Understanding Factors that Suppress Immune Function and Protective Immune Responses

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Native Defense Mechanisms
- Protects naïve animal
- Protects immediately
- Not antigen specific
- Activated by pathogen associated molecular patterns (PAMPs)

Acquired Defense Mechanisms
- Develop after Ag exposure
- Require several days to weeks
- Antigen specific
- Memory and tolerance
- Activate native defense mechanisms

Neutrophils: Critical for Defense Against Bacterial Infections

Native Defense Mechanisms
- Phagocytic cells
- Complement
- Native defense cytokines
- Antimicrobial peptides
- Natural killer (NK) cells

Acquired Defense Mechanisms
- Antibodies
- Cell mediated immunity
  - T-Helper Cells (Cytokines)
  - Cytotoxic T cells
  - Gamma Delta T cells

Neutrophil
**Antibody-Dependent Cell-Mediated Cytotoxicity**

- Antibody binds antigen on the surface of target cells
- Fc receptors on NK cells recognize bound antibody
- Cytotoxic T cells kill the target cell
- Target cell dies by apoptosis

**Neutrophil Phagocytosis**

- Trap and kill bacteria
- Consist of:
  - DNA
  - Histones, and
  - Granular proteins (no membranes)
- Released from stimulated neutrophils; not due to cell death
- Stress reduces release of NETs

**Neutrophil Oxidative Metabolism**

**Variation of Neutrophil Function with Age in Calves**

Calves Up to 5 Months of Age Have Decreased Neutrophil Function

Neutrophil Random Migration

Effects of in vivo dexamethasone administration on in vitro bovine polymorphonuclear leukocyte function


Neutrophil Phagocytosis

Effects of ACTH administration on bovine polymorphonuclear leukocyte function and lymphocyte blastogenesis


Neutrophil Oxidative Metabolism

Fig. 1. Effect of in vivo dexamethasone administration on the NBT reduction by bovine PMNs. Values and statistically significant differences are as in Fig. 1, except that n = 48 for the control group. * = 0.05 < P < 0.005.
Serum Cortisol Levels

Fig 1.—Serum cortisol concentration in the control and ACTH-treated steers. Serum cortisol values are represented as the mean ± SE (n = 5).

Effects of bovine viral diarrhea virus infection on bovine polymorphonuclear leukocyte function


Influence of ACTH Administration on Neutrophil Function

TABLE 2.—The raw function parameters in the control and ACTH-treated groups during the three-day treatment period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>ACTH-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random migration (mm²/hr)</td>
<td>62.6 ± 5.2</td>
<td>86.3 ± 5.1*</td>
</tr>
<tr>
<td>S aureus ingestion (%)</td>
<td>38.1 ± 4.1</td>
<td>32.1 ± 4.6</td>
</tr>
<tr>
<td>nkt reduction (OD)</td>
<td>0.333 ± 0.028</td>
<td>0.208 ± 0.031</td>
</tr>
<tr>
<td>Isolation (umol of NaI/10⁶ PMN/hr)</td>
<td>4.1 ± 2.8</td>
<td>10.8 ± 2.2</td>
</tr>
<tr>
<td>AIDC (%)</td>
<td>86.7 ± 1.6</td>
<td>85.3 ± 1.4</td>
</tr>
</tbody>
</table>

* P < 0.01, † P < 0.05 when compared with control values. Values expressed as mean ± SEM (n = 15).


Infection With BVD Virus Inhibits Neutrophil Function

Suppression of neutrophil and lymphocyte function induced by a vaccinal strain of bovine viral diarrhea virus with and without the concurrent administration of ACTH


Influence of ACTH Administration on Lymphocyte Blastogenesis

TABLE 3.—Lymphocyte blastogenesis in response to mitogens in the control and ACTH-treated groups during the three-day treatment period

