Nitrate Toxicity and Sodium Deficiency Associated with Hypomagnesemia, Hypocalcemia and the Grass tetany Syndrome in Herbivores.

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The factors inducing the grass tetany syndrome have been a mystery to scientists since the syndrome was first described in the 1930. It is hypothesized that important factors for the pathogenesis of the grass tetany syndrome are nitrate toxicity and a dietary sodium deficiency which induces an electrolyte and mineral imbalance. The grass tetany syndrome is associated with a deficiency of magnesium (hypomagnesemia), and a coexisting calcium deficiency (hypocalcemia), and sodium deficiency (hyponatremia) and an excess of potassium (hyperkalemia) in the blood of affected animals.

Grass tetany affects cattle and other herbivores that are high producing and being fed a ration excessive in protein which includes non-protein nitrogenous compounds. A common factor is excessive nitrogen fertilization of pastures. Yet, the mechanism of action by which excessive nitrogen or nitrogenous compounds predispose cattle to grass tetany has not been adequately investigated. The following discussion will disclose the current important scientific literature and the author's clinical and pathological experience with the grass tetany syndrome in herbivores. During the last decade the unprecedented late frosts and freezes to lush pasture forages provided important clues to the current knowledge on the grass tetany syndrome as well as other disorders associated with nitrate toxicity in ruminant and non-ruminant herbivores.

In 1930, the original scientific report on the pathogenesis of grass tetany, Sjollema states that grass staggers (tetany) occurs most frequently during springs when there is a superabundance of young, rank, quick-growing grasses rich in proteins. He also notes that if occurs during the winter when feed is excessive in protein. In some herds , cattle manifest pica suggesting that some necessary ingredient is lacking in the fodder. He also observed animals grazing in strongly manured pastures stripped all trees within their reach of herbage until they were barren. Interestingly, he also found that the sodium-content in the blood was subject to fluctuations, probably greater than in normal animals. [8] It is likely that the pica cattle were experiencing was due to a sodium deficiency.

There has been very little progress in the understanding of the factors responsible for the syndrome since the original report by Sjollema.[8] However, he and other early workers did observe some very important clues that were later confirmed by other workers, but these clues have not been appreciated until recently. He observed that high nitrogenous diets and an unknown factor, which was later identified as sodium by other workers, are important in the pathogenesis of hypomagnesemia and hypocalcemia in cattle.

In the 1950s Smith and Aines experimentally deprived sodium from dairy cows and induced clinical signs of grass tetany. [9] This landmark research was confirmed by other workers. Paterson and Crichton found that low concentrations of sodium were found in tetany-prone grass, and they prevented grass tetany by supplementing cows with sodium chloride. [7] In a field study, Butler observed an increased incidence of grass tetany at low sodium concentrations in the grass and the incidence of grass tetany disappeared at sodium concentrations above 0.2% in the grass. [3]

Unfortunately, this early work on the importance of adequate sodium has been either overlooked or ignored, as the majority of mineral supplements currently used in an attempt to prevent grass tetany are deficient in sodium and excessive in magnesium. This is causing weight loss, wasting, severe diarrhea, and reduced milk production when fed with high protein rations. The consequence of excessive magnesium supplementation was reported by Urdas, et. al. They reported on the importance of appropriate amounts of magnesium in rations for dairy cows, especially in rations high in protein, as excessive magnesium had drastic adverse effects on milk production and other clinical signs, including diarrhea. [14]

The clinical signs of grass tetany or hypomagnesemia are unlikely to occur unless there is also a hypocalcemia. In many cases the clinical signs of grass tetany and milk fever are similar, and probably the triggering mechanisms or factors inducing the syndromes are similar. The clinical signs are usually seen in animals in full lactation and high producing cows. The increase in feed and forage intake, even with adequate magnesium and calcium, may only partially compensate for loss of magnesium and calcium in the milk. Without exception, most researchers have observed that clinical signs of grass tetany rarely occur unless affected animals are high producing and being fed a ration high, or excessive in protein which includes non-protein nitrogenous compounds. [2]

