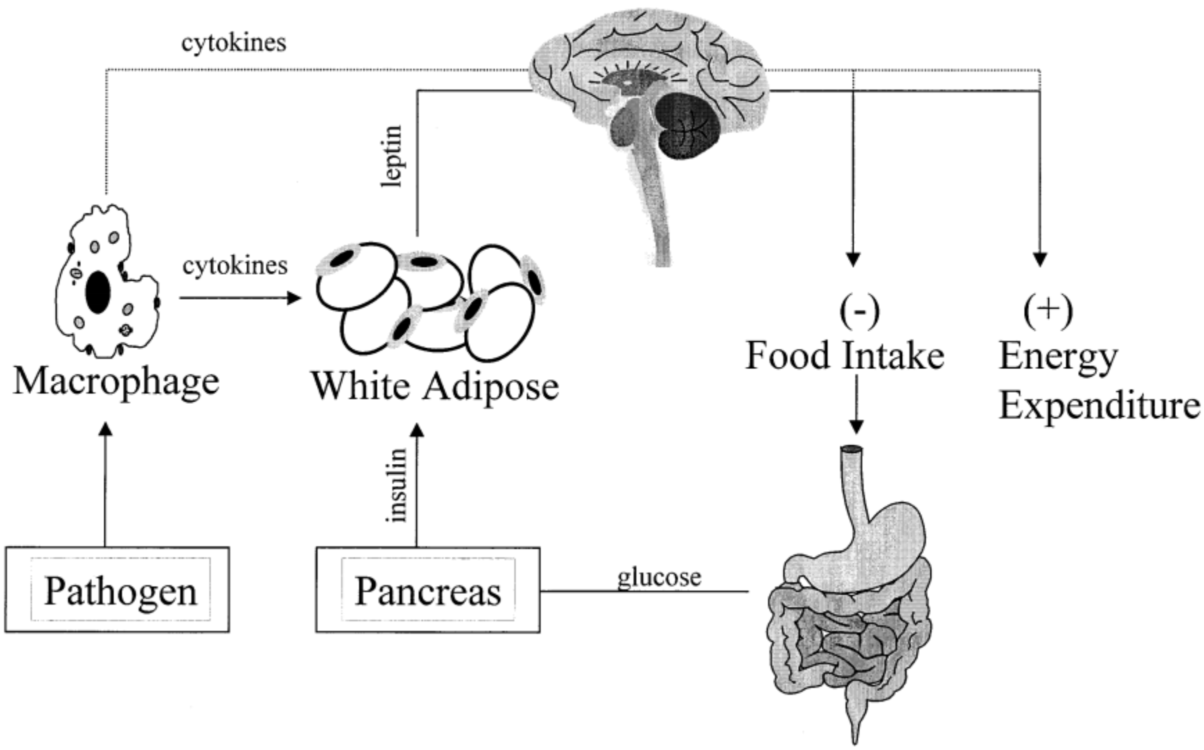

Figure 1. Cytokines act directly in the brain to reduce food intake and increase energy expenditure but may induce similar effects indirectly by modulating other physiological systems. Recent studies suggest inflammatory cytokines induce adipocytes to secrete leptin, a blood-borne factor that acts centrally to reduce food intake and increase energy expenditure. Therefore, immune system activity and energy balance may be coupled by leptin.

Adopted from Johnson (1998)

Cytokines can also indirectly effect DMI through leptin secretion form adipocytes (Johnson, 1998). Early research by Sarraf et al. (1996) demonstrated that rodents infused with TNF-α and IL-1 had increased leptin concentrations and subsequently lower feed intake. Lippolis et al. (2017) infused steers (485 kg) with saline or bacterial lipopolysaccharide (LPS). Subsequent cytokine and leptin concentrations were increased following the LPS infusion, and a decrease in DMI was observed (Lippolis et al., 2017). Leptin can influence DMI by acting on the satiety center within the central nervous system and by limiting gastrointestinal motility (Matson and Ritter, 1999). Infusing steers with either saline and LPS, Waggoner et al. (2008) reported decreases in ruminal passage rate, motility, and pH. These same observations were made by Lippolis et al. (2017) further demonstrating the interactions between the immune system and GI tract.

Energy

It is well established that an activated immune system utilizes a large amount of nutrients. Activated immune cells have been shown to increase their glucose consumption for the generation of energy, biosynthetic precursors, and signaling intermediates (Calder et al., 2007). To estimate glucose requirements of an activated immune system Kvidera et al. (2016) jugular catharized Holstein steers and infused saline or LPS with or without a euglycemic clamp (Figure 2.). The authors then infused a dextrose solution to maintain euglycemia in the steer with the euglycemic clamp. Over the course of nine hours, 516 g of glucose was infused to maintain euglycemia, and insulin concentrations were also greater for steers challenged with LPS. Kvidera et al. (2016) estimate that that glucose requirements to be approximately 1.0 g/kg BW$^{0.75}$.