<table>
<thead>
<tr>
<th>Mitogen</th>
<th>Control</th>
<th>ACTH-treated</th>
<th>Control</th>
<th>ACTH-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>500 ± 140</td>
<td>600 ± 396</td>
<td>113 ± 16.4</td>
<td>50.9 ± 14.9*</td>
</tr>
<tr>
<td>PHA-P</td>
<td>50,317 ± 6,783</td>
<td>55,619 ± 5,631*</td>
<td>11.2 ± 19.8</td>
<td>77.3 ± 13.6†</td>
</tr>
<tr>
<td>ConA</td>
<td>31,906 ± 3,922</td>
<td>33,362 ± 2,687</td>
<td>11.2 ± 15.1</td>
<td>55.3 ± 12.4</td>
</tr>
<tr>
<td>PWM</td>
<td>32,217 ± 3,106</td>
<td>35,463 ± 6,309</td>
<td>11.2 ± 15.1</td>
<td>55.3 ± 12.4</td>
</tr>
</tbody>
</table>

* P < 0.05, † P < 0.01, when compared with control values. Values expressed as mean ± SEM (n = 15).

MLV BVDV Vaccine Inhibited Neutrophil Function

MLV BVDV Vaccine Plus High Cortisol Inhibited Neutrophil Function Even More

Fig 13—Inhibition by neutrophils for each treatment group expressed as a linear percentage of control based on the number of neutrophils which could be converted to a neutrophilic form by the action of 10% granulocytes in 1 hour (experimetal method of calculation). The mean (±SEM) for 56 values from control culture were 4,11.4 ± 1.05. Levels, initially groups 3 and 4 were 3,70 and 4,2, respectively, but were 7,10 and 4,2 days (P < 0.05, n = 20, group 3, and group 4; P < 0.05, n = 20.

Roth, T.A., Keshwala, M.I. AIDS 44:2356-2372, 1989

Experimental Design

Alteration of Neutrophil Function Associated With Coccidiosis in Cattle: Influence of Decoquinate and Dexamethasone


Dexamethasone Induced Clinical Coccidiosis

Deccox Prevented Clinical Coccidiosis

TABLE 1. Estimated number of coccidia oocysts/gram of fecal material (n=5/group).

<table>
<thead>
<tr>
<th>Sample day</th>
<th>Controls</th>
<th>Dexamethasone</th>
<th>Deccox</th>
<th>Deccox + Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>173</td>
<td>95</td>
<td>120</td>
<td>215</td>
</tr>
<tr>
<td>Day 38</td>
<td>155</td>
<td>34,350</td>
<td>60</td>
<td>333</td>
</tr>
</tbody>
</table>

Bovine Respiratory Disease

- The feeding of Decoquinate had been associated with reduced morbidity and mortality from respiratory disease in feedlot cattle infected with coccidia.
- Hypotheses:
  - Infection with coccidia is immunosuppressive
  - Feeding Decoquinate inhibits immunosuppression associated with coccidiosis
  - Reduced immunosuppression reduces the incidence of respiratory disease.

Feeding Deccox Enhanced Neutrophil Function in Clinically Normal Calves

TABLE 2. Neutrophil function (after dexamethasone treatment) for the 4-day period beginning 25 days after the start of Deccox feeding (n=5/group).

<table>
<thead>
<tr>
<th>Neutrophil function assay</th>
<th>Controls</th>
<th>Deccox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random migration (mm²)</td>
<td>37.5</td>
<td>34.1²</td>
</tr>
<tr>
<td>Staphylococcus aureus ingestion (%)</td>
<td>25.9</td>
<td>27.7</td>
</tr>
<tr>
<td>Cytokine C reduction (%)</td>
<td>0.396</td>
<td>0.481²</td>
</tr>
<tr>
<td>Isolation (mm)</td>
<td>24.9</td>
<td>31.1²</td>
</tr>
</tbody>
</table>

² Excess neutrophil function indicated by increased values for random migration, reduced values for S. aureus ingestion, cytokine C reduction, isolation.

