TOPIC

New Prospects of PPAR Nuclear Receptor Modulation

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SUMMARY

Modulation of the function of the PPAR (peroxisome proliferator-activated receptors) nuclear receptor group is one of most promising fields in pharmacological research. Today it is commonly associated with the clinical use of antidiabetics and hypolipidemics (PPAR alpha and gamma). Significant developments are expected in PPAR beta modulation and in drugs influencing multiple receptor families (double and triple sensitisers). PPAR modulating drugs will be used in future in dermatology, obesitology, oncology, surgery, gastroenterology and also in neurology and psychiatry.

Key words: diabetes, atherosclerosis, double sensitisers, triple sensitisers, wound healing, anti-inflammatory effect, neuropsychiatry.

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Nuclear receptors are modulated by, for example, steroid and thyroid hormones and also by retinoids. They regulate gene expression in particular and therefore have extensive and very complex, mainly metabolic effects. For a long time, the ligands of a number of other nuclear receptors remained unknown and were considered "orphan" receptors. Later it became known that they were influenced by a number of endogenous and exogenous ligands of mainly the prostaglandin type. It has been observed that their stimulation causes peroxisome proliferation, thus the name peroxisome proliferator-activated receptors (PPAR). Receptor groups ("families") started being labeled using Greek characters. A number of exogenous ligands were described and drugs modulating these receptors developed. PPAR alpha stimulation is today one of the basic effects of fibrate hypolipidemics. Stimulation of PPAR gamma represents a significant anti-diabetogenic effect of insulin sensitisers (thiazolidindions). Insulin sensitisers and fibrates are among the drugs commonly used to treat metabolic diseases. It would be difficult to imagine modern diabetology or preventive cardiology without these drugs. The history and current use of PPARs is the subject of an on-coming monograph (1). The prospects of this drug group are, however, much broader.

PPAR BETA (DELTA)

The hitherto clinically unexploited and important PPAR group was at first labeled delta receptors. Later the same receptors were also called PPAR beta, and a number of authors still consistently use both labels, with "delta" in brackets – PPAR beta (delta), or separated by a stroke – PPAR beta/delta.

Like many other nuclear receptors, PPAR beta complexes with heterodimers, with the so-called receptor X, for retinoid acid receptor alpha (RXR), giving rise to a complex governing functional transcription. While PPAR alpha and gamma are expressed only in certain tissues and organs, the expression of PPAR beta is relatively widespread in most tissues and organs (2, 3).

PPARs beta are probably very important in the development of the individual; receptor knockout leads to high fetal mortality in animals. They participate subsequently in muscle and skin differentiation. In the muscle they support the utilization of lipids and reduce fat deposition (4). Unlike the PPAR gamma and alpha effects, stimulation of PPAR beta does not result in increased plasma and blood volumes and in heart hypertrophy. PPARs beta are also involved in prostacyclin-induced cell apoptosis (5). They also have a significant impact on the development of the brain by, for example, regulating the differentiation of oligodendrocytes.

The prospects of the PPAR beta effect are most promising in dermatology (6, 7). Keratinocytes are cells that, on the one hand, resist many insults and, on the other hand, must switch rapidly from the latent stage into the growth stage to restore the skin cover.

PPAR beta regulates the processes of apoptosis, proliferation and differentiation in the skin. The role of PPAR beta was clarified most thoroughly in PPAR beta -/- mice, in whom, unlike in heterozygous individuals, wounds did not heal. Pro-inflammatory cytocinines increase significantly PPAR beta expression in the vicinity of any type of wound. Dermatology is thus the major field of development of PPAR beta utilization.

All three PPAR isoforms occur in fetal skin. Expression of alpha and beta in adult age may be rectified by a number of stimuli, resulting in proliferation and differentiation of keratinocytes; it also protects keratinocytes against apoptosis. The active signals for the beta receptor promoter are, for example, TNF alpha and other cytocinines. The cytocinines alone then enhance the production of PPAR beta ligands by providing positive feedback.

While PPAR gamma increases both the uptake and output of lipids in the macrophages and in atherosclerotic lesions (foam cells), beta inclines to modulate inflammation (8). Deletion of beta receptors enhances the activity of inflammation suppressors. Loss of the gamma receptor or of LXR alpha leads to the prevention of efflux of lipids from cells and to the progression of atherosclerosis. Negative PPAR delta effect, on the other hand, coincides with a significant reduction of lipid stripes.

