combustion of fat is forced by the failure of combustion of other fuel.

Other methods of oxidation have been claimed and some of these appear to be promising. Simultaneous oxidation at both ends of the chain as claimed by Verkade (23) is somewhat doubted as a general mechanism by Flaschenträger and Bernhard (24). Simultaneous oxidation at various points in the chain as suggested by Smedley-MacLean and Pearce (25) and Jowett and Quastel (26) seems probable under certain conditions. According to Flaschenträger and Bernhard, β-oxidation is possible only with the free COOH group and the purpose of ω-oxidation is to furnish COOH groups where these are lacking, e.g., when the fatty acid carboxyl is combined as it is in neutral fat. However, dicarboxylic acids are difficult to oxidize, the β-oxidations on the two ends interfering with each other. Protecting one carboxyl by an ester or amide group results in almost complete (90%+) disappearance. Quantitatively this ω-oxidation is not very important. Even with the 9 and 10 acids which yield the most, the excretion of dibasic acids in the urine is not over 2-3 per cent.

Deuel and associates (27) bring evidence to show that caprylic, capric, lauric and myristic acids give more than double the acetone body excretion when fed to rats as the lower fatty acids. Palmitic and stearic acids yield three of these fragments while odd-numbered acids give none.

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The Functions Of The Phospholipids In The Animal Body

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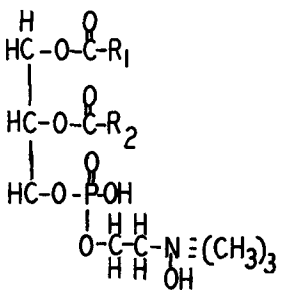
Abstract

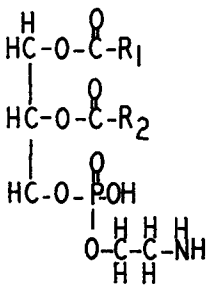
This paper deals with the bearing of some of the recent information on the three proposed functions of the phospholipids: that they are intermediary metabolites in fat metabolism; that they serve as an oxidation-reduction system; and that they are essential elements in cell structure. The rapid turnover of phospholipids in intestinal mucosa, liver and blood plasma indicates an active part in fat metabolism. The slow turnover in other tissues, notably skeletal muscle, points to a non-metabolic function. The amount of phospholipid present in various skeletal muscles is shown to be a function of the relative extent to which they are used. The adaptation seems to be a slow process since forced activity of a muscle produces a comparatively slight increase in phospholipid content.

Introduction

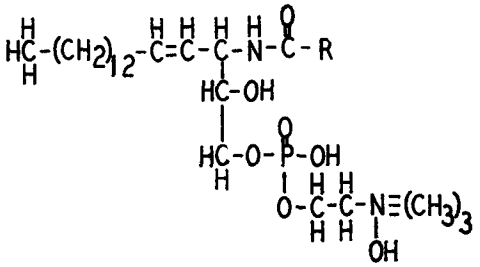
Before proceeding with a discussion of the functions of the phospholipids in the animal body, it is perhaps advisable to review very briefly their chemical nature. At the present time, three distinct types of phospholipids, the lecithins, the cephalins and the sphingomyelins, are recognized as occurring in mammals on which, thus far, most of the work has been done. The general formulae are as follows:



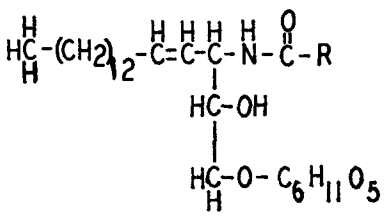
Lecithins



Cephalins



Sphingomyelins



Cerebrosides

Each type of phospholipid is made up of a considerable number of individuals which differ from one another in the nature and relative position of the fatty acid molecules occupying the positions indicated by R in the general formulae. In the case of the lecithins and cephalins, the phosphoric acid molecule may be attached to either the α- or β-carbon of the glycerol, so that *two* lecithins (and two cephalins) containing the same two fatty acids may exist.

The sphingomyelins are related to the lecithins and cephalins on the one hand and to the cerebrosides on the other. To make this clear, the general formula for the cerebrosides has been included above. Unfortunately very little is known at present as to the function or functions of the sphingomyelins in the body. The fact that they are most plentiful in the myelin sheaths of the nerve fibers suggests that, together with the cerebrosides and cholesterol, they contribute to the insulating property of myelin, if such, indeed, is its purpose.