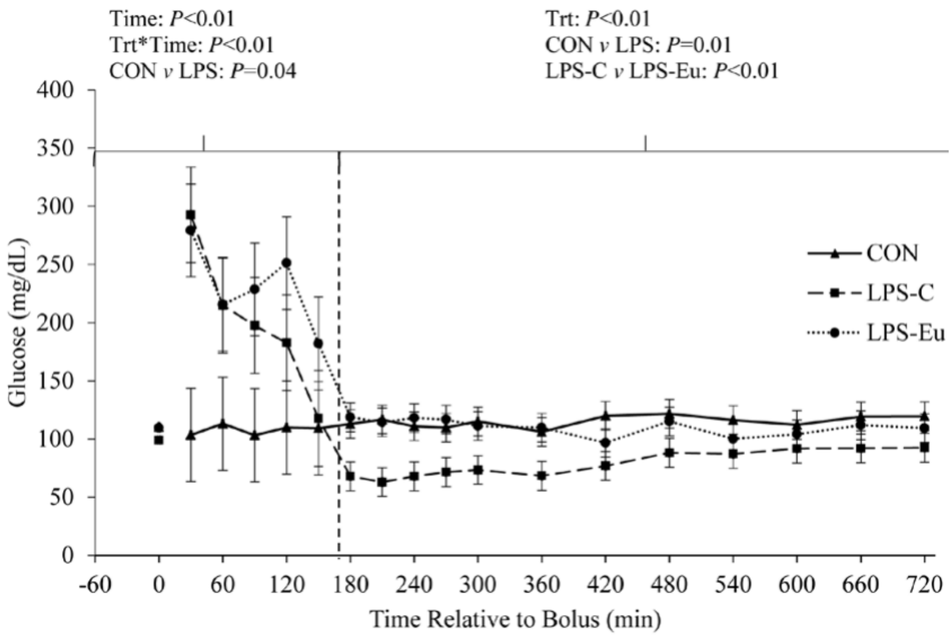

Figure 2. Blood glucose levels in steers administered a bolus of saline (CON), lipopolysaccharide (LPS-C), or lipopolysaccharide accompanied with a euglycemic clamp (LPS-Eu) during both hyperglycemic (0–150 min) and hypoglycemic (180–720 min) phases.

Adopted from Kvidera et al. (2016)

Although efforts to quantify the energy demand of the immune system have only recently been evaluated, the effectiveness of different diets to improve an immune response has been researched previously. Lofgreen et al. (1975) fed different levels of concentrate (20, 50, and 72%) to calves exposed to marketing and transportation stress. Overall, relatively minimal differences were detected for the animal health parameters regardless of diet. Similarly, Berry et al. (2004) compared two different energy levels (0.85 or 1.07 Mcal NEg/kg DM) fed to calves (186 kg) over a 42 d receiving period. The authors reported no differences for the number of calves treated once or twice, however, the number of calves treated a third time tended to be lower for calves feed the high energy diet. Crawford et al. (2021) fed either a receiving or finishing (1.07 or 1.50 Mcal NEg/kg) diet to 252 kg steers. Similar to Lofgreen et al. (1975) and Berry et al. (2004), no differences were detected for the total number calves treated.

Reuter et al. (2008) fed two different levels of concentrate (30 or 70%) to steers (247 kg) for 50 d. On d 28 of the experiment steers were challenged with LPS and injected with saline or an antibiotic. Area under the curve (AUC) for proinflammatory cytokines IFN-γ, TNF-α, and IL-6 were greater (Table 1.) for the steers consuming high roughage diets. Concentrations of the anti-inflammatory cytokine IL-4 were greater prior to the challenge when steers were fed the 70% concentrate diet, however, AUC for IL-4 was only numerically greater during the challenge. Results from this experiment do not necessarily favor one diet over the other . The greater anti-inflammatory response when feeding the 70% concentrate diet could have prevented a larger pro-inflammatory response to the LPS. Kuhla (2020) reported ruminal LPS, following an acidotic event, can enter blood circulation and trigger a pro-inflammatory response that eventually will trigger an anti-inflammatory response to maintain balance and prevent an overreaction by the immune system. It is plausible the steers from Reuter et al. (2008) consuming 70% concentrate diets had an acidotic episode prior to the LPS challenge, that lead to greater concentration of IL-4 were reported prior to the LPS challenge.

