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The Metabolism Of African Trypanosomes In Relation To Pathogenic Mechanisms A Review

[1]a. Abubakar, [2]h. M Sabo, [2]a. Y. Onaolapo [3]s. S. Abdullahi, [3] H. M. Kabir , [4]l. O. Danladi.

[1]Nigerian Institute for Trypanosomiasis Research P.M.B. 2077, Kano state Liaison office,
[2]Department of Trypanosomiasis Research Kaduna P.M.B. 2077 Kaduna state.
[3]Vector and parasitological Department N.I.T.R Kaduna P.M.B. 2077 Kaduna state.
[4] Monitoring, Management, Information System Service Department N.I.T.R Kaduna P.M.B. 2077 Kaduna state.

Abstract: *The paper looked into pathogenesis which is complex and the cause of death is still somewhat obscure. Damage to the tissues is brought about through the metabolic activities of the trypanosomes, more certainly through the repeated insults offered by the emergence of successive trypanosome variants and the attempts made to suppress them by the hosts' defence mechanisms, It was suggested that so much glucose was consumed that the hosts' carbohydrate reserves became exhausted resulting in a breakdown of liver function and the onset of lethal hypoglycemia Feeding glucose to infected animals may prolong their lives for short periods but does not prevent the onset of terminal hypoglycemia. The major end-products of glucose breakdown by trypanosomes are pyruvate and glycerol, which are readily metabolized by the host to produce a considerable amount of energy. In the light of these and other facts, it was suggested that terminal hypoglycemia in trypanosomiasis is more likely to be due to a breakdown in hepatic or endocrine mechanisms controlling the mobilization of carbohydrate reserves than a direct result of the massive consumption of glucose by trypanosomes.*

Key word: *(pathogenic mechanisms, trypanosomes, metabolism)*

I. Introduction

Trypanosomosis is a disease caused by blood and tissue dwelling protozoan parasites of the genus Trypanosoma and transmitted by the tsetse fly Glossina. Animal trypanosomiasis is a disease complex caused by protozoa in the genus Trypanosoma which develops cyclically in the vector, the tsetse-fly. It is ranked the fourth most important disease of cattle in Nigeria The disease is highly endemic in many areas in the country trvpanosornes are insect borne and their epidemiology is determined by the ecology of their vectors, The parasites undergo part of their life cycle in tsetse fly and are mostly limited to Africa, Trypanosoma vivax, Trypanosoma congo, Trypanosoma brucei and Trypanosoma simiae are the four main species responsible for Africa trypanosomosis The metabolism of a parasite might affect its host in two ways: by depleting essential nutrients and/or producing toxic metabolites. The possibility that glucose consumption, pyruvate production, and the domination of the amino acids tyrosine and tryptophan might be important in the effects of African trypanosomiasis is examined in the light of recent work The disease in animals usually results in reduced reproduction and quality, low feed conversion ratio and possible death of animals, hence, affecting the farmer's overall profit. The pathogenic animal trypanosomes have had a major influence on livestock productivity in tropical Africa.

II. Methodology

The review is based on the information curled from internet and document and online published papers and workshops hold across the globe.

2.1 The Metabolism Of African Trypanosomiasis

In a recent discussion on the mechanisms of pathogenesis in African trypanosomiasis, (7) stated: "The pathogenesis is complex and the cause of death is still somewhat obscure. Damage to the tissues is brought about perhaps through the metabolic activities of the trypanosomes, more certainly through the repeated insults offered by the emergence of successive trypanosome variants and the attempts made to suppress them by the hosts' defence mechanisms." Clearly, the metabolic activity of a parasite might affect its host in two ways: by depleting essential nutrients and/or producing toxic metabolites. These two possibilities have been discussed in relation to trypanosomiasis for more than half a century, but we still lack firm evidence that either plays a key role in pathogenicity and in recent years attention has focused more on immunologic reactions and the release

(from host tissues or damaged parasites) of pharmacologically active substances than on the effects of trypanosome metabolism. Studies on the physiology and biochemistry of trypanosomes have tended to centre on carbohydrate metabolism and, in particular, on the changes in oxidative pathways associated with the developmental cycle of the T. brucel group (15). The story that emerged is too well known to warrant detailed discussion here: the difference in cyanide sensitivity between blood and culture forms, the development of a functional cytochrome system in the latter, the differences in the end products of glucose metabolism, and the presence of the glycerophosphate oxidase pathway in blood forms are all well documented and have been the subject of several excellent reviews (4) (28) (8). In terms of pathogenic mechanisms, these aspects of metabolism seem singularly unpromising because, to quote (7) once more, "none of the metabolites along the several pathways available are recognizable as dangerous poisons."

