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COMMENTARY

On the Role of the Peroxisome in the Metabolism of Drugs and Xenobiotics

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ABSTRACT. One of the most rapidly developing areas of organellar biology, and one with major involvements in biochemical pharmacology, is that of peroxisomal function. In this commentary, several recent research findings in this area are described, along with their significance in relation to the metabolism of drugs and xenobiotics. Topics that are covered include the peroxisome proliferation caused by a wide variety of chemical compounds, the metabolic implications of this phenomenon, interactions between peroxisomal transcription factors and the eicosanoids, and the close relationships between peroxisomal metabolism and the control of functional damage caused by oxygen free radicals. Examples are also provided on interactions between peroxisomal function and such diverse drug groupings as analgesics, anti-inflammatories, nutritional ingestants, insecticides, antifungals, herbicides, and plasticisers. It is concluded that the peroxisome plays a central role in the metabolism of many drugs, displays a significant potential in furthering an understanding of pharmacological mechanisms, and is deserving of greater emphasis in future research considerations in this area. BIOCHEM PHARMACOL **56**;6:667–673, 1998. © 1998 Elsevier Science Inc.

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In recent years, the vital role of the peroxisome in cellular function has become more widely appreciated, as has its wide-ranging and important involvements in metabolism [1–3]. As yet, though, the extensive range of contributions that this organelle may contribute to drug metabolism and physiological detoxification has not received general recognition. Consequently, a critique of the unique and significant interactions of the peroxisome in xenobiotic metabolism was considered to be timely, and of interest to many scientists in areas such as pharmacology, toxicology, and medical biology.

In considering the potential scope of the peroxisomal involvement in xenobiotic metabolism, an initial point that needs to be considered is the wide range of enzymic options that are available in this organelle. Some of these activities are listed in Table 1, and it may be seen that the extent of enzymic involvement has broadened considerably in recent years; it covers both hydrophilic and hydrophobic substrates, and has the potential to interact with many xenobiotics, both directly and indirectly. Indeed, the possibilities of interaction are so extensive that it is not possible to treat them individually in an article of this length, but only to divide examples into broad categories of peroxisomal function such as the unique ability of this organelle to proliferate in response to many xenobiotics, the attendant widespread perturbations in lipid metabolism, the relationships with transcription factors and the eicosanoids, the involvements of the peroxisome with the cytochrome P450 system, the intimate relationships with cellular signalling and the reactions of oxygen free radicals, and individual aspects of pharmacological significance.

It is concluded from this overview, nevertheless, that the involvement of the peroxisome in xenobiotic metabolism is widespread, diverse, and of considerable biological and toxicological significance.

PEROXISOME PROLIFERATORS

One of the most singular aspects of peroxisomal involvement in detoxification is the induction of this organellar compartment by a number of drugs and pollutants. Probably the best known of these peroxisome proliferating agents is the hypolipidaemic drug clofibrate (ethyl-*p*-chlorophenoxyisobutyrate), which has the capacity to increase the number of peroxisomes and the oxidative capacity of this compartment in rat liver by approximately an order of magnitude [1–4]; however, the list of peroxisome proliferators has lengthened considerably in recent years, and now includes a diversity of structures, some structurally related to clofibrate and some unrelated chemicals. In the latter category are pharmaceuticals (such as aspirin), industrial plasticisers (such as di-2-ethylhexylphthalate), insecticides (such as dimethrin), herbicides (such as chlorophenoxyacetic acid), antifungal agents (such as biofonazole), degreasing agents (such as tetrachloroethylene), industrial lubricants (such as perfluorocarboxylic acid), wood preservatives (such as chlorophenolates), by-products of water chlorination (such as trichloroacetic acid), and several other industrial chemicals [3–6]. Clearly, then, this unique character-

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TABLE 1. Major enzyme activities of mammalian peroxisomes

