PATHWAYS OF FATTY ACIDS INTO MITOCHONDRIA

Qodirov Rahmatillo Shakirovich
Senior teacher of the Department of Biological Chemistry,
Andijan State Medical Institute

ABSTRAKT: Fatty acids in fish can arise from two sources: synthesis de novo from non-lipid carbon sources within the animal, or directly from dietary lipid. Acetyl-CoA derived mainly from protein can be converted to saturated fatty acids via the combined action of acetyl-CoA carboxylase and fatty acid synthetase. The actual rate of fatty acid synthesis de novo is inversely related to the level of lipid in the diet. Freshwater fish can desaturate endogenously-synthesized fatty acids to monounsaturated fatty acids via a A9 desaturase but lack the necessary enzymes for complete de novo synthesis of polyunsaturated fatty acids which must therefore be obtained preformed from the diet. Most freshwater fish species can desaturate and elongate 18:2(n-6) and 18:3(n-3) to their C20 and C22 homologues but the pathways involved remain ill-defined. Cyclooxygenase and lipoxygenase enzymes can convert C20 polyunsaturated fatty acids to a variety of eicosanoid products. The dietary ratio of (n-3) to (n-6) polyunsaturated fatty acids influences the pattern of eicosanoids formed. The ß-oxidation of fatty acids can occur in both mitochondria and peroxisomes but mitochondrial ß-oxidation is quantitatively more important and can utilise a wide range of fatty acid substrates.

KEY WORDS: Fish: Carp: Lipid metabolism: Polyunsaturated fatty acids

Although all the fatty acids which are present in the lipids of fish tissues can arise directly from the diet, some saturated and monounsaturated fatty acids can also be synthesised de novo from non-lipid precursors within the fish itself. Regardless of whether they are assimilated from the diet or formed endogenously, fatty acids can be subjected to various processes within the fish as outlined in Fig. 1. They can, for example, be esterified into phospholipids, the structural lipid of biomembranes, or, alternatively they might be incorporated into triacylglycerols, the netural reserve lipid. The degradation of fatty acids via ß-oxidation can also be

used for the provision of energy. In addition, fatty acids can also be subjected to various modification processes such as reduction to fatty alchohols, elongation to longer chain fatty acids or the insertion of additional double bonds via the process of desaturation. Polyunsaturated fatty acids can also be converted to eicosanoids. All of the foregoing are possible metabolic fates of fatty acids in fish. Space does not permit a detailed description of all the above processes and for this reason they are only outlined in the following pages with emphasis on the current state of knowledge. The article concentrates on the processes occurring within fish and does not consider the digestion and absorption of fatty acids from dietary lipid. Details of the digestion and absorption of dietary fatty acids along with their transport in plasma can be found elsewhere (Henderson and Tocher, 1987; Sargent et ah, 1989).

The basic pathways involved in synthesising fatty acids from non-lipid precursors in fish are believed to resemble those occurring in animals in general. Thus, a two carbon acetyl-CoA unit is carboxylated to malonyl-CoA which is then converted to fatty acids by the fatty acid synthetase complex via a series of condensation and reduction reactions involving the utilisation of NADPH (Gurr and Harwood, 1991). Although glucose from carbohydrate can be used as a carbon source for fatty acid synthesis in animals, in the case offish the high protein content of the diet means that amino acids derived from protein are usually the main carbon source (Walton and Cowey, 1982; Henderson and Sargent, 1981). Carbon derived from amino acids is incorporated eventually into citrate, an intermediate of the TCA cycle, within the mitochondrion (Fig. 2). Citrate can leave the mitochondrion and enter the cytosol where it is cleaved to oxaloacetate and acetyl-CoA by the enzyme ATP citrate lyase. AcetylCoA so produced is then available as a substrate for the enzyme acetylCoA carboxylase, the first specific enzyme in fatty acid synthesis. As its name suggests, acetyl-CoA carboxylase carboxylates acetyl-CoA to form malonyl CoA which is then utilised by the fatty synthetase complex to produce fatty acids. Reducing power in the form of NADPH produced

by the enzymes of the pentose phosphate pathway, NADP-malate dehydrogenase (malic enzyme) and NADP-isocitrate dehydrogenase, is consumed during fatty acid synthesis The only species of freshwater fish from which acetyl CoA carboxylase has been isolated is the rainbow trout (McKim et al., 1989). In this species, the enzyme is located in the cytosol of liver cells and is composed of several subunits, the MW of each subunit being 230,000 daltons. Each subunit contains biotin and, because of this, binds avidin strongly. The enzyme is activated by citrate which causes the subunits to aggregate into their active polymeric form and it is inhibited by NaCl. These properties are also characteristic of the same enzyme in warm blooded animals such as the rat and, overall, it would appear that this first enzyme specifically involved in fatty acid synthesis is very similar in fish to that in mammals. In comparaison with the situation in mammals and microorganisms fatty acid synthetase has not been well studied in fish and has never been isolated from freshwater fish. When the cytosol fraction of liver cells from the trout and carp was incubated with radiolabelled acetate most of the radioactivity recovered in fatty acids was located in 14:0 and 16:0 with much smaller amounts present in 10:0, 12:0, 18:0 and 20:0 (Eberhagen et al., 1969). The purified fatty acid synthetase from the plaice, a marine species, is known to produce only 16:0 and 18:0 (Wilson and Williamson, 1970). Overall, the products of the fatty acid synthetase in fish would therefore appear to be saturated fatty acids with chain length between 12 and 18 carbons. This is very similar to what is produced by mammalian and microbial fatty acid synthetases and freshwater fish seem to resemble mammals in terms of the products of the fatty acid synthetase system. The rate of fatty acid synthesis in fish is influenced by the diet. This point has been demonstrated in studies in vivo with coho salmon maintained in freshwater in which the incorporation of tritiated water into fatty acids (a measure of total fatty acid synthesis independent of carbon source) was examined in relation to the composition The results of these measurements of fatty acid synthesis are consistent with the conclusion that fish only make fatty acids de novo from non-lipid precursors to a limited extent when preformed fatty acids are

abundant in the diet and, conversely, that the rate of endogenous fatty acid synthesis is increased when the diet contains very low levels of fatty acids. Such results also demonstrate that during starvation when all dietary components are low, the rate of fatty acid synthesis is also low. The capacities of all the various tissues in fish for the synthesis of fatty acids have not been assessed. It is known, however, that in the rainbow trout the liver, adipose tissue and ovary are all capable of making fatty acids de novo (Henderson and Sargent, 1981; Lin et al., 1977a, b; Weigand and Idler, 1982). On the basis of the rates of fatty acid synthesis measured for these tissues in vitro, it can be calculated that on a whole body basis the liver is the principal site of fatty acid synthesis de novo (Henderson and Sargent, 1981; Lin et al., 1977 a, b). Following their synthesis in the liver, fatty acids can be transported to the extrahepatic tissues (for review see Sheridan, 1988). This situation is likely to be true of all freshwater fish although this remains to be verified.

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