However, one of the earliest and for 30 years one of the most controversial, hypotheses on the cause of death in trypanosomiasis stemmed from the observation that the motility of trypanosomes in blood depends upon adequate supplies of glucose (20). It was suggested that so much glucose was consumed that the hosts' carbohydrate reserves became exhausted resulting in a breakdown of liver function and the onset of lethal hypoglycemia. This view was accepted by many workers, and evidence in support of it was published as recently as (28); however, as von Brand points out, this hypothesis is not easily reconciled with a number of observations: Blood sugar levels return to normal, even in fasting animals, after administration of trypanocidal drugs (19). Liver glycogen reserves, although lowered, are not eliminated in infected animals (14); (1). Feeding glucose to infected animals may prolong their lives for short periods but does not prevent the onset of terminal hypoglycemia. The major end-products of glucose breakdown by trypanosomes are pyruvate and glycerol, which are readily metabolized by the host to produce a considerable amount of energy. In the light of these and other facts, (28) suggested that terminal hypoglycemia in trypanosomiasis is more likely to be due to a breakdown in hepatic or endocrine mechanisms controlling the mobilization of carbohydrate reserves than a direct result of the massive consumption of glucose by trypanosomes. However, it may be premature to dismiss this metabolic activity of the parasites as being of no consequence to the host: (29) has suggested that the continual demand for glucose by the parasite in acute infections may result in decreased glucose metabolism in the hosts' peripheral tissues leading to a condition resembling diabetes mellitus. This idea merits further investigation. Another aspect of the high glucose consumption by bloodstream trypanosomes is the production of pyruvate and how it relates to pathogenesis. Although pyruvate is readily used by host tissues, it has been shown in laboratory infections to accumulate in the blood in amounts directly proportional to the numbers of parasites present (8), (2). High concentrations of pyruvate could lead to depletion of alkali reserves, acidosis, and a lowered affinity of hemoglobin for oxygen. (1) drew attention to the dark purple colour of blood in late stages of T. brucei infections, and (4) proposed that deficient oxygenation of hemoglobin coupled with mechanical blockage of the circulation leads to death by asphyxiation. (2), on the other hand, conclude that pyruvate does not reach a generally toxic level in the bloodstream. It must be stressed, however, that the T. brucei group, which are humoral rather than hematic parasites (13), may very well produce toxic levels of pyruvate at extravascular sites (5) using their elegant "hair-curler technique" have studied pyruvate levels in blood and tissue fluids ofT. brucei-infected rabbits and have found increases to five times the normal value. They suggest that the high concentrations of pyruvate in tissue fluid may be associated with the observed changes in the structure of connective tissues covering the subcutaneously implanted hair curlers. In control animals this connective tissue, which is composed mainly of collagen fibres, fibroblasts, and blood vessels, is smooth, well organized and free from lipid, whereas in T. brucei-infected animals it has a rough surface. Moreover, the fibroblasts in infected animals contain lipid droplets, cease to produce collagen fibres, and may become detached into the surrounding tissue fluid (6). Discussing these results, (7) points out that although fibroblasts normally produce and store lipids, they rarely exhibit large lipid droplets in cytoplasm (7). Fibroblasts cultured in the presence of excess fatty acids do accumulate such droplets. Thus, it seems possible that the high in vivo concentrations of pyruvate, which occur in T. brucei infections, produce a similar effect on fibroblasts and are responsible for, or at least contribute to, the degenerative changes observed in the connective tissues of infected rabbits. In considering this possibility, it is interesting to note that infections with hematic trypanosomes (T. con golense and T. vivax) are not characterized by extensive inflammatory, degenerativ, and necrotic changes and that these organisms do not produce as much pyruvate per mole of glucose metabolized as do T. brucei group trypanosomes. Compared with our knowledge of carbohydrate metabolism, we know relatively little about the metabolism of amino acids by hematozoic trypomastigotes. Tracer experiments have shown that alanine is the major amino acid produced from glucose by T. rhodesiense and T. gambiense (8); (10) (12). A number of other amino acids are also labeled (aspartate, glutamate, glycine, and serine), and there is 19 evidence that trypanosomes can interconvert some of them, but there is no estimate of the proportion of the total amino acid requirement for growth that is satisfied by de novo synthesis. Exogenous amino acids are known to enter trypanosomes by both diffusion and specific transport systems (13); (19), and there is evidence that blood forms of T. brucei are capable of ingesting and digesting proteins (11). Again, the relative importance of these