*P < 0.05 vs control; **P < 0.01 vs control
**Feeding Decoxx Reduced the Suppression of Neutrophil Function Induced By Dexamethasone**

<table>
<thead>
<tr>
<th>Neutrophil Function</th>
<th>Control</th>
<th>Decoxx</th>
<th>Dexamethasone</th>
<th>Decoxx + Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random migration (mm)</td>
<td>132.4</td>
<td>108.9*</td>
<td>121.3</td>
<td>28.2**</td>
</tr>
<tr>
<td>Phagocytosis assay (mg)</td>
<td>205.5</td>
<td>180.7**</td>
<td>195.6</td>
<td>154.1</td>
</tr>
<tr>
<td>Neutrophil C reduction (%)</td>
<td>55.0</td>
<td>65.4</td>
<td>59.5</td>
<td>24.4</td>
</tr>
</tbody>
</table>

* Significant difference of neutrophil migration in comparison with 3 Ano Licker. **Significant difference of neutrophil C reduction in comparison with 3 Ano Licker. *P<0.05 vs control. **P<0.05 vs control. ***P<0.05 vs Decoxx. 

**Conclusions**

- Most cattle carry coccidiosis
- Sub-clinical coccidiosis suppresses the ability of neutrophils to control bacterial infection
- Immunosuppression leads to clinical coccidiosis
- Control of subclinical coccidiosis can help calves resist bacterial pneumonia, especially before times of stress

**Passive Transfer of Cytokines Through Colostrum**

**Concentrations of Cytokines in Bovine Colostrum and Milk**

**Serum Cytokine Levels in Neonatal Calves**

**IL18 in Bovine Colostrum and Neonatal Serum**

**Table 3.** Neutrophil function for the 5-day period beginning 6 days after the last dexamethasone treatment and 16 days after the start of Decoxx feeding (n=5/group).
Recombinant bovine interferon gamma as an immunomodulator in dexamethasone-treated and non-treated cattle.


Improvement in interleukin-10 (IL-10) production in H. somnus-induced pneumonia in immunosuppressed calves

Gamma Interferon Reduces H. somnus Induced Pneumonia in Immunosuppressed Calves

Interferon Gamma Can Enhance Neutrophil Function in Immunosuppressed Calves

Neutrophil Function for the Two-Day period of Dexamethasone (0.06mg/kg) and/or (IL-10) (0.5mg/animal) Administration

Values expressed as mean ± SEM (n=10), i.e., 2 samples from 10 animals per group

Enhancement of neutrophil function by ultrafiltered bovine whey


Influence of recombinant bovine interferon gamma and dexamethasone on pneumonia attributable to Haemophilus somnus in calves


Ultrafiltered Bovine Colostral Whey Enhances Neutrophil Function In Vitro

Cytoschrome C reduction (OD)

SODination (nmol Na1/107 PMN/hr)

Dilution UFBW

* p<0.05 different from no UFBW

J Dairy Sci. 2001;84:824-829
Treatment with Ultrafiltered Bovine Whey Enhances Neutrophil Function in Periparturient Cows

Periparturient cows with and without ultrafiltered bovine whey UFW treatment, three treatment days combined.

- Values expressed as mean ± SEM.
- Probability of >1: 0.009 determined by analysis of variance followed by Student's t-test pre- and post treatment.

Modulation of Neutrophil Function

- Decreased neutrophil function
  - Neonates and young animals
  - Distress (glucocorticoids)
  - Some viral infections
  - Bacterial virulence factors
  - Coccidiosis
  - Peri-parturient period
- Increased neutrophil function
  - Native defense cytokines
  - T helper cytokines

Immunomodulators

- Work best to reverse immune suppression
- Administer before disease occurs
- Moderate efficacy
- May be useful in some situations in place of antibiotics
- Animal to animal variation
- Problems with side effects

Bovine Respiratory Disease

- Immunosuppression is an important component of the Bovine respiratory disease complex
  - Stress
  - Viral infection (BVD, BHV1, BRSV, PI3)
  - Inadequate nutrition
- Immunosuppression leads to Bacterial pneumonia

Immunomodulators

- Cytokines and cytokine antagonists
  - Recombinant proteins
  - Expression vectors
- Cytokine inducer
  - Bacterial products
  - Plant extracts
  - Chemicals to bind TLRs
- Pharmaceuticals
  - Hormones and blockers
  - Alter AA cascade, signal transduction, etc

Resistance to Bacterial Pneumonia