Table 1. Effect of concentrate level and intake restriction on cytokine production of steers challenged with LPS.

Item	70 AL	30 AL	70 RES	SE	Contrast[1]	
					Level	Intake
IFN-γ, pg/mL						
Prechallenge	16	26	16	21	*P* < 0.05	NS
Maximum	443	3,832	1,013	1,542	NS	NS
AUC	5,219	38,789	10,359	14,488	*P* < 0.05	NS
TNF-α, pg/mL						
Prechallenge	17	17	19	183	NS	NS
Maximum	4,100	11,174	6,568	3,296	*P* < 0.05	NS
AUC	24,027	73,815	38,002	23,332	*P* < 0.05	NS
IL-6, pg/mL						
Prechallenge	20	23	41	37	NS	NS
Maximum	8,148	15,982	13,829	1,957	*P* < 0.05	*P* < 0.05
AUC	90,104	172,232	142,434	18,664	*P* < 0.05	*P* < 0.05
IL-4, pg/mL						
Prechallenge	21	1	20	16	*P* < 0.05	NS
Maximum	68	82	82	103	NS	NS
AUC	681	129	677	957	NS	NS

[1]Level=concentrate level: 30AL vs (70AL+70RES/2); Intake=intake level: 70AL vs 70RES

Changing the dietary energy concentration had relatively little impact on animal health (Lofgreen et al. 1975; Berry et al., 2004; Crawford et al., 2021). Perhaps other factors such as performance and logistics should be considered more when formulating a diet for high-risk calves. Rivera et al. (2005) reported feed cost of gain was lower when feeding lower roughage diets, in which a diet with 60 to 70% concentrate is advantageous. However, if a producer struggles with proper bunk management and consistent feeding then limiting concentrate to no more than 50% of the diet may be appropriate to minimize the risk of an acidotic event.

Protein

Inflammation is known to increase N excretion and decrease N retention (Cole et al., 1986). It is hypothesized when an animal is infected imbalances between AA supply and AA demand for acute-phase protein production (Reeds and Jahoor, 2001). In ruminants, protecting specific AA is necessary to prevent their degradation by microbes if they are to be available for absorption. Feeding greater amounts of RUP can also increase the flow of dietary protein from the rumen, however, matching specific AA requirements with RUP can still be challenging.

Waggoner et al. (2009a) challenged steers (262 kg) with a LPS and supplemented diets with rumen-protected methionine. Dry-matter intake was limited for all steers so N intake would not be influence by LPS infusion or Met supplementation. Greater amounts of N were detected in the feces of steers supplemented with Met. Urinary N was also greater in steers infused with LPS. Overall N retention was not improved with the supplementation of rumen protected Met (Fig. 3).

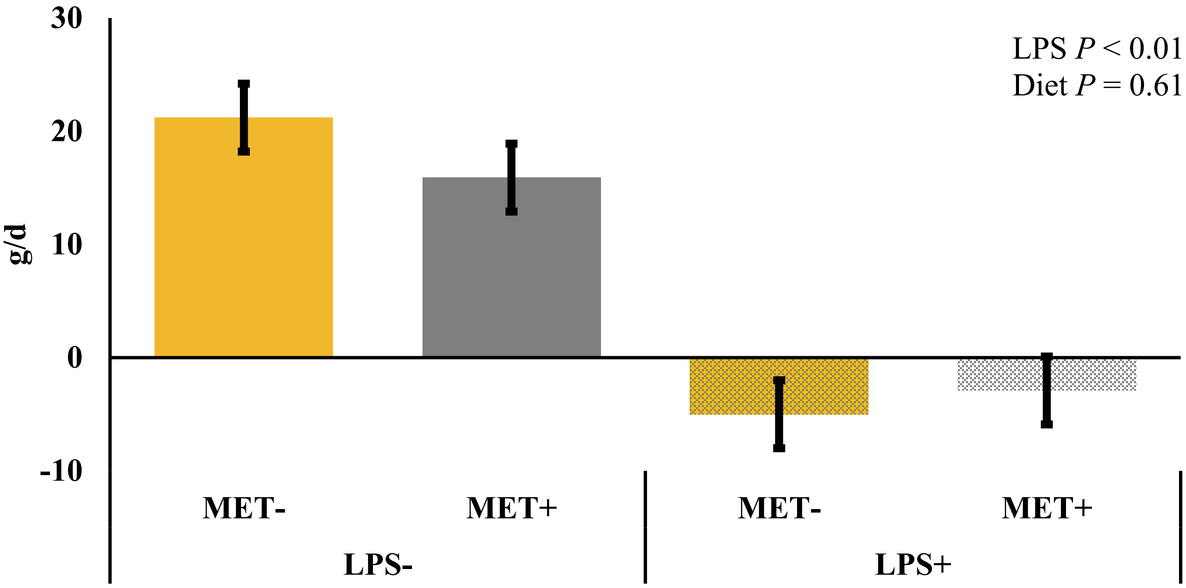

Figure 3. Nitrogen retention in response to LPS challenge and Met supplementation.
Adopted from Waggoner et al. (2009a)