processes in satisfying the organism's requirements is unknown. It has been suggested (3) that the availability of ingestible proteins, amino acids, and other nutrients is an important factor in determining when, during an infection, tiypanosomes begin to develop in the cerebrospinal fluid (CSF). The parasites may have access to the CSF throughout an infection (17) but be unable to grow until it has been enriched by proteins and other nutrients from degenerating tissues. How much stress to the host's nitrogen metabolism results from the parasites' demand for amino acids is unknown. Serum and tissue fluid albumin levels faN steadily during the course of aT. brucei infection in rabbits, and levels of nonprotein nitrogen (particularly proline, alanine, creatinine, and urea) rise (5). A detailed study of free serum amino acids in voles (Microtus montanus) infected with T. gainbiense has also revealed major changes (16). In control animals, the majority of amino acids showed diurnal variation, levels being highest during the dark period: this pattern was not found in infected animals and the levels of 7 (threonine, serine, valine, isoleucine, leucine, tyrosine, and tryptophan) of 18 amino acids studied fell significantly below the levels in the controls. In agreement with (5) rabbit experiments, it was found that alanine and proline levels were markedly increased at certain stages of the infection. Of the amino acids that were reduced, tyrosine and tryptophan were most affected: tyrosine to about 50% of control levels and tryptophan to undetectable levels. The fall in tyrosine was predicted by (22) when they found elevated serum and hepatic tyrosine aminotransferase levels in T. gambienseinfected voles. They point out that tyrosine metabolism has seldom been investigated during a parasitic infection, although this amino acid is an important precursor of catecholamines. (7) drew attention to the fact that norepinephrine alleviates the shock that accompanies protozoal infections and suggested that catecholamine metabolism is defective in African trypanosomiasis: the work of (22) and (16) seems to support this idea given that in other mammalian systems a fall in serum tyrosine, relative to other neutral amino acids, restricts tyrosine transport across the blood-brain barrier and lowers derivative catecholamine pools in the brain (30). In keeping with these findings, Newport and Page have found a reduction of 32-457c in brain, liver, and skeletal muscle tyrosine in T. gambienseinfected voles. Speculating on the significance of these results, (22) suggest that a reduced brain tyrosine level accounts for some of the neurological syndromes occurring in T.gamhiense infections: it is known that depression of catecholamine biosynthesis results in changes in sleep or activity patterns (21), body temperature (23), glycogen, and lipid metabolism and possibly causes mental depression (21). Similarly, it is possible that the observed fall in serum tryptophan (15) could result in decreased synthesis of niacin and serotonin by the host, leading to a pellagra-like syndrome, changes in sleep patterns, and depression (24). There is increasing evidence that the accumulation of end-products of amino acid metabolism contributes to the characteristic pathology of African trypanosomiasis.

