

BETA-ADRENERGIC BLOCKERS AND LIPID METABOLISM. II. EFFECT OF REPEATED PROPRANOLOL APPLICATION ON SERUM FREE FATTY ACID LEVELS

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Suspected atherogenic activity of beta-blockers especially after a long-lasting usage and in patients with disturbed lipid metabolism presents still an unsolved problem, indeed. Evaluation of their action on lipid metabolism is complicated by numerous factors, e.g. the individual pharmacological characteristics of single representatives (sympathico-mimetic activity, cardioselectivity, membrane stabilizing effect), dosage, pathway and duration of application, combined application with other drugs, concentration of research on a limited number of parameters of lipid metabolism, etc. Studies of beta-blockers' effects on serum free fatty acids (FFAs) are commonly restricted to the determination of their total concentrations [3,5,6,9 a. oth.].

Our previous investigations [2] of serum levels of 8 FFAs in rats singly treated with propranolol showed a quantitatively differently expressed participation in the total reduction responding in three of these acids (C16:0, C18:1, and C18:2) to a linear dose- and time-dependence.

In the present paper demonstrating a component of our investigation of the effect of the non-selective beta-blocker propranolol on lipid metabolism the influence of this drug after repeated application on the serum levels of eight FFAs is followed-up. White male rats are used. The following FFAs are analyzed: myristic acid (C14:0), palmitic acid (C16:0), palmitoleic acid (C16:1), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), eicosatrienic acid (C20:3), and arachidonic acid (C20:4).

MATERIAL AND METHODS

The study covered 66 white male rats with b.w. between 130,0 and 160,0 g. Beta-blocker was intraperitoneally applied in a dose of 3 mg/kg b.w. two times daily for 20 days. Control animal group was treated by the same way for the same period with an equal volume of saline solution. Blood was taken on the 10th and 20th day after treatment by two ways: on the 2nd and 16th hour after the last drug administration as well as on the 15th day after treatment cessation. Serum was extracted after Folsh's et al. method (1957). After thin-layer chromatography of lipid extract [1] FFAs were quantitatively isolated, methylated with diazomethane and gas-chromatographically estimated.

RESULTS AND DISCUSSION

It is established that under these experimental conditions propranolol reduces statistically significantly total FFAs on the 10th day after treatment. Its effect is slightly marked on the 20th day (fig. 1). The comparison of the quantitative manifestation of the effect reveals its dependence on the interval after the last treatment: on the 2nd hour after the last application FFA level decreases by 21 per cent while after an interval of 16 hours - by 14 per cent only. Most probably, on the 2nd hour the effect of the last propranolol dose is added to that of repeated beta-blocker

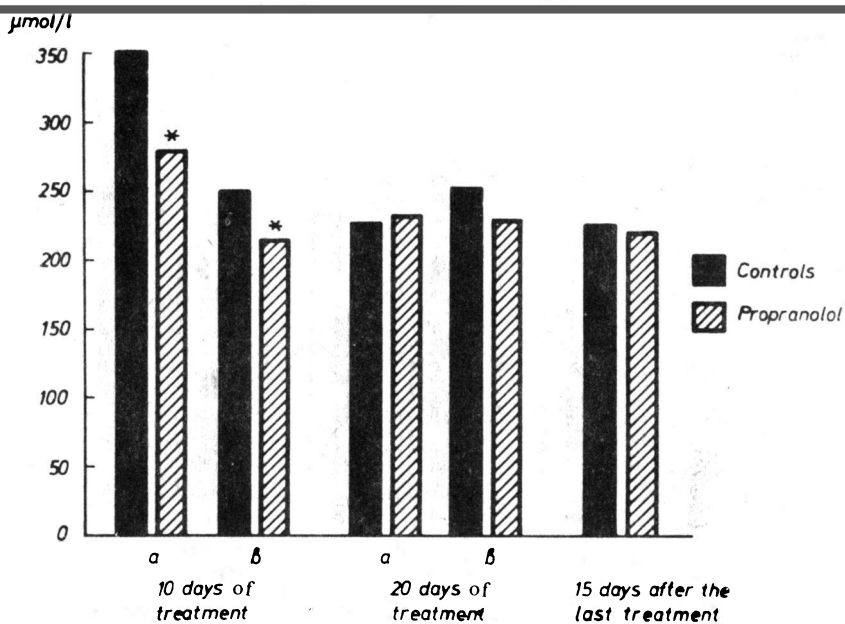


Fig. 1. Serum levels of total FFAs after propranolol administration for 20 days after cessation of treatment: a) 2 h after the last application, and b) 16 h after it. Asterisks indicate significant differences

