Chemical and Biochemical Aspects of Photosensitization in Livestock and Poultry

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ABSTRACT—Certain synthetic and naturally occurring chemicals, particularly those found in some range plants, may interact with livestock and poultry in the presence of activating light to produce photosensitization. Such photosensitization may have serious implications for livestock producers as a result of causing reduced performance of and even death of affected animals. The mechanisms producing photosensitization in livestock and poultry are discussed in context with the chemical nature of major livestock photosensitizers. The possibility that photosensitizing agents for livestock may have toxicologic significance in humans consuming photoactive residues in meat or animal by-products is considered.—JNCI 1982; 69:259-262.

Livestock and poultry producers face many obstacles in their attempts to produce economically and profitably meat, edible animal by-products, and animal fibers. In addition to wide and often unpredictable fluctuations in production costs and market stability, animal disease and toxicity problems may be encountered that are often unanticipated but which may be devastating. Although many animal diseases may be dealt with quickly and effectively, either by prophylaxis or by prompt diagnosis and drug therapy, problems involving toxicants are generally more difficult to manage. This difficulty of management arises because causal agents in animal toxicoses are often difficult to define and effective treatment procedures are often lacking.

A wide variety of substances may interact with livestock and poultry, with toxicologic consequences. Among such substances are pesticides, animal drugs, and industrial chemicals. Certain natural products to which animals are exposed in the diet, particularly toxic range plants, are of special significance. While the nature of the toxic responses elicited by any one or combination of these toxic agents may vary greatly, depending on the mechanisms of action involved, this report will deal with only those agents known to elicit light-dependent toxicities in livestock and poultry.

MANIFESTATIONS OF PHOTOSENSITIZATION

Livestock.—From the perspective of the producer or veterinary diagnostician, livestock photosensitization can be defined as an abnormal blistering and peeling of skin due to increased sensitivity to sunlight. Although such a definition is overly simplistic and does not take into account all biochemical and physiologic ramifications of the syndrome, from a practical standpoint it is a workable and generally accurate description of photosensitization as normally observed in such animals as cattle, sheep, and horses. The lesions of photosensitization appear almost exclusively on areas, comb, wattles, and feet. Edema, blistering, and scabbing may be succeeded by blindness, sloughing of the comb and wattles, and deformation of the beak and feet. Deformities are particularly severe and often permanent in young birds photosensitized during active growth stages (3-6).

GENERAL MECHANISMS PRODUCING PHOTOSENSITIZATION

It is generally considered that livestock photosensitization can be classified into one of three categories depending upon the origin of the ultimate photosensitizing agent (1). Some classifications include a fourth, "miscellaneous," category (7). In primary photosensitization, the photoactive chemical(s) arise from some source external to the animal, such as from a foodstuff. Once in the animal, these chemicals or their phototoxic metabolites reach the peripheral circulation where they absorb incident sunlight and transfer the absorbed energy to cellular components in such a manner that cellular damage results. Hepatogenous photosensitization occurs when exogenous chemicals or their metabolites, though not inherently phototoxic, cause hepatic damage that results in retention of photoactive bile pigments. Such pigments reach abnormally high concentrations in the peripheral circulation and, in the presence of sunlight, result in phototoxicity. Congenital photosensitizations in livestock are genetic disorders of porphyrin metabolism that result in unusually high concentrations of photoactive porphyrins or porphyrin precursors in the peripheral circulation. Miscellaneous syndromes of photosensitization represent those instances in which the etiology is unknown. Such photosensitizations are not hepatogenous because liver damage is not associated with the syndrome; they are not congenital because photosensitization is associated with some external source (such as a photosensitizing plant). Thus, of necessity, most if not all miscellaneous photosensitizers of an undefined type are probably primary photosensitizers in which the chemical nature of the photosensitizing agent is not known.