Most researchers agree that a common factor associated grass tetany is excessive nitrogen fertilization of pastures. [1] Yet, very few have investigated why excessive nitrogen, or nitrogenous compounds predispose cattle to grass tetany. Martens and Schweigel summarized work on excessive nitrogen as it relates to grass tetany. These studies suggest that excessive NH+ may interfere with the absorption of magnesium from the gut, but did not offer any other explanation. [6] However, their research shows that the lack of sodium and excessive potassium seemingly also interferes with the absorption of magnesium from the gut. [5,6]

Since the first report and all subsequent research on the pathogenesis of grass tetany in cattle, excess nitrogen was suggested as the primary initiating factor for inducing hypomagnesemia and hypocalcemia. Yet, the factor associated with excessive nitrogen has not been identified. It is hypothesized that the nitrogen factor is related to the nitrate anion. The subsequent discussion will outline the observations and findings that suggest that excessive nitrate is involved in the pathogenesis of hypomagnesemia, hypocalcemia, hyponatremia and hyperkalemia, all of which are involved in the grass tetany syndrome in cattle, and other herbivores.

Several researchers report that hypomagnesemia may occur in animals foraging on diets low in magnesium, but it may also occur when diets have adequate magnesium in the forages or rations. This suggests that there is some factor(s) that is either tying up the magnesium and/or chelating the magnesium making it unavailable, or causing it to be removed from the body excessively through the kidneys, mammary glands and in the feces, thus causing an acute hypomagnesemia. This was suggested by Grunes et. al. after demonstrating that fertilization with high nitrogen appreciably increased the nitrogen in plants, thus increasing their potential for causing grass tetany. In addition, they found that fertilization with broiler litter markedly increased the potassium and magnesium concentrations , as well as the ratio of K/ (Ca+Mg), which would make the forage more likely to produce grass tetany. They also found that there was an increase in organic acids and suggested that these anionic organic acids may be chelating with magnesium and calcium creating a hypomagnesemia and hypocalcemia when forages were high in organic acids. [4] Organic acids are more likely to be excessively high in diets high in

carbohydrates, but when the diets are high in protein and non-protein nitrogenous compounds, the anionic ions likely to be excessive are related to nitrate.

Numerous researchers have found that grass tetany occurs most often in older brood cows grazing lush growth of pastures in early spring, and the triggering of the grass tetany syndrome includes environmental conditions of cool, cloudy and wet weather, promoting rapid, lush growth of cool season grasses. These environmental conditions, which also include frosts and freezes, will cause acute spikes in potassium as well as nitrate in affected growing pastures. Analyses of these affected pastures during and after periods of frosts and freezes revealed elevated levels of potassium and nitrate. [11] Nitrate in the form of potassium nitrate is reportedly the form which herbivores are exposed to nitrate. During periods of stress to pastures forages, the acute spike in potassium and nitrate is seemingly causing an electrolyte and mineral imbalance in affected herbivores. These imbalances, in pastures forages include an increase ratio of K/ Ca+Mg, and a deficiency in sodium. These imbalances may not be readily apparent, unless blood samples are obtain while animals are suffering from marked clinical signs, as the body can obtain cations from tissues until they are depleted, then severe acute clinical signs and death occur.