It is evident from the general formulae that the lecithins and cephalins are structurally related to the neutral fats. If one neglects for the moment differences in the nature of the fatty acids isolated from the phospholipids and the triglycerides, one can readily imagine that the phospholipids are derived from the neutral fats by the substitution of the phosphoric acid-base complex for one of the fatty acid molecules. It was this seemingly simple inter-relationship together with the fact that the phospholipids, in sharp contrast to the neutral fats, are miscible with water that led to the suggestion, many years ago,[1] that the phospholipids (at that time called the lecithins) are a machine for the transport and burning of the fatty acids in the animal body. This I shall refer to as the *metabolic* function of the phospholipids.

In the course of time, the results of numerous studies led to considerable doubt in the minds of many concerning the correctness, or at least the sufficiency, of the view that the phospholipids in tissues are intermediates in fat metabolism. It was consistently observed that the fatty acids in the tissue phospholipids are considerably more unsaturated than those of either the stored or the food fat. Although Leathes,[2] to the satisfaction of many, interpreted this as evidence that the fatty acids, before or while they were combined as phospholipids, are desaturated as a primary step in their combustion, the idea persisted that the large number of double bonds in tissue phospholipids serve as a mechanism for alternately combining with and handing on oxygen within the cells. This may be called the *oxidase* function of the phospholipids.

Contrary to what one would be inclined to expect of an intermediary metabolite, it was observed that the amount of phospholipid in the various organs of the body, with the exception of the blood plasma and the liver, remains essentially constant regardless of the nutritional state of the animal. In this respect the phospholipids behave as if they were an essential component of the cell, an element in their structural make-up. This evidence, together with the observation that the ability of certain substances to penetrate into living cells is a function of their solubility in organic solvents, thus suggesting that the permeability of the cell to these substances is governed by the presence of lipids in the cell membrane, has led to the view that the phospholipids are essential structural elements of the cell. This may be called the *structural* function of the phospholipids.

Let us now review some of the more recent evidence bearing on this question of the function of the phospholipids.

The Rate of Turnover of Tissue Phospholipid

If the phospholipids of any given organ are involved as intermediary products in the metabolism of fatty acids in that organ, it is evident that the fatty acids which are present in the phospholipids at any one time must have come either from ingested fat or synthesized fat. By feeding a high fat diet, the synthesis of fat in the body can probably be reduced to negligible quantities. Now, since the amount of phospholipid even in the entire body of an animal is less than the customary fat intake, the passage of large amounts of fat through the stage of phospholipid in those organs which are most actively burning fatty acids must involve a very rapid turnover of phospholipid in those organs. On the other hand, if the phospholipids of those actively metabolizing organs are *not* involved as intermediaries in fat metabolism, then the rate of turnover of phospholipid can be expected to be comparatively slow, since it will presumably be a consequence of wear and tear. The measurement of the rate of turnover of phospholipid ought therefore to provide direct evidence as to whether they have a metabolic or a non-metabolic function.

Until comparatively recent times, the only means of approach to the study of changes in tissue phospholipids has been to determine the amount present in any given organ and to observe whether or not that amount was affected by various experimental conditions. It has already been stated that this line of attack led to the indication that the amount of phospholipid in a tissue is rather constant. The inference was that the nature of the phospholipid was also constant. It is evident, however, that such an inference is entirely unjustified. One can obtain no information as to the rate or volume of flow of water in a river by measuring its level. Neither can one get any idea as to the rate of flow of phospholipid through an organ by measuring the amount present from time to time. Obviously, to measure the rate of turnover of phospholipid we must use some means of labelling the phospholipid in some way and then measure the rate at which this labeled phospholipid appears in and disappears from the organ being studied.