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Primary Photosensitization

Relatively few agents have been shown to cause primary photosensitization in livestock and poultry. A schematic representation of how such agents interact with animals to elicit phototoxic responses is shown in text-figure 1. Structures of some primary photosensitizing chemicals are shown in text-figure 2. Hypericin, fagopyrin, and protofagopyrin are highly conjugated naphthodianthrone derivatives that are responsible for the photosensitizing action of *Hypericum* spp. and *Fagopyrum* spp. in cattle and sheep (8, 9). Psoralens (linear furcoumarins) are well-known potent photosensitizers when activated by near UV light, and they occur in a large number of plant species from several families. Psoralens have been shown to account for the photosensitizing actions of *Ammi majus* and *Cymopterus* spp. in both livestock and poultry (10–13). The synthetic drug phenothiazine, used as an anthelminthic in several livestock species, can result in photosensitization under certain circumstances. It is thought that an oxidative metabolite, phenothiazine sulf oxide, may be the major photosensitizing agent in phenothiazine phototoxicity (1, 2).

Hepatogenous Photosensitization

Most agents known to elicit photosensitization in ruminants appear to be of the hepatogenous type. The progression of the syndrome is presented schematically in text-figure 3. In typical cases, foodstuffs such as range plants or moldy forage grasses that contain hepatotoxic chemicals or their precursors are consumed by the animals, and the toxin(s) are absorbed and transported to the liver. Hepatotoxicity ensues, which may be manifested as severe damage to liver cells and/or occlusion of the bile ducts. Ultimately, normal biliary excretion mechanisms are circumvented and photoactive bile pigments accumulate in the blood at abnormally high levels.

The chlorophyll derivative phylloerythrin is apparently the major ultimate photosensitizer in hepatogenous photosensitization in ruminants (1, 2, 9), although other photoactive bile pigments may possibly be involved. Phylloerythrin is a normal metabolite of the anaerobic fermentation of chlorophyll in the rumen (text-fig. 4). Phylloerythrin is a potent photosensitizer, but because it is normally eliminated rapidly through the bile, it usually has no significant effects on the animal. In liver-damaged animals, however, phylloerythrin is not eliminated normally; it accumulates in the blood, and its occurrence in the peripheral circulation at levels as low as 0.1 μg/ml, in the presence of sunlight, is sufficient to induce photosensitization (14).

A number of agents are known to induce hepatogenous photosensitization in ruminants, on the basis of liver damage associated with photosensitivity, but the exact nature of the hepatotoxic chemicals is known in few cases. Two sources of such hepatotoxic chemicals are *Lantana* spp., which contain the hepatotoxins lantadene A and other closely related chemicals (15), and the fungus *Pithomyces chartarum*, a saprophyte of some forage plants, which contains the hepatotoxin sporidesmin (16) (text-fig. 5). It should be emphasized that chemicals such as the lantadenes and sporidesmins are hepatotoxic and not inherently photoactive.

Hepatogenous photosensitization in ruminants has been associated almost exclusively with the consumption of certain forage plants, but it seems probable that in some cases metabolites of fungi or other micro-organisms associated with these plants may be the actual hepatotoxic agents involved. The occurrence of hepatogenous photosensitization in livestock is often sporadic, unpredictable, and difficult to reproduce experimentally. Further, hepatogenous photosensitivity is sometimes associated with very palatable and important forage plants including alfalfa and Bermuda grass (8, 16). These observations strongly suggest that in such cases the hepatotoxins associated with photosensitivity may not be normal constituents of the plant species themselves.

Congenital Photosensitization

Photosensitization associated with inherited disorders of porphyrin metabolism in livestock is known but is of little economic or practical significance in livestock production. Congenital protoporphyria occurs in cattle and swine, and the syndrome as observed in cattle may have importance as a human model of the disease (17, 18). In congenital pro-
toporphyrinia, phototoxicity is caused by elevated levels of phototoxic protoporphyrin in blood, which result from genetic deficiencies in heme biosynthesis (text-fig. 6).

Poultry disorders known as “turkey blindness syndrome” and “light-induced avian glaucoma” may occur when birds are reared under continuous artificial light (19-21). The mechanisms involved in producing these disorders are apparently not clearly understood, but it seems doubtful that such disorders should be classified as congenital photosensitizations in the context considered here.