The partially unexplained effect of PPAR beta on atherosclerosis was tested also on other models. A hypothesis was then formulated on the basis of these models that PPAR delta binds

with a certain suppressor of the immune response. It has been proven that this transcription repressor is BCL-6 (beta cell lymphoma gene 6). BCL-6 is a substance found in a number of tumors, especially in lymphomas, and is one of the anti-apoptotic factors and can have a prognostic relevance (8).

It seems that PPAR gamma and beta have a different role in the cell. Gamma affects the lipid metabolism of macrophages. Beta dissociation with BCL-6 is anti-inflammatory; association is pro-inflammatory. And it is in the PPAR beta effect field that new modulators of inflammatory (and atherogenic) reactions are sought (9, 10).

As for lipid metabolism, PPAR beta can lower triglyceride levels by enhancing VLDL elimination. It has been demonstrated in makakus rhesus that PPAR beta agonists increase HDL-cholesterol and reduce LDL-cholesterol, triglycerides and insulin.

The relation between PPAR beta and tumors has also been described. The most detailed analyses are of the relation between PPAR beta and colorectal carcinoma (11). It probably plays an important role in the beta-catenin pathway, which plays a role in polypous intestinal adenomatosis. Inoculation of grafts with PPAR beta -/- cells reduced significantly the number of newly formed tumors compared to PPAR beta +/- and PPAR beta +/+ animals. PPAR beta thus releases gene suppression and leads to the formation of colorectal carcinoma in sensitive mouse species. It has also been demonstrated that the clinically familiar and repeatedly described preventive effect of non-steroid antirheumatics on colorectal carcinoma may be attributed to, namely, suppression of PPAR beta by these drugs (11, 12).

Another matter of interest is the role of PPAR beta in adipose tissue. PPAR beta stimulation increased oxidation of fatty acids in experiments and reduced their deposition. This effect can be demonstrated in a number of animal obesity models, e.g. in animals without a leptin receptor and in other diet-induced models of obesity. Activation of beta receptors leads to increased burning of energy and the utilization of fatty acids not only in adipose tissue but also in striated muscle. A receptor beta knockout mouse (PPAR beta-/- mouse) is susceptible to diet-induced obesity. Therefore there is reason to believe that a future effective group of anti-obesity drugs could be developed from members of the beta sensitiser group (13, 14). PPARs beta, moreover, modulate the formation of the uncoupling protein 3 (UCP-3) in the muscle (15), which could also be applied effectively in the treatment of obesity.

PPAR gamma, as is well known, contributes to the build up of liver steatosis. It is interesting that PPAR beta, on the other hand, facilitates the removal of lipids from the liver both into the bile and HDL particles (16). The connection between PPAR beta and liver cirrhosis has been described recently. PPARs beta are overexpressed on liver stellate cells, both in acute and chronic liver disease (17). There is an indisputable relation between PPAR beta activation and fibroproduction. PPARs beta also have a stimulating effect on the formation and progress of hepatocellular carcinoma. This effect is caused by the cyclooxygenase-2 stimulation pathway (18).

PPAR beta is present in practically all tissues. Of the connections mentioned above, the most significant is the relation to skin diseases, lipid levels and colorectal carcinoma. That is why, repeatedly, clinically significant polymorphisms have been sought. The relation to cholesterol levels and atherosclerosis has been demonstrated in some polymorphisms. None of the polymorphisms had any relation to colorectal carcinoma.

Some very interesting facts were presented in 2003 on the rare PPAR beta CC genotype. Both diabetics and non-diabetics with this genotype have a higher atherogenic index. Blood samples were taken from patients to determine the genotype; the patients were then followed for six years. Diabetics with this genotype who started getting insulin treatment had a significantly worsened atherogenic index and also higher mortality (19)! In spite of the favorable effect of insulin therapy in type II diabetics (e.g. according to the UKPDS study) insulin treatment may be harmful for a certain group of type II diabetics.

PPAR beta/delta has been a somewhat neglected member of the PPAR family. These receptors probably play a key role in cell and tissue differentiation, during embryonic development, lipid utilization and the formation and growth of tumors. It seems at the moment that they will gain some significance in the treatment of skin diseases and components of the X metabolic syndrome. Their importance for oncology is not yet clear.