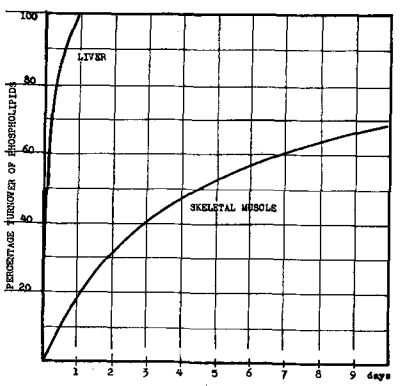
The first attempt to measure the rate of turnover of tissue phospholipid by following the rate of change in its composition involved the use of the degree of unsaturation of the constituent fatty acids as a label. By this method it was shown that the phospholipids of the intestinal mucosa undergo a rapid turnover during fat absorption.[3] In the case of skeletal muscle, the results indicated a comparatively slow turnover.[4] However, these results were complicated by the finding that phospholipids in muscle and other organs appear to select and retain highly unsaturated fatty acids in preference to those of lower degree of unsaturation. The mechanism and the purpose of this selection has not yet been explained. Also we are still without an adequate explanation for the fact that, in general, the phospholipids contain large amounts of fatty acids, not only of higher degree of unsaturation, but of greater molecular weight than those found in the stored or food fat of the animal.

A few years later, iodized fatty acids were used as a means of labelling ingested fat in order to trace

fatty acids through the stage of tissue phospholipid and to measure the rate of turnover of the latter. While this method did demonstrate beyond doubt that food fatty acids do enter into the phospholipids of intestinal mucosa,[5] liver, and blood,[6] the amounts found were so small, except in the case of intestinal mucosa, that it was difficult to draw any conclusions as to the metabolic or non-metabolic function of the phospholipids.

A few years ago elaidic acid, the stereoisomer of oleic acid, was introduced as a means of labelling tissue phospholipids and measuring their rate of turnover. At about the same time deuterium was introduced by Schoenheimer and Rittenberg as a general method of labelling fatty acid molecules. However, to date, the only use made of deuterium in the study of phospholipid metabolism has been to confirm the fact that ingested fatty acids do enter into the phospholipids of the liver.[7]

By the use of elaidic acid as a label, it has been possible to demonstrate clearly that the phospholipids of the intestinal mucosa,[8] the blood plasma,[9] and the liver [10] undergo a rapid turnover during the process of fat absorption. In the skeletal muscles (Fig. 1), the



Rate of turnover of phospholipids as measured by the rate of uptake of elaidic acid.

FIGURE 1.

brain[11] and red blood cells,[9] the organs, in addition to those above, which were studied most extensively, the phospholipids show a comparatively slow rate of turnover. Such results as have been obtained indicate that there is also a slow rate of turnover of phospholipid in heart, kidneys, and smooth muscle. Recently it has been shown by means of the elaidic acid method, that the phospholipids in rat sarcoma show a comparatively slow rate of turnover.[12]

On the basis of these results, the conclusion appears justified that certain organs of the body contain metabolic phospholipid while others contain very little if any, practically all being non-metabolic in function. In the case of the intestinal mucosa, though the evidence is quite clear that there is a rapid and extensive turnover, the correct interpretation of that turnover is not yet settled.[8] It may mean that phospholipid is acting as an intermediary stage in the resynthesis of fat in the epithelial cells, or that phospholipid, during fat absorption, is continuously being synthesized in the mucosa and is passing into the blood both directly and by way of the thoracic lymph. In the case of the blood plasma, there appears to be no reason to doubt that part, at least, of the phospholipid consists of material which has been synthesized out of recently absorbed fatty acids and is being carried to the actively metabolizing tissues where it is burned. It appears likely that most of this metabolic phospholipid that is being transported in the blood is burned in the skeletal muscles. But since the phospholipid of the muscles shows a slow turnover, the metabolic phospholipid which has diffused in from the bloodstream is apparently burned as rapidly as it enters and thus never contributes appreciably to the total phospholipid present in the muscle.

The site of synthesis of the metabolic phospholipid of the blood plasma is still not clear. It may be the intestinal mucosa; it may be the liver; or it may be both. It seems hardly likely that it is neither.

