I. BACKGROUND

Docosahexaenoic acid (22:6n3) is one of the two principal n-3 fatty acids in fish oils. In nervous tissues, there is little or no 18:3n3 or 20:5n3 and 22:6n3 predominates as not only the main n-3 fatty acid but also as the principal polyunsaturate (PUFA) since it occurs at a higher concentration than arachidonic acid (20:4n6) [1]. This acid is particularly concentrated in the aminophospholipids of neuronal membranes such as the synaptosomal plasma membrane and synaptic vesicles and in several phospholipids in retinal membranes such as the rod outer segment [2]. For this reason, many have speculated that there is a crucial function that this polyunsaturate subserves in neurons and retinal cells in particular. This notion has been supported by a variety of studies that have suggested a functional deficit in an organ system after an n-3 deficient diet. These studies have been reviewed elsewhere [1,2], but the field is now developing at a more rapid pace and several new studies have been published. Recent studies by Connor and colleagues have indicated a visual acuity loss in non-human juvenile primates when the mothers were given safflower oil as the sole source of fat during their prenatal development and maintained on this diet after birth [3]. It has been known for two decades that the mammalian nervous system is difficult to deplete of its essential fatty acids, particularly in the adult. Therefore, the rather extreme dietary deprivation of the sort used in this study across more than one generation is required if a significant loss of 22:6n3 in the brain is desired. These authors were able to demonstrate a visual acuity loss that was not reversible when the diet was supplemented with menhaden oil to an extent that was successful in repleting brain 22:6n3. These findings also appear to be relevant to humans as premature infants appear to have cognitive deficits [4] and visual acuity losses [5] when fed formulas that do not contain long chain n-3 fatty acids.

These studies give rise to two immediate questions, namely, "What is the critical biological function of 22:6n3 that is disrupted when the brain level falls?" and "What are the mechanisms through which the brain is supplied with 22:6n3 and which maintain this level?" These will each be dealt with briefly below.

II. LIPOXENATION

It may be reasonably hypothesized that 22:6n3 may be the substrate for a highly specific reaction such as enzymic oxygenation and that this product may be bioactive. Although no cyclooxygenase products of this fatty acid have been described, several lipoxygenase products have been found [1,2]. There is an platelet 12-lipoxygenase that is about as active towards 22:6n3 as 20:4n6. However, it is the presence of this activity and therefore of these metabolites in the nervous system that is of the most relevence since this is the site of the highest concentration of the substrate and the presumed site of action. It is for these reasons that an intensive effort was made to evaluate rat brain as a source of lipoxygenases by our research group. It was generally found that a variety of hydroxylated derivatives of 22:6n3 are formed by rat brain homogenate and that they had the characteristic conjugated diene structure [1]. Their formation was inhibited by several "lipoxygenase inhibitors" and not by cyclooxygenase nor monooxygenase inhibitors. This is usually regarded as sufficient evidence that a product is formed by the lipoxygenase enzyme and has been interpreted that way by several workers. However, Kim et al. have investigated this issue in a detailed manner with the use of stereochemical analysis [6].
This approach may be viewed as the most definitive criterion for support of the enzymic mechanism since all known lipoxygenase reactions proceed in a stereoselective manner; it has been shown that some of these enzymes produce the all-R enantiomer but the feature of stereochemical purity remains. Analysis of rat brain homogenate revealed a nearly equal ratio of the R and S forms of all of the major 22:6n3 "lipoxygenase" products. It may then be argued that the brain enzyme has a high degree of substrate specificity and is selective for 20:4n6 since there were several reports of such products in the literature. However, this was not borne out by stereochemical analysis of hydroxylated products of 20:4n6 produced by rat brain homogenate or brain slices [7]. It seems that there are true lipoxygenases in brain microvessels [8] and perhaps also in particular brain regions such as the pineal gland. However, it is still difficult to reconcile the low level of these activities and the limited availability of the products to the brain as a whole with the proposition that this is the essential function of 22:6n3 in the brain and retina.

It is apparent that the maintenance of an adequate level of 22:6n3 in the brain and retina is of importance for proper nervous system and visual function. This research has focused attention on the practical issue of whether long chain n-3 fatty acids and 22:6n3, in particular, must be present in infant formulas as it is in human milk. Since this is the sole source of fat, an infant receiving formulas is deprived of long chain polyunsaturates. In most formulas, there is an adequate source of the 18-carbon essential fatty acids, 18:2n6 and 18:3n3. However, it is not known whether humans are capable of converting these into the 20 and 22-carbon polyunsaturates that appear to be required by the brain and retina.

It has often been said that cats are incapable of desaturation and are obligate carnivores. Our initial results indicate that they are indeed capable of producing 20:4n6 from 18:2n6 and that at least part of this may proceed via the traditional pathway as 18:3n6 is formed. An essential fatty acid deficient diet leads to an increase in the production rate of these compounds.

Rhesus monkeys have also been the subjects of essential fatty acid metabolism study when kept on a "chow" diet that contains long chain polyunsaturates. Both 20:4n6 and 22:5n3 have been observed in their blood stream 1-3 days after a single dose of 18:2n6 or

III. SUPPLY OF 22:6N3 TO THE BRAIN

Initial studies have explored the relationship of liver and brain metabolism to the appearance of the precursors and various metabolites in the bloodstream of young rats. It was observed that the 18-carbon essential fatty acids are taken up into all three compartments and that a progression of metabolites begins in both the liver and brain. In the rat, there is clearly 18:3n3 uptake into brain and 22-carbon metabolites are formed after several days. It thus appears that the brain is metabolizing fatty acids and not relying solely upon liver export in young rats.

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18:3n3, respectively. The latter is depicted in figure 1 below. It thus appears that non-human primates are quite capable of producing both n-3 and n-6 polyunsaturates. The production in very young and adult humans is now critical for the important area of lipid nutrition.

![Diagram](image)

Figure 1. The conversion of deuterated-18:3n3 to 22:5n3 in the rhesus monkey in vivo.

REFERENCES:


