FENOFIBRATE TREATMENT MODULATES GENE EXPRESSION ACTIVITY IN PERIPHERAL BLOOD MONOCYTES OF HEALTHY VOLUNTEERS.

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Fenofibrate is a lipid-lowering drug used in the treatment of dyslipidemia. Fenofibrate effects have been assigned to activation of the nuclear transcription factor peroxisome proliferator-activated receptor-a (PPARa). Activated PPARa forms a heterodimer with the nuclear retinoid X receptor, which then binds specific peroxisome proliferator response elements (PPRE) located in target gene promoters, thereby modulating gene expression. PPARa activation has been reported to improve levels of triglycerides, HDL cholesterol, and the overall atherogenic plasma lipid profile, while also potentially modulating inflammation as well insulin resistance itself.

The present study investigated the molecular aspects of the response to fenofibrate treatment in peripheral blood monocytes of healthy subjects. This was achieved through the assessment of short-term (1 week) and middle-term (6 weeks) changes in the expression of genes related to metabolic pathways known to be modulated by fenofibrate treatment.

Functional analysis was performed to identify significant biological functions and pathways modulated by a PPARa-dependent or independent mechanisms.

Subjects and Study Design

Twenty-six males or post menopausal (natural or chirurgical) females not receiving hormone replacement therapy (HRT) or having stopped HRT for at least 1 month, aged 40-65 years inclusive, healthy (as determined by vital signs, medical history, physical examination, ECG, hematologic, biochemistry and urinalysis) were recruited in this open-label, single centre study to receive a standard dose of fenofibrate. Subjects and Study Design

Recruited in this open-label, single centre study to receive a standard dose of fenofibrate. All these DES, clusters showing different trends over time in gene expression after fenofibrate treatment (see Fig. 4). Gene identities eligible for network and functional analysis were in particular involved in metabolic and inflammatory pathways (see Fig. 5).

Statistical Analyses

A global effect of the treatment on the 78 (2+5) intensity profiles was determined using a 2-way ANOVA considering subject and visit (time) factors, adjusted by using the Benjamini-Hochberg false-discovery rate (FDR) method to adjust p-values and control for the first species error. Pairwise comparisons of the differentially expressed sequences (DES) between study visit values were performed using Newman-Keuls (NK) test. A significant effect of the treatment on the sequences was concluded for p ≤ 0.01.

For functional analysis, pathways and networks were constructed based on the classification of all the DES modulated in at least one pairwise comparison (p ≤ 0.01 to NK test via k-means clustering approach [user defined nb of cluster = 11, cosine correlation and centroid based search]).

SUMMARY OF FINDINGS

- Significant short-term and middle-term effects of fenofibrate on gene expression were observed in monocytes of healthy volunteers: 3,924 and 1,973 differentially expressed sequences (DES) were identified after 1 and 6 weeks of fenofibrate treatment, respectively. All these DES, differentially expressed sequences mapped gene identities and allowed for functional analyses. K-means clustering led to the identification of 11 clusters showing different trends over time in gene expression after fenofibrate treatment (see Fig. 4). Gene identities eligible for network and functional analysis were in particular involved in metabolic and inflammatory pathways (see Fig. 5).

- In a cell type with low fold-change levels of PPARa expression, only few genes were modulated by fenofibrate in a PPARa-dependent manner mainly between 1 and 6 weeks of treatment, whereas many others appeared to be modulated in a PPARa-independent manner.

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