Since sodium aids in the prevention of hypomagnesemia and hypocalcemia, and these syndrome are both associated with high producing cows on high nitrogenous rations, it was suspected that similar syndromes are occurring in other herbivores including horses where high nitrogenous diets are suspected of inducing an immune suppression, reproductive losses and other syndromes associated with a host of opportunistic diseases, likely related to increase in nitrate in the diet. [11] Also, as with cattle, adequate sodium in the diet seemingly aids in the prevention of these syndromes. To test this hypothesis, horses were given a high protein diet with and without the addition of sodium in the diet and the levels of nitrate in the blood were analyzed. Diets without the addition of sodium chloride caused a marked elevation of nitrate in the blood, whereas, the supplementation of sodium chloride, sodium bicarbonate, or zeolytes high in sodium, to the same high protein ration returned the nitrate levels in the blood to normal levels or levels seen in horses on low protein diets, within 24 hours after the addition of sodium to the diet. [12] These findings suggest that sodium indeed is neutralizing the nitrate in the blood, and/ or gut by excreting the excessive nitrate that is exogenously in the diet, or the nitrate that is endogenously produced by bacteria in the gut. The excess nitrate is likely being eliminated as an anionic complex associated with the sodium by the kidneys, in the feces, or in the milk in lactating animals. The high nitrate in the milk, associated with the feeding of high protein diets in herbivores, may also affect suckling neonates with the same detrimental effects as in adults. This explains why neonates on dams that are fed excessive proteins seemingly are affected with a multitude of opportunistic gastrointestinal diseases, including gastric ulcers and other intestinal disorders. Conversely, dams fed a low protein diet and adequate sodium, their neonates rarely suffer from these gastrointestinal disorders.

When there is a deficiency of calcium and sodium and excessive potassium and nitrogen in the soil, there is likely a more dramatic spike in potassium and nitrate in plants during and after stress, like frosts and freezes, to pasture forages. If the excessive potassium and nitrate in affected forages is consumed by herbivores, it may induce a toxicity and/or mineral and electrolyte imbalances. Nitrate in the diet is utilized in protein metabolism. However, if the nitrate is excessive in ruminants, in some cases, nitrate is converted to nitrite by the gut bacteria and methemoglobinemia may occur. The majority of excessive nitrate is eliminated through the gut and kidneys, or mammary glands in lactating herbivores.

Since cations utilized to eliminate the excessive nitrate from the body have different solubilities and affinities for nitrate, the body will utilize the cations, if available in adequate concentrations, that have the highest affinity for nitrate. Magnesium, calcium and then sodium are the most soluble and potassium the least soluble [13] , and likely the affinity of each cation for nitrate is similar to their solubility with nitrate. It is hypothesized that if there is a deficiency of sodium, and most forages and rations are deficient in sodium and excessive in potassium, and when there is a spike in nitrate, or excessive nitrate in the body, anionic nitrate is eliminated from the body as an ionic complex associated with magnesium and calcium. If nitrate is excessive, a hypomagnesia and/or hypocalcaemia may develop as the body is eliminating magnesium and calcium with the excessive anionic nitrate. However, if there is adequate sodium in the diet and organs and tissues, the excessive anionic nitrate is removed by the gut, kidneys, and mammary glands in lactating animals, as a ionic complex associated with sodium, and magnesium and calcium are maintained at physiologic levels and hypomagnesia and/ or hypocalcaemia will not occur. For this reason adequate levels of sodium in the body and ration will lessen or prevent the drastic effects of nitrate toxicity. Also, it explains why adequate sodium in the diet will aid in the prevention of grass tetany, which is associated with high potassium and low magnesium levels. It also explains why the grass tetany syndrome cannot be readily induced experimentally unless cattle are exposed to high nitrogen or nitrate forages, and likely low sodium diets.

Most cattlemen assume they have adequate sodium if cattle are exposed to salt blocks. Cattle and other herbivores cannot obtain enough salt or sodium from hard salt blocks during periods of acute needs. The most dominate animals in a herd will horde a salt block and the remainder will leave without any salt. Even the animals that horde the block cannot consume enough salt to neutralize the acute excessive dietary nitrate during periods of acute stress to forages, like frosts and freezes to high nitrogenous forages. Therefore, it is imperative to either have adequate sodium in the complete rations, which is preferable, and/ or to have readily available sodium in the form of sodium chloride, and/or sodium bicarbonate in the loose form always available, especially in times when environmental conditions are conducive for nitrate spikes in forages. Seemingly, the excessive potassium in forages, which occurs along with the excessive nitrate after a frost and freeze, discourages animals to consume salt, or sodium compounds free choice as potassium substitutes for sodium in plants as well as in animals. This further increases the ratio of K/Ca+Mg and for this reason sodium needs to be force fed in complete rations for optimum results. It is important to have fresh water available and place salt mixtures near water sources.