The nature of the metabolic phospholipid is obviously of considerable interest and importance. Does it consist of lecithins, of cephalins, or both? It has been suggested that the metabolic phospholipids are probably of the lecithin type,[13] largely on the basis of the observation that blood plasma contains much more lecithin than cephalin while the red cells, which contain only non-metabolic phospholipid, contain more cephalin than lecithin. Even if this is correct, it would probably not be correct to say that all lecithins have a metabolic function, since brain and muscles, which do not appear to contain metabolic phospholipid, do contain lecithins. A preliminary study has been made of the distribution of elaidic acid between lecithins and cephalins. Provided the alcohol precipitation method gave a reasonably good separation, it can be said that, within the limits of error of the method, the percentage of elaidic acid was the same in the lecithins and cephalins.[14]

Quite recently, the radioactive isotope of phosphorus P^{32} has been used to study the rate of turnover of tissue phospholipids.[15] This is obviously of great importance since it measures the rate of turnover of the phosphoric acid in the phospholipids whereas other methods to date have measured the turnover of fatty acids. The results are

TABLE I

Comparative Turnover of Phospholipids of Various Organs in 9-hour period after Feeding Radioactive Phosphate.

(Artom et al., Arch. intern. Physiol. 45, 32, 1937.)

Organ	Per gram fresh tissue P (mg)	Radioactive P (Units)	Specific Activity
Liver	1.633	9.85	6.03
Intestine ...	0.916	9.55	10.40
Kidneys ...	1.170	3.40	2.90
Spleen	0.810	0.55	0.70
Heart	1.045	0.11	0.12
Muscles ...	0.495	0.05	0.10
Red cells ..	0.103	0.00	0.0
Plasma	0.026	0.04	1.50

shown in Table I. Two facts are especially noteworthy. One is that the rate of turnover of the phospholipids in liver and intestinal mucosa is very rapid. This agrees with the results with elaidic acid and iodized fatty acids and thus indicates that the entire molecule either is being broken down and reformed or is disappearing and is being replaced by synthesis. The other very significant fact is that the rate of turnover of muscle phospholipid is found to be slow, also in agreement with the conclusions arrived at by means of elaidic acid. Contrary to results with the elaidic acid method, the data in Table I indicate that kidney phospholipids undergo a rapid turnover. The explanation of this apparent contradiction must await further work by both procedures.

If, as appears almost certain, the phospholipids of the skeletal muscles, and the red blood cells—to cite only those tissues which have been extensively studied—have a slow turnover and therefore do not participate as intermediaries in fat metabolism, what function do they fulfill? Are they solely of importance to the structural make-up of these tissues? Or do they as well participate in cell metabolism by acting as oxygen transport agents?

The Oxidase Function of the Phospholipids

Satisfactory proof of the ability of phospholipid to act as an oxygen transport agent involves, in the first place, evidence that it will take up oxygen and then give it up to some

readily oxidized substance, under conditions which simulate those existing in the living cell. That phospholipid will add oxygen at its double bonds when exposed to air has been known for many years. Recently it has been shown that this uptake of oxygen is very rapid in the presence of reduced glutathione at pH 3.5, amounting to 76 per cent of the theoretical uptake—based on iodine number—in 6 hours.[16] The question is: Is this oxidation of phospholipid readily reversible? There is some evidence to indicate that it is. If previously oxidized phospholipid is added to reduced methylene blue kept under anaerobic conditions, the methylene blue is reoxidized considerably more rapidly than in control tubes without phospholipid.[17] However, this evidence can scarcely be regarded as more than suggestive that phospholipid may indeed act as an oxygen transport agent.

The Significance of the Amount of Phospholipid

On the basis of the extensive work of Mayer and his coworkers, it had been quite generally believed until recently that the percentage amount of phospholipid in any one organ is essentially the same from one individual of the same species to another and furthermore is unaffected by over-feeding and prolonged fasting. Only extreme conditions causing violent changes in the temperature and energy production of the animals were capable of altering the phospholipid content, and this applied only to certain organs of the body.[18] It was observed also that the phospholipid content of any single type of organ tended to be substantially the same, regardless of the species of the animal. The suggestion was made that the phospholipid content of a tissue is a characteristic of that type of tissue just as the histological structure is characteristic.

In the light of more recent and more extensive investigations, it now appears that these generalizations were too sweeping and, in certain cases, incorrect. In the case of the liver, for instance, there is abundant evidence that the amount of phospholipid present can be increased very considerably by feeding a large meal of fat.[10, 19] This increase in liver phospholipid, like the increase in plasma phospholipid during alimentary hyperlipemia, is in all probability due to the accumulation of newly formed metabolic phospholipid.