There is evidence that tryptophol can cause sleep, convulsions, and death by respiratory depression when injected into mice, rats, and cats (18), and it has been suggested that trypanosomes in extravascular sites of the central nervous system produce sufficient quantities of this indole to produce similar effects. Tryptophol has also been reported to cause immunodepression in laboratory rodents (27) and may contribute to it in humans and other animals. It is thought that tryptophol acts on cell membranes, perhaps by combining with the outer lipid bilayer (25), and in support of this, recent work (26) has shown that tryptophol rapidly lyses red blood cells. Similar action on synaptic membranes may cause changes in the transmission of nerve impulses, give rise to behavioural changes, and induce a sleep-like or comatose state. An essential step in testing the hypothesis that tryptophol produced by trypanosomes is important is the determination of in vivo levels of the metabolite during infection and the correlation of these with the various states observed. This work is in progress in Seed's laboratory. As a first step, (25) have estimated from in vitro measurements that a minimum of 3.2 mg tryptophol/kg body weight could be formed in an infected mouse. This level is, they believe, compatible with their hypothesis, which is further supported by the finding that levels of indole lactate and indole acetate in the urine of trypanosomeinfected mice are about three times those found in control animals. It is not yet possible to say from any of this work that tryptophol or other metabolites of aromatic amino acids are responsible for the abnormal behavioural and/or pathological changes observed in infected animals, but the investigations by Seed and his collaborators have opened up a whole new area of research that may lead to an explanation of at least one aspect of African trypanosomiasis. Mental disturbances are often found (80-95%) in chronic human infections (13); histological studies have thrown no light on their cause, and the behavioural syndromes of the disease remain a clinical mystery. Perhaps the answer will come from detailed studies of trypanosome metabolism and investigation of the pharmacological activity of the metabolites they produce.

III. Result And Discussion

Understanding the trypanosome organism is the first step in developing measures to control it. Its structure, surface coat, locomotion, secretions, attachment mechanisms, and ability to modify its surface coat all contribute to the pathogenesis of trypanosomiasis. What is known about the organism is little in comparison with what is unknown. For instance, whether or not there are differences in ultra structures between drug-sensitive and drug-resistant lines of trypanosomes is not clear. To date, no differences have been reported. Studies of certain forms, such as metacyclics, are hindered by the difficulty in obtaining them. Investigators

collecting metacyclics, however, have found that the female tsetse fly produces up to three times as much infected saliva as the male because of her larger salivary glands. Even the mode of attachment is not completely clear; if the flagellum plays a part in the trypanosome's attachment then it is likely that T. con golense attaches in the same way to the proboscis of Glossina as it does to small calibre blood vessels. Although the idea that plasmanemes ("filopodia') from bloodstream trypanosomes attach to red blood cells and blood vessel endothelium is attractive because it would explain the generation of antigenantibody complexes, there is no good evidence for the production of plasmanemes in vivo much less their adhesion to host cells. Recently the organism's secretions have received attention. They appear to activate the host's complement system and pharmacologically active substances, such as serotonin and kinins. Although the acid phosphatase secreted by trypanosomes may have a pathogenic effect on the host, it appears simply a convenient lysosome marker enzyme, less important than other enzymes in the pathogenesis of trypanosomiasis. There is some evidence that T. cruzi produces catecholamines; however, there is little evidence implicating catecholamines in T. brucei pathogenesis. In rats infected with the former, there is complete depletion of norepinephrine whereas the latter is associated with only slight depletion of heart norepinephrine. Surface Coat and Antigenic Variation The nature of the trypanosome's surface coat and the ability to change the antigenic character of this coat are intriguing problems to scientists studying the organism.

The surface coat appears to be a single glycoprotein; according to Cross and Johnson, the carbohydrate is predominantly located near the C-terminus of the polypeptide chain. Cross believes that carbohydrate contributes little to cross-reactions between different antigenic types; however the results of (4) tell a different story. The cross-reactions reported by (4) are of considerable interest but as yet are not refined enough to be applicable to trypanosomiasis control programs. Experiments in mice and goats so far have not been successful in demonstrating cross-protection between variants. The carbohydrate may be involved in attaching the glycoprotein to the surface of the cell, possibly through a glycolipid receptor in the membrane. The trypanosome is capable of replacing a surface coat that has been artificially removed, e.g., by capping. Within 3 hours, a new antigen of the same type as was removed appears on the surface. The renewal is not affected by inhibitors of protein synthesis; therefore, the antigen may come from an internal store. How relevant capping studies are to the antibody actions in vivo is questionable. One mystery of antigenic variation is the number of antigens that can be expressed by a single trypanosome. One study has shown that at least 101 variable antigen types were produced by a clone of T. equiperdum. (23) suggests that the type is determined by the relative rates of transcription of different mRNAs; and another possibility is that differential translation rates account for the variable antigen type expressed. The host species, which affects the parasitemic profile of the trypanosome, does not seem to affect its repertoire of antigens, although there is little information on this (24) showed a similar antigen sequence in rabbits and goats and is supported by the report of (25)

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