The livestock industry has limited sodium chloride in mineral supplements to encourage livestock to consume more minerals, and this has led to the over consumption of essential minerals that are normally not toxic if fed at correct levels, but can be if fed in excessive amounts. The restriction of sodium is seemingly contributing to a multitude of syndromes, including hypomagnesemia, hypocalcemia and the downer cow syndrome as well as a host of opportunistic diseases. Also, the restriction of sodium and the prolonged over feeding of magnesium may result in decreased performance, especially milk production in dairy cows and severe reduction of calf weights in calves on beef cows. Furthermore, the forced feeding and overfeeding minerals that are contaminated with heavy metals have drastic effects on performance due to toxicities, mineral imbalances, immune suppression, and the induction of a host of opportunistic diseases. It is important to have adequate, pure forms of calcium and magnesium of high quality in the diet for high producing animals. Most diets have adequate calcium and magnesium, but when there are acute spikes in anionic ions, the calcium and magnesium may be acutely depleted, resulting in hypocalcemia, hypomagnesemia and a hyponatremia. But, adequate access to sodium appears to help alleviate these acute deficiencies during spikes in nitrate.

It is not an uncommon practice for some cattlemen to either intentionally or unintentionally allow cattle to go without salt. The practice is sometimes used to allow the easily gathering of cattle that are salt starved. If there is a spike in potassium and nitrate due to adverse environmental conditions while cattle are deprived of salt, cattle are often found dead, or suffering from a host of metabolic and opportunistic diseases. Seemingly, cattlemen with the healthiest cattle are very aware of the need for cattle to have unlimited access to loose salt and/ or loose trace mineralized salt at all times. These same cattlemen have observed that if cattle are without salt, even for short periods of time, some may be found dead, or suffering from clinical signs of grass tetany, especially after periods of severe environmental stress, like frosts or freezes to lush pastures containing legumes. [10]

According to the scientific literature, nitrate is relatively non toxic, unless the excessive nitrate is converted to nitrite by bacteria in the gastrointestinal tract. This may lead to methemoglobinemia and anoxia in affected animals. However, another form of nitrate toxicity that is likely more common and more detrimental, and previously overlooked may occur when the nitrate depletes essential cations in an attempt to maintain critical ionic balances. The excessive nitrate anions are excreted along with cations to maintain a critical ionic balance. This may result in mineral and electrolyte imbalances that may initiate a host of metabolic diseases in ruminants, as well as monogastric animals, including horses. This explains why cattle, and other ruminants, and horses appear to be suffering from a host of metabolic disorders when exposed to forages and diets high in protein, non-protein nitrogenous compounds and nitrate. The nitrate anion *per se* may not be that toxic in cattle and horses, but indirectly it appears to be inducing mineral, electrolyte and ionic imbalances, and secondary immune suppression associated with these disorders. Sodium chloride, sodium bicarbonate, and high sodium zeolite compounds appear to neutralize the toxic effects of excessive nitrogenous diets, including nitrate toxicity.