Several years ago, in the course of a comprehensive study of lipid composition of various organs, Bloor observed that the phospholipid content of the beef muscle differed considerably from one type of muscle to another. Heart muscle was comparatively rich in phospholipid, jaw muscle was high, and the leg muscles were very poor in phospholipid.[20] It was noticed that those muscles which were most active in the beef had the highest phospholipid content. In keeping with older work, it was observed that the continuously active organs such as brain, liver and kidney, were comparatively rich in phospholipid. These findings were interpreted as evidence that the phospholipid content of an organ is a function of its physiological activity. A shift in the activity of any given organ ought therefore to be accompanied by a parallel shift in its phospholipid content.

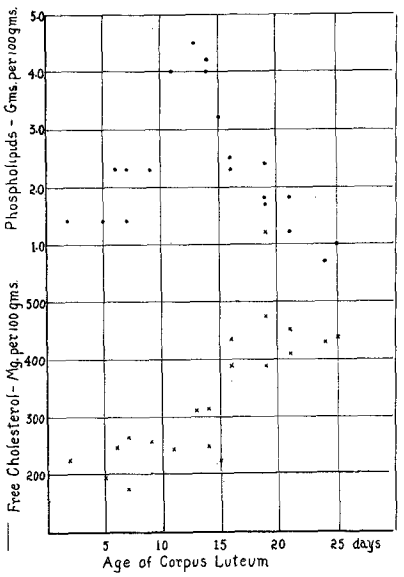


FIGURE 2.

One of the earliest and most striking pieces of evidence in apparent confirmation of this relationship was the finding that the phospholipid content of the corpus luteum of the sow increases several fold in the course of a few days (Fig. 2).[21] If implantation of the ovum occurs, the corpus luteum remains functionally active and its phospholipid content remains high. If on the other hand, pregnancy does not ensue, the corpus luteum retrogresses. Chemically, the retrogression is characterized by a decrease in the phospholipid content and relative increase in cholesterol esters. It is noteworthy that the peak of the phospholipid content of the corpus luteum has been shown to coincide with the peak of progesterone content.[22]

In the white blood cells as well, the amount of phospholipid has been shown to undergo a pronounced increase in humans following operation and in the course of an infection. In some instances this increase in phospholipid content failed to occur and it was observed that these patients either did not recover or experienced a more prolonged convalescence. It has been suggested, therefore, that the defence mechanism of the body involves not only a mobilization of more white cells but an increase in their phospholipid (and cholesterol content), thereby improving their functional capacity to overcome the infection.[23, 24] It is noteworthy that the polymorphonuclear leucocytes have a higher phospholipid content than lymphocytes.[25] Therefore, a relatively greater increase in the polymorphonuclear cells would lead to an apparent increase in the phospholipid content of the white cells as a whole. However, the increase which occurs during infections can not be explained in this way.[26]

In order to simplify and make more definite the apparent functional relationship between the activity of a cell and its phospholipid content, an extensive study has been made of the comparative phospholid content of the same muscle or group of muscle in animals, which, under natural conditions, use it to markedly different extent.[27] Some of the results are shown in Table II, (Page 74). The differences are very striking. In the case of the pectoralis major, for instance, the phospholipid content is high when as in pigeons, the muscle is used almost continuously in flying, and is much lower when, as in the rooster, the muscle is used very little. Similarly, the same muscles in tame rabbits which lead a relatively sedentary life have a much lower content of phospholipid than in wild rabbits.

The question naturally arises: How is this change in phospholipid content brought about? Is it a compensatory response to a strain on the capacity of the muscle to meet the demands placed on it? In other words, is it an acute change in the chemical composition of an intact cell to fit the cell for increased functional activity? Or is it a progressive and long-continued

TABLE II
Phospholipid Content and Activity in Muscle
(Bloor and Snider, J.B.C. 107, 459, 1934)