SUBSTANCES AFFECTING MULTIPLE RECEPTORS – DOUBLE AND TRIPLE SENSITISERS

Endogenous ligands may affect more than one member of the PPAR family, and it is therefore not surprising that drugs are being developed which affect several PPAR types simultaneously. The most significant effect is the simultaneous activity of PPAR alpha and gamma. Such substances can function at the same time as antidiabetics and hypolipidemics. Substances modulating delta receptors may affect the muscle in particular, as a fat-infiltrated and insulin-resistant organ and, simultaneously, the coagulation system (4). The assumption is that substances affecting all three types of receptors could have a complex effect on Reaven's metabolic syndrome X and on atherosclerosis.

Mogensen (20) explains the procedure in an outline of research done by Novo Novordisk. Targeted radical substitution of a substance with PPAR alpha and gamma activity was carried out and the effect on all three receptors compared. Some drugs are of the non-thiazolidindion type (more details in 1).

The relations between receptor families may be even more complex. According to Bastie (9), PPAR alpha expression is probably regulated with the help of PPAR delta. Fatty acids affecting PPAR delta have no effect on the differentiation and proliferation of adipose tissue, unless PPAR gamma is present. A substance affecting multiple receptors simultaneously can thus have truly complex functions.

The double sensitiser effect is additive to simvastatin, which is probably due to the fact that the substance modulates not only the synthesis, but also the secretion of cholesterol.

Dual agonists (alpha and gamma) have been developed by several companies – AstraZeneca (Tesaglitazar), Bristol-Myers Squibb (BMS 298585) and Merck/Kyorin (MK.767), and others. Experiments are being carried out with all the substances to determine their efficacy and toxicity (21).

The double sensitiser aryl-thiazolidindion TZD18 category has a marked hypocholesterolemic effect in animals by reducing cholesterol synthesis in the liver and increasing secretion of cholesterol and bile acids.

The new MCC-555 sensitiser has not only a hypoglycemizing and hypolipidemic effect but also a very marked vascular effect on the expression of adhesive molecules. This effect is mediated by alpha and delta activity, not gamma activity (22).

According to Duval (13), it is namely the development of PPAR triple agonists that is the most promising area of deve-

lopment of drugs against atherosclerosis. Affecting all three receptors simultaneously may have the most comprehensive anti-atherogenic effect.

DISCIPLINARY AND ORGAN VIEW OF PPAR

For any physician, the term PPAR invokes a connection with diabetology and lipidology. Within a couple of years, though, PPAR related issues will affect the whole medical sphere.

In oncology, the topics will be the anti-cancerogenic effect (both prophylatic and therapeutic), the effect of synchronization of tumor growth and the danger of triggering tumors. Most works concern colorectal carcinoma (12) and urological tumors. Nonetheless, works on tumors of almost any organ or system are available (more details in 1).

In neurology and psychiatry, research into application of PPAR modulating drugs has advanced both in the dementias group and in the autoimmune diseases group (multiple sclerosis and certain types of parkinsonism), and also in the prevention and treatment of cerebrovascular accidents. The enormous likely importance of PPAR beta in dermatology has already been mentioned. Besides wound healing, it could have a significant role in treating skin inflammations, allergies and psoriasis. A number of works concern symptoms of aging as such. Of the mentioned disciplines, the effect of PPAR modulation on striated muscle, on obesity, steatosis and liver cirrhosis, as well as prevention of diabetes, should be remembered. There is also a significant effect on the hibernation of animals, differentiation of a number of organs and tissues, the effect on acute pancreatitis or the effect on coagulation.

CONCLUSION

Nuclear receptors modulate the effect of key hormones, like the thyroid or steroid hormones. It can be claimed with confidence that this is an issue concerning medicine as a whole as well as all the foundations of organ, tissue and organism functions. Nobody would have thought ten years ago that the topic of nuclear receptors, especially PPAR, would be so extensively developed. It is evident today that the administration of PPAR antagonists and agonists, i.e. of alpha, beta, gamma or single, double and triple sensitisers (substances modulating one, two or all three PPAR families) will have an impact on all medical specialisations. It could be claimed, with only slight overstatement, that we may be standing close to the invention of a universal prophylactic pill that would prevent the development of diabetes, atherosclerosis, tumors, and inflammatory and degenerative diseases – that is, close to the invention of an anti-aging pill or elixir of youth.

Abbreviations

PPAR – peroxisome proliferator-activated receptors
RXR – receptor X for retinoid acid alpha

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