ECONOMIC CONSIDERATIONS

It is probably safe to say that photosensitization, when considered in the context of other livestock diseases and toxicities, is not a major economic problem in livestock production. Photosensitization tends to occur sporadically and infrequently and may affect only a limited number of animals within a given herd. Also, photosensitization does not usually result in mortality, thus rapid action on the part of the producer to remove affected animals from the source of the photosensitizing agent or to provide protection from sunlight often results in the animals’ rapid and complete recovery. This is not to imply, however, that livestock photosensitization is of no significant economic importance, for such is clearly not the case. Photosensitized animals, particularly those affected by hepaticogenous photosensitizers, can in fact be killed by the disease or by complications arising from it, and surviving animals may be permanently affected (with blindness, scarring, deformation) such that their market value is destroyed or greatly reduced. In addition, weight gains may be affected, milk production may be reduced, animals photosensitized on the udder and teats may refuse to nurse their young, and the stresses associated with photosensitization may result in abortions. Thus, in some instances, livestock photosensitization can and does have significant economic impact. The relatively widespread occurrence of “facial eczema” in New Zealand among dairy cattle grazing forage that contains P. chartarum is an example of a livestock photosensitization syndrome that has considerable local economic impact (16).

In contrast to the economic effects attributable to photosensitization in livestock, essentially no economic effects result from poultry phototoxicities because photosensitization in poultry is rare except under experimental conditions. I am aware of only one circumstance in which domestic poultry have suffered severe nonexperimental photosensitization, and that was in Israel among pasture-raised ducks and geese that grazed the psoralen-containing weed A. majus (22). The rarity of photosensitization in poultry is understandable in view of production practices in which dietary regimens are usually carefully regulated and because much of the poultry production worldwide is done indoors under relatively low-intensity artificial light. However, photosensitization of domestic poultry reared under less intensive practices, particularly among free ranging-birds, probably occurs periodically because of the widespread occurrence of photosensitizing agents in nature and because of the generally omnivorous dietary habits of many avian species.

RESEARCH NEEDS

Photosensitization is at present not a major economic problem in livestock production, except in localized situations, but it seems appropriate to continue to develop research data that will allow a more complete understanding of these disorders in livestock and poultry. Further studies aimed at defining the chemistry of livestock photosensitizing agents and their biochemical modes of action could lead to the development of more accurate procedures for predicting photosensitization and possibly even effective antidotes or prophylaxes. Because the expressions of photochemical toxicities in food animals and humans are often identical or very similar, studies in livestock reasonably may be expected to generate data applicable to a more complete understanding of certain photochemical disorders in humans.

Photoactive agents that interact with food animals are often extremely active biologically, certainly as photosensitizers but perhaps also through mechanisms not dependent on light. Therefore, it may be that some photosensitizing
chemicals have direct toxicologic significance for humans, if these chemicals or their metabolites are retained by edible tissues or are secreted into milk or eggs. Such possibilities have thus far not been evaluated by suitable research approaches, although appropriate residue and metabolism studies with selected photosensitizers in food animals would provide data of considerable value toward an assessment of the toxicologic significance of these chemicals to humans.

REFERENCES


DISCUSSION

Anonymous: I was requesting from the speaker knowledge of the exposure situation whereby livestock meet the phenothiazine molecule.

G. W. Ivie: Phenothiazine is an anthelmintic used to control intestinal parasites. Earl, is it given orally, by injection, or whatever? Do you know?

A. E. Johnson: Orally.

N. Towers: I want to make a comment about what Dr. M. Pathak said after the last talk. In Artemisia, the photosensitizing chemicals are polyacetylinic compounds and not furocoumarins. I thought I should make that statement, because the Compositae, which are the largest group of flowering plants, have this very large group of photosensitizers in them. These compounds have a totally different mechanism in terms of photosensitization in that they act on cell membranes rather than on the nucleic acids.

T. Nigra: This is a comment, perhaps about evolution, but nature seems to have provided for protection automatically, at least in terms of psoralens, when they are eaten. Herbivores are extremely difficult to photosensitize if you try to feed them drugs by mouth, whereas omnivores are much easier to sensitize, and the carnivores are easier yet.

I think it is very interesting that there seems to be some natural protective mechanism. If you look at serum levels of psoralen when you give the drug by mouth, the amount needed by mouth to produce phototoxic-inducing serum levels in the herbivores is markedly higher than the amount needed in the carnivores.