Muscle	Phospholipid fatty acids Pigeon	Owl	Rooster	Cholesterol Pigeon	Owl	Rooster
	(per cent of dry weight)					
Pectoralis major	4.7	3.7	1.4	0.25	0.26	0.17
P. minor	2.1	1.9	1.1	0.18	0.28	0.18
	Wild Rabbit	Tame Rabbit		Wild Rabbit	Tame Rabbit	
Heart	5.2	6.1		0.45	0.57	
Jaw	3.2	3.8		0.36	0.38	
Diaphragm	3.2	3.0		0.29	0.47	
Front leg	3.1	2.0		0.27	0.32	
Thigh	2.9	1.6		0.25	0.15	
Abdominal wall	2.5	1.3		0.24	0.24	
Back	2.4	1.2		0.22	0.26	
Gastrocnemius	2.1	1.7		0.22	0.25	

adaptation brought about only in the course of evolution?

In an effort to answer this question, Bloor has studied the effect of enforced activity on the phospholipid content of various muscles of the white rat and of pigeons.[28] The muscles of exercised animals were compared with those limited to as little activity as possible. The average results are shown in Table III in which the phospholipid and

TABLE III
Changes in Lipid Content of Muscles of Exercised Rats
(Values for muscles of resting controls = 100)

Muscle	Weight	Phospholipid	Cholesterol
	per cent body weight	per cent dry weight	per cent dry weight
Heart	117	115	113
Neck	121	102	96
Diaphragm	139	86	83
Thigh	113	104	93
Front leg	116	116	107
Abdominal wall	108	106	108
Gastrocnemius	121	114	112
Back	118	112	105
Pectoralis	109	109	100

cholesterol contents of the muscles of the exercised animals have been expressed as percentages of the corresponding values in the unexercised controls. The average differences are, in general, quite small, especially when compared with those, for instance, between tame and wild rabbits. Apparently, the much greater differences found between muscles of widely different *natural* activity are the result of a progressive adaptation. Indeed, the differences in the rats, taken muscle by muscle, are not statistically significant. There is, however, an unmistakable tendency towards higher values in the exercised muscles.

Included in the table are the comparative average weights of the various muscles in the two groups. Hypertrophy of the muscle in response to exercise has occurred in every instance and, in general, is more pronounced than the increase in the phospholipid content. It is noteworthy that the diaphragm showed, on the one hand, the greatest average hypertrophy and, on the other hand, a decrease in the phospholipid and cholesterol contents. Obviously the relationship between the activity of a tissue and its phospholipid content is not a simple and direct one. Bloor has suggested that a tissue may respond to an increased demand on it in either or both of two ways: by increase in the mass of functioning tissue, i.e., hypertrophy; and by improvement in its chemical make-up—specifically, by increasing the phospholipid and cholesterol content, especially the former.

The inconsistency of the response of various muscles to increased activity perhaps offers the best clue to the failure of other workers to find any increase in the phospholipid content of the hearts and kidneys of rats when the load on these organs was increased by feeding a high protein diet.[29] In this instance, pure hypertrophy was the only discernible change.

Granted, at least for the purpose of discussion, that an increase in the phospholipid content of a muscle does take place in response to increased activity of the muscle, the question arises: What is the mechanism of that increase? No satisfactory answer seems possible at the present time. However, it would appear to be highly significant that, in rats, the feeding of thyroid causes a definite increase in the phospholipid content of the muscles and, in mice, a 40 per cent increase in the phospholipid content of the entire animal.[30]

Our concern at present is with the functional significance of the high phospholipid content of the naturally more continuously active muscles as compared with less active muscles. One's natural inclination would be to interpret a higher level of phospholipid in a muscle as an increased reserve of fuel to supply energy for muscular contraction. But, in the face of the rather definite evidence that muscle does not contain appreciable amounts of metabolic phospholipid, this explanation would appear to be incorrect. It is possible, of course, that the *increase* in phospholipid above the normal level is due to metabolic phospholipid, but the evidence available at present is against it. Further work is needed to settle the point. If it is not metabolic phospholipid, then the only apparent alternatives are that it is either an adjustment of the structural composition of muscle substance, possibly to facilitate, by physical means, an increased transport of fat into the cells, or an increase in the ability of phospholipid to act as an oxygen transport system. It is possible, of course, that both are correct. In any case, the evidence that the phospholipid content of a tissue cell is in some manner related to its activity does not help much in arriving at an answer to the question: What is the function of non-metabolic phospholipid?

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