Nitrate toxicity is difficult to evaluate and it is imperative to consider nitrate levels in forages and well as in the blood and biological fluids of affected animals. Nitrate levels in the blood are difficult to interpret as both the amount and the duration of exposure need to be considered. The excessive nitrate in the blood is eliminated by excretion with essential cations, thus giving the false impression that nitrate toxicity did not occur as the nitrate level in the blood may appear to be too low to be significant. However, the excessive nitrate may have been previously excreted along with essential cations inducing imbalances which are manifested clinically as hypocalcemia, hypomagnesemia, hyponatremia, and often a hyperkalemia. Nitrate toxicity, that may have induced these disorders, may not be apparent when blood or biological fluids are analyzed. Also, nitrate toxicity may be overlooked by only analyzing forages for nitrate levels. The over feeding of protein and non-protein nitrogenous compounds may lead to nitrate toxicity by the endogenously production of nitrate by the bacteria of the gut. This too may induce mineral and electrolyte imbalances, and a host of opportunistic diseases that have been confusing to the livestock industry because the primary cause, nitrate toxicity is not apparent and overlooked.

Cattle and horses with apparent nitrate toxicity, and cattle with clinical signs of grass tetany, will have elevated levels of aldosterone suggesting a sodium deficiency, yet the blood levels of sodium may be in the low normal range, suggesting that a sodium deficiency is not present, but it drops below normal levels shortly before death. Unless blood samples are obtained shortly before death, the severe sodium deficiency may not be apparent. Aldosterone is a steroid hormone belonging to the mineralocorticoid family that is produced by the adrenal gland and acts to conserve sodium and secrete potassium, and increase blood pressure. The elevated aldosterone indicates that the system is attempting to conserve sodium, which is deficient, and substituting potassium, which is excessive, for sodium. While the

system is sparing sodium, likely calcium and magnesium is being utilized to eliminate the excessive nitrate, thus creating hypomagnesemia and hypocalcemia. Therefore, aldosterone levels may be the best indicator of ionic imbalances induced by the excessive nitrate anion.

In summary, hypomagnesemia and hypocalcemia are more likely to occur in high producing animals that are fed diets high or excessive in protein, and non-protein nitrogenous compounds, including nitrate. When these components of the diets are high, anionic imbalances due to nitrate are occur in forages as exogenous sources, but they are further produced endogenously by the bacteria of the gut of affected animals. When this occurs, the excessive anionic ions need to be neutralized by cations and this causes a "washing out" effect of essential cations including calcium, magnesium and sodium in the urine, feces and milk, and then hypocalcemia, hypomagnesemia and hyponatremia occur. Even when these cations are at recommended levels in the diet, they may not be adequate and become acutely depleted during periods of environmental stresses. A simple prophylaxis is not to overfeed protein to herbivores, but this is not always practical when producers are striving for maximum production. When there are severe environmental stresses like frosts and freezes to lush forages, especially forages containing legumes, cationic and anionic imbalances in affected forages are further exacerbated. However, the over feeding of protein can be somewhat alleviated by feeding adequate calcium, magnesium and sodium preferably in complete rations, but also they should be available free choice if affected animals desire and need more to neutralize the anionic excesses. Calcium and sodium if fed at optimum concentrations are non toxic, but magnesium if fed at high levels for prolonged periods, may be toxic and may result in chronic wasting, reduced milk production and diarrhea. Seemingly, the feeding of adequate levels of magnesium and increased levels of calcium and sodium during period of environmental stress will aid in the prevention of grass tetany that is induced by acute anionic imbalances due to nitrate in high producing animals.

It is apparent that nitrate toxicity in herbivores is much more prevalent than previously reported. A well documented form of nitrate toxicity occurs in ruminants when nitrate is converted to nitrite by the microflora of the gastrointestinal tract and then the nitrite induces a methemoglobinemia and anoxia. However, It is hypothesized that a much more common mode of nitrate toxicity, and previously not recognized, is when nitrate toxicity induces a severe electrolyte and mineral imbalance in ruminant and non-ruminant herbivores. This form of nitrate toxicity is an important factor in the pathogenesis of the grass tetany syndrome and likely other syndromes in herbivores, including reproductive disorders in all herbivores, including horses. Seemingly, adequate dietary sodium not only protects against nitrate toxicity, but also aids in the prevention of the grass tetany syndrome in herbivores, and other metabolic and reproductive disorders induced by nitrate in herbivores.

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