In a separate experiment, Waggoner et al (2009b) fed 14.5% CP, 16.0% CP high RDP, or 16% CP high RUP diets to steers infused with saline or LPS (LPS- and LPS+ respectively). Dry-matter intake was again limited to limit the effects of LPS on DMI. As expected, increasing dietary CP increased N intake, and although dry-matter intake was limited, steers challenged with LPS ate less. Authors reported a decrease in fecal N for LPS+ steers. However, greater amounts of N were detected in the urine of LPS+ steers. Feeding LPS+ steers 16.0% CP diets, regardless of source, increased N retention to levels similar as LPS- steers (Fig. 4).

When formulating diets for high-risk calves, dietary protein concentrations and sources has received less attentions compared to dietary energy. Perhaps this is the result of an abundance of high protein by-products available for much of the last two decades leading to diets often exceeding requirements. Formulating and feeding diets as high as 16% CP could improve N balance when calves are stressed or sick. Source of protein does not appear to impact N balance, therefore cost of different protein sources should dictate which are used.

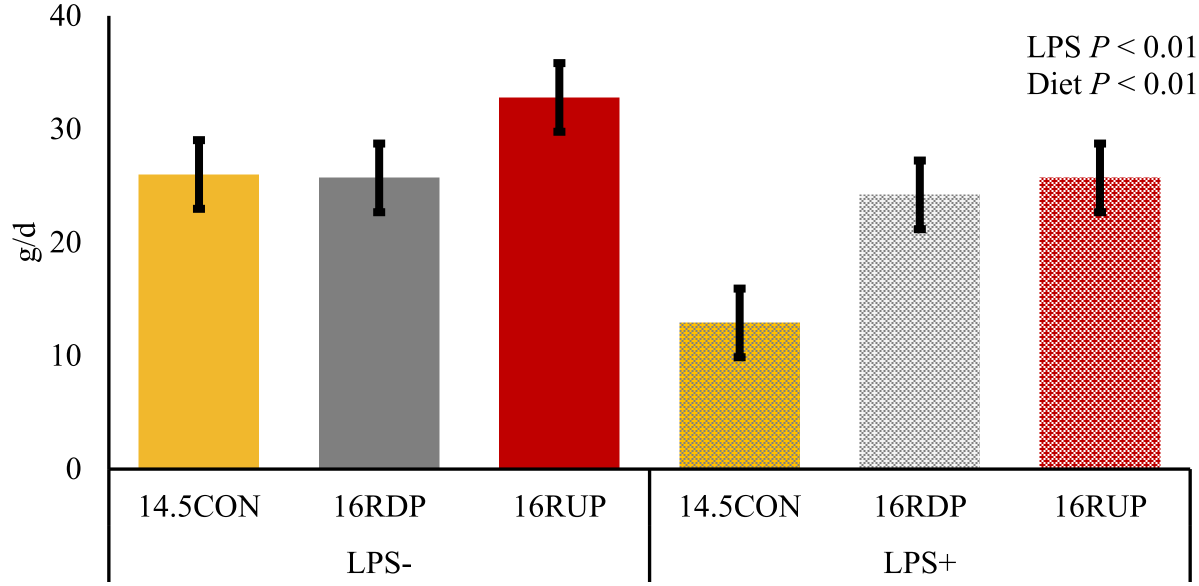

Figure 4. Nitrogen retention in response to LPS challenge and dietary protein.

Adopted from Waggoner et al. (2009b)

Conclusion

The stress and exposure to foreign antigens is greatest when calves are weaned, comingled, and transported long distances. As a result, high-risk calves pose a serious challenge nutritionally. Cytokines from an activated immune system feedback to reduce DMI. Increasing the dietary energy of the diet does not appear to improve animal health but does reduce feed cost of gain through improved performance. Attention to basic cattle feeding principles, such as bunk management, when feed high concentrate (> 70%) diets to high-risk calves is important. Increasing dietary protein regardless of source, to at least 15% can help maintain N balance when calves are sick.

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