Enzyme	Native substrates
Oxidases	
Fatty acyl-CoA	Long-chain fatty acyl-CoA
α-Hydroxy acid	α-Hydroxy acids, glyoxylate, thiohemiacetals
Urate	Uric acid
D-Amino acid	D-Amino acids, thiazolidine carboxylates
Pipecolic acid	Pipecolic acid
Polyamine	Spermidine and spermine
Dehydrogenases	
Glucose-6-phosphate	Glucose-6-phosphate
Glycerol phosphate	Glycerol phosphate
3-Hydroxy fatty acyl-CoA	3-Hydroxy fatty acyl-CoA
Isocitrate	Isocitrate
Catalase	
	H_2O_2 (catalytic)
	Ethanol, methanol, formate
	Nitrite (peroxidatic)
Acyl transferases	
Acyl-CoA:Dihydroxyacetone phosphate	Palmitoyl CoA, DHAP*
Carnitine acetyl-CoA	Acetyl-CoA
Carnitine octanoyl-CoA	Octanoyl-CoA
Sundries	
Alanine:Glyoxylate aminotransferase	Alanine, glyoxylate
Alkyl-DHAP synthase	Acyl-DHAP, alcohols
Enoyl-CoA	Enoyl-CoA
Epoxide hydrolase	Arene and alkene oxides
Fatty acyl CoA synthase	Long-chain fatty acids
Hydroxymethyl glutaryl-CoA reductase	Hydroxymethyl glutaryl-CoA
Thiolase	3-Oxo-fatty acyl CoA

*DHAP = dihydroxyacetone phosphate.

istic of peroxisome proliferation is intimately involved with a range of common drugs and xenobiotics and their detoxification, and warrants further comment in this regard.

As to the nature of the effect of these peroxisome proliferators at a cellular level, the most marked effect is at the level of oxidative enzymes. Acyl CoA oxidase activity in the peroxisomes of liver cells may be increased 20-fold, for example [3, 4]. Apart from the peroxisomal compartment, lesser increases are generated as well in the mitochondrial β-oxidation sequences, and marked increases in the microsomal laurate hydroxylase activity (up to 30-fold) [3]. The latter activity has been shown to be due to the cytochrome P452 isoenzyme [7], and this link between the peroxisomal and microsomal compartments, which has wide relevance in relation to both the scope of cellular detoxification and the molecular mechanics of peroxisome proliferation, is discussed in more detail later in this article.

To comprehend the widespread metabolic ramifications of peroxisome proliferation, an understanding of the mechanistic background is necessary, and to this end attention is drawn to the connections between the biological mediator of peroxisome proliferator action and members of the steroid hormone/thyroid hormone/vitamin D receptor superfamily of nuclear receptors (Fig. 1; Ref. 8). This family of receptors, besides binding to their cognate ligand, are also capable of binding to nuclear DNA, recognizing motifs that are termed hormone response elements and behave as transcriptional enhancers. The receptor that is activated by peroxisome proliferators (PPAR*) recognizes the same DNA response sequence (AGGTGA) as the other members of the steroid hormone receptor superfamily. Consequently, there is an indicated confluence of these wide-ranging and important signalling systems at this juncture, and, in the particular case of the lipid-activable transcription factors, the PPARs, a breakthrough in the molecular understanding of lipid homeostasis [4, 9].

As a logical next step in this sequence under consideration, then, attention is drawn to the significant influence of peroxisomal metabolism on several common lipid ingestants and body lipids.

METABOLISM OF COMMON LIPID INGESTANTS

Lipids are, of course, common components of many organisms and tissues [10], and, in this sense, may not seem, at first glance, to fit into a xenobiotic classification. When considered in a nutritional sense, though, it is clear that the ingestion of lipid from alien sources exerts a significant influence on the composition, function, and health of the host organism, and, as a chorus of nutritional comment

* *Abbreviations*: LT, leukotriene; and PPAR, peroxisome, proliferator activated receptor.

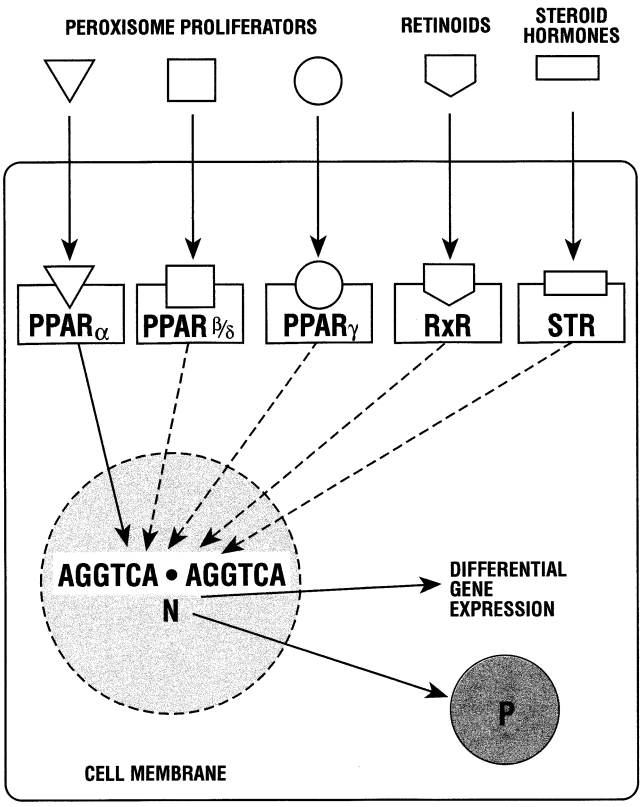

FIG. 1. A representation of the mechanism of action of peroxisome proliferator activated receptors (PPARs), and their relationships to that of the steroid hormone receptor superfamily. In this model, the agonist enters the cell and binds to a specific cytoplasmic receptor, and the resultant complex moves to the nucleus where it initiates differential gene expression. Dimerization is essential for the function of most of these receptors. PPARs, for example, hetero-dimerize with the 9-*cis*-retinoic acid receptor in activating gene activity. All of the indicated receptors recognize the same nucleotide sequence (AGGTCA) in the nucleus in producing their individualistic responses, and in the case of the PPAR subtypes, different PPAR activators may preferentially activate one or other of these subtypes. Other abbreviations: RxR, retinoid receptor; STR, steroid hormone receptor; N, nucleus; and P, peroxisome.

attests, should often be considered as a potentially harmful xenobiotic. Fatty acids and cholesterol probably rank as the chief *bêtes noires* of nutritionists in this area, at present [10], and in this regard, it is appropriate to re-emphasize the fact that the major physiological process for the oxidative disposal of fatty acids (namely the β-oxidation spiral) occurs not only in mitochondria but also in peroxisomes [3, 11]. As to the relative substrate preferences in these organelles, the available evidence would appear to indicate that mitochondria are the primary site of oxidation of the common, saturated fatty acid components of mammalian tissues under normal physiological conditions, while peroxisomes make their most significant contribution to the oxidation of unsaturated fatty acids. Studies on isolated hepatocytes, for example, have indicated that the peroxisomal contribution to the cellular oxidation of the common monounsaturated fatty acids may be 4–5 times that of the corresponding saturated fatty acids, and that an even greater margin in favour of the peroxisome obtains with polyunsaturated fatty acids, or in conditions of stimulated peroxisomal activity [3, 12]. Other lipids that may be ingested as drugs or xenobiotics, and that possess deleterious properties, include the very long chain fatty acids, the *trans*-fatty acids and cholesterol, and it is worthy of note that the peroxisome is now known to play an important and often critical role in the metabolism of all these substances [3, 13]. Clearly, then, the peroxisome should be recognized as playing a major role in the physiological removal of nutritionally undesirable lipids.

A further class of lipids that has excited widespread pharmacological involvement in recent years is that of the ω-3 unsaturated fatty acids. Much has been written on the remarkably wide-ranging clinical correlations of these essential components of the human diet, and they have been beneficially implicated in a variety of medical conditions such as cardiovascular disease, rheumatoid arthritis, neural and retinal function, cancer, and diabetes mellitus [14, 15]. In this connection, it should be noted that the peroxisome has been shown to exert a major influence on both the synthesis and degradation of the ω-3 fatty acids, with these effects flowing on to the determination of tissue levels of these acids and their derivative eicosanoids [15, 16]. These latter substances (such as the prostaglandins, thromboxanes, prostacyclins, and leukotrienes) are important extracellular mediators with widespread physiological implications (as indicated in a later section), so that, overall, it may be said that there are several aspects of peroxisomal function which together argue that the peroxisome should be accorded a pivotal position in the wide-ranging biomedical involvements of these particular ingested lipids, as well.

PEROXISOMES AND THE CYTOCHROME SYSTEM

No discussion of the metabolism of drugs and xenobiotics would be complete without a consideration of the role of the cytochrome P450 system. As is well known, this family of isoenzymes is capable of numerous and complex hydroxylation reactions in which an organic substrate (RH) is converted to a hydroxyl derivative (R-OH) [17]. Of particular note in the latter context is the broad involvement of these cytochromes in the hydroxylation of many different drugs and xenobiotics, with hydroxylation of such compounds generally making them more soluble in water and allowing their excretion in the urine. A powerful series of oxidations converts even relatively unreactive compounds to epoxides, which are hydrolysed to hydroxyl groups by epoxide hydratase, then coupled to glucuronic acid or other conjugates, and eliminated from the body [10].

Among those members of the cytochrome P450 family that catalyse the metabolism of exogenous substrates, a subfamily that is particularly relevant to peroxisomal involvement is the cytochrome P450 IVA subfamily. This subfamily is inducible by peroxisome proliferators, and has

a substrate specificity that is mainly directed towards the ω-hydroxylation of fatty acids and prostaglandins [17, 18].

Recent studies have demonstrated an excellent and specific correlation between the induction of this subfamily of cytochrome P450 by peroxisomal proliferators, peroxisomal volume, the activity of peroxisomal marker enzymes, and the ω-hydroxylation of lauric acid. All peroxisome proliferators studied to date, for example, are inducers of the cytochrome P450 IVA subfamily. There is obviously a need for the magnitude of the activity response to xenobiotics in these separate subcellular locations to be coordinated, and it is therefore of interest to note the results of recent experiments, which demonstrate that many xenobiotics initiate a sequence whereby peroxisome proliferation is caused, and followed by induction of both the enzymes for microsomal ω-oxidation and for peroxisomal β-oxidation. Furthermore, the extent of induction is similar in each case (10- to 20-fold), thereby enhancing the overall capacity for sequential oxidation. Of further interest here is that the induction of the microsomal hydroxylase has been shown to precede that of the peroxisomal enzymes involved in β-oxidation, indicating that signalling between cellular compartments is intimately involved in these detoxifications and coordinated via the peroxisome [19].

The products of hydroxylation by the cytochrome P450 superfamily may, of course, subsequently feed into one or other of the many areas of peroxisomal metabolism. The nature of these hydroxylation products is too diverse for an exhaustive listing in the present article, and readers need to refer to one of the many excellent general reviews to consider specific correlations [17]. Some obvious examples of putative interaction, though, include the widespread epoxidation capacities of the P450 system, oxidative dehalogenations, hydroxylations of aliphatic sidechains, and some dealkylations.

TRANSCRIPTION FACTORS IN PEROXISOMAL METABOLISM

In addition to those involvements of PPARs in peroxisome proliferation which have already been mentioned, some further discussion of these transcription factors is warranted in view of their major role in lipid homeostasis and their impressive pharmacological potential.

As we have seen, the PPARs are a group of transcription factors that are activated by fatty acids and other lipids, and regulate gene expression of enzymes associated with lipid homeostasis, including fatty acid degradation [3, 9]. Thus far, three types have been identified (α, β/δ, γ), and one or another is expressed at all developmental stages in mammals. Although it is not yet clear to what extent PPAR subtypes can be specifically activated by different fatty acids, they are distinct with respect to their activation by various synthetic or natural compounds.

In the liver, the functions of PPARα are mainly to degrade fatty acids and detoxify various xenobiotics, by means of the action of the β- and ω-oxidation pathways [3]. PPARs also appear to be involved in the regulation of adipose cell numbers, the transport and cellular uptake of lipids, intracellular balance between free and bound fatty acids, conversion of fatty acids to their activated CoA form, penetration of fatty acids into membrane-delineated organelles, microsomal ω-oxidation, mitochondrial β-oxidation and ketogenesis, as well as the production of glycerol for triglyceride synthesis. Indeed, essentially all of the major pathways of lipid metabolism appear to be under the control of one or more PPAR-regulated genes [20, 21].

This wide scope of influence and the range of specific agonists for specific PPAR subtypes clearly raise many exciting possibilities in relation to xenobiotic metabolism and the pharmacological treatment of disorders such as obesity, atherosclerosis, and Type II diabetes. Indeed, it may be fairly said that the discovery that fatty acids can activate transcription factors and many metabolic pathways changes the view of lipids from that of a mainly passive role to that of active participants in cell differentiation and metabolic regulation.

One example of an area where these transcription factors exhibit a broad pharmacological potential is the eicosanoids. As is well known, eicosanoids are fatty acid derivatives with a variety of extremely potent hormone-like actions on various tissues of vertebrate animals. Unlike hormones, they are not transported between tissues in the blood, but act on the tissue in which they are produced [10]. Eicosanoids are involved in a wide variety of processes that are important in human health and disease, e.g. the inflammation, fever, and pain associated with injury or disease, reproductive function, gastric acid secretion, the process of blood clotting, and the regulation of blood pressure [10]. Because of this broad and diverse influence of the eicosanoids, a great deal of pharmacological interest has centered on drugs that are designed to modify their synthesis and degradation, and it becomes important to understand the role of the peroxisome in these processes.

One interesting and specific connection in this area that has been established recently is that between PPARα and LTB_4, a potent chemotactic agent that initiates, coordinates, sustains, and amplifies the inflammatory response [22]. In many inflammatory disease states, LTB_4 induces a complex cascade of cellular events that ultimately recruit cells from the immune system to the site of injury and produce an inflammation. It has now been shown that LTB_4 is a natural ligand and activator of PPARα, and that activation results in the induction of genes involved in eicosanoid degradation and the subsequent reduction of the inflammation. Thus, other compounds that enhance PPARα function should be anti-inflammatory, and, given the number of established ligands for PPARα, then a variety of eicosanoids could regulate their own inactivation or clearance via an influence in the activity of PPARα. There is also evidence that the PPARα ligands include thiazolidinediones (anti-diabetic agents), fibrates, eicosanoid metabolites, fatty acids, and phthalates, and the suggestion has been made that these relationships open up

opportunities for drug design in diverse conditions such as obesity and cardiovascular disease, as well as inflammatory conditions such as rheumatoid arthritis. As a result, questions have also been raised as to the influence of the non-steroidal anti-inflammatory drugs and cyclooxygenase inhibitors on abnormalities of lipid metabolism through interactions with PPAR [20–22]. It may be concluded that these established and putative connections between peroxisomal function and xenobiotic metabolism represent an extensive potential for pharmacological involvement in human disease conditions.

OXYGEN FREE RADICALS

Oxygen free radicals are now recognized as playing a major role in many degenerative processes associated with drugs, xenobiotics, and disease. Hence, in the context of this commentary, it is important to note that the peroxisome plays a critical role in the metabolic removal of oxygen free radicals, and in alleviating the damage caused by these agents.

Oxygen free radicals, of course, arise whenever the cell is involved in oxygen utilization in its conversion to water, and this production may be exacerbated considerably by drugs, xenobiotics, and disease, as mentioned above. All of these intermediates (hydrogen peroxide and the superoxide and hydroxyl radicals) are extremely toxic to cells and tissues, causing damage to essential proteins, nucleic acids, and membranes, and hence to cell and tissue function [23–25]. Consequently, for a state of good health, their formation in the cell needs to be balanced by efficient disposal.

The peroxisome also plays an important role in the detoxification of these oxygen free radicals, and this is indicated in Fig. 2. By the combined action of catalase and superoxide dismutase (both of which activities have been identified in the peroxisomal compartment), hydrogen peroxide and the superoxide free radical are detoxified, and the formation of the hydroxyl radical abated. Any residual hydrogen peroxide from the peroxisome plus any hydrogen peroxide produced by extraperoxisomal sources may be removed by a combination of degrading systems: first, the cytoplasmic space contains further catalase, which extends the role of this enzyme outside the peroxisome, and, additionally, the presence of glutathione peroxidase allows further decomposition. Glutathione peroxidase catalyses the destruction of hydrogen peroxide and the coincident conversion of reduced glutathione to glutathione disulfide, whereas glutathione reductase allows a continuation of this reaction by catalysing the conversion of glutathione disulfide back to the reduced form [3].

In the general context of subcellular damage caused by these toxic oxygen metabolites (e.g. hydrogen peroxide, superoxide and hydroxyl radicals), the subject of membrane damage due to epoxide formation at the site of double bonds in the component fatty acids should also be mentioned. Epoxides may arise during the metabolism of xenobiotics and other endogenous compounds, are deactivated to diols by epoxide hydrolase (which has been identified in peroxisomes as well as in other cellular compartments), and confer an ability to convert arene or alkene groups into dihydrodiols, thus enabling peroxisomes to metabolize fatty acids containing an oxirane ring, and to participate in areas of sterol metabolism [3, 26].

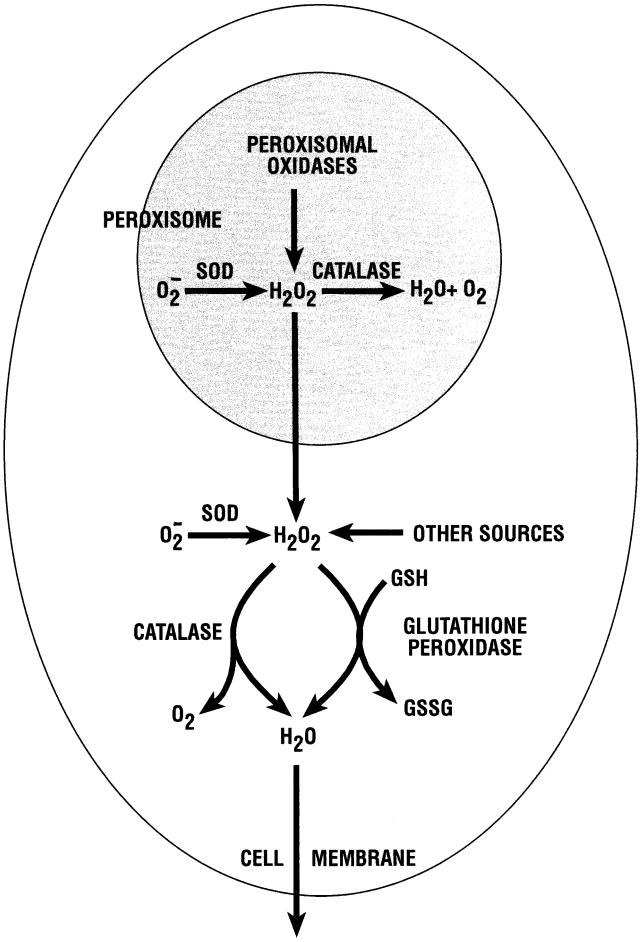

FIG. 2. Subcellular mechanisms that are available for the detoxification of hydrogen peroxide and superoxide radicals. Abbreviation: SOD, superoxide dismutase.

In regard to this major topical area of drug and disease involvement, then, the peroxisome is uniquely placed to participate in the amelioration of free radical damage, and the preeminent role of this organelle in these functions is deserving of much wider recognition than generally accorded at present.

CONCLUDING COMMENTS

The previous discussion has centered mainly on the role of the peroxisome with compounds of hydrophobic character, but it should be emphasized that there are also extensive involvements with hydrophilic substrates. Some idea of the scope of these hydrophilic reactions may be gleaned from an examination of the major peroxisomal substrates in

Table 1, but it should be realized that such possibilities are magnified many times by a unique combination of organellar factors—the ability of peroxisomal catalase to operate in both a catalytic and peroxidative fashion, the broad substrate specificity of other peroxisomal enzymes, and the widespread relationships with intermediary metabolism and cellular signalling. To take one example, ethanol is widely recognized as a major drug of abuse, but there is little common recognition of the role of the peroxisome in its cellular oxidation and detoxification. In this regard, it needs to be remembered that in addition to the cytosolic and microsomal pathways for alcohol metabolism, there is also a substantial peroxisomal capacity, which is activated by the presence of a number of other peroxisomal substrates, e.g. fatty acids or ethanol itself [27, 28].

In regard to size and shape, too, it may be noted that many xenobiotic compounds with bulky substituents appear unable to enter into mitochondrial metabolism, but readily enter into and are acted upon by the peroxisome. An example is provided by the fatty acid analogue 12-(1-pyrene)dodecanoic acid, an intensely fluorescent compound used to distinguish between normal and lipidotic cells. It has been demonstrated that this substrate, although unable to enter mitochondria, is rapidly metabolized by peroxisomes [29].

Another aspect of the role of the peroxisome that warrants comment in this review is the belated nature of the recognition of the extent of peroxisomal involvement in drug metabolism. One reason for this is the complicated character of the multiple involvements in many cases. As an example that may be instructive in this regard, mention of one of the more widely used therapeutic drugs, namely aspirin, may be made: this drug, like many others, interacts with peroxisomal metabolism at several levels. At one level, it acts as a peroxisome proliferator and, like many other chemicals of this class, induces the activity of a number of xenobiotic-metabolizing enzymes such as diaphorase, expoxide hydrolase, and cytochrome P450 IVA [30]. Thus, one action of aspirin is at the level of facilitating the removal of potentially harmful substances from the body. At another level, it is well known that aspirin inhibits the synthesis of prostaglandins and related eicosanoids from arachidonic acid by blocking cyclooxygenase activity [10]. Also, cytochrome P450 IVA (induced by aspirin treatment) may metabolize arachidonic acid, reduce its effective concentration, and so reduce the production of eicosanoids. Much of the analgesic and anti-inflammatory action of aspirin, then, can be explained by these peroxisomal connections. Finally, the recent discovery that aspirin triggers the biosynthesis of a previously unrecognized class of compounds from cell–cell interactions [31] shows that aspirin may influence other processes involving the peroxisome (e.g. inflammation, differentiation, proliferation) by pirating endogenous biosynthetic mechanisms and producing new mediators. It seems clear then that the interaction between aspirin and the peroxisomal processes is complex and operative at several levels, and that many other therapeutic drugs may display similar levels of complexity in their interactions.

One further aspect of the metabolism of drugs and xenobiotics that needs to be mentioned in the present context is that of cellular signalling. As with other areas of metabolism, signalling plays a critical role in the final direction and extent of peroxisomal functions, but it is only very recently that the details of the unique peroxisomal imprint on cellular regulation have been clarified [32, 33]. These signalling functions offer an exceptional degree of regulatory diversity, and confer a singular ability on the peroxisome in its capacity to metabolize the wide range of chemical structures that are characteristic of drugs and xenobiotics. Systems involved in peroxisomal signalling include hormones, eicosanoids, messengers of the phosphatidylcholine cycle, membrane transport, and activities of adenyl cyclase and protein kinases. Clearly, these involvements are too extensive to cover here, and for a more detailed consideration of these signalling functions than is possible in the present commentary, the reader is referred to a more specifically targetted discussion [33].

In a final summary then, this commentary has drawn attention to the broad role of the peroxisome in xenobiotic metabolism and its significant interactions with several major areas of metabolism. Among the examples cited are many hypolipidemic drugs, analgesics, anti-convulsants, herbicides, anti-inflammatory drugs, insecticides, antifungal agents, plasticisers, and carcinogens, as well as common dietary ingestants and industrial chemicals. While this listing is by no means exhaustive, it should be sufficient to emphasize that the peroxisome deserves to be regarded as a major area of pharmacological involvement. Indeed, in some of the most important aspects of the interactions between drugs and disease processes, this organelle needs be accorded the preeminent role among cellular compartments. As well, the peroxisome displays an exciting potential in some of the most topical areas of drug design, and clearly it is deserving of a more prominent commitment in future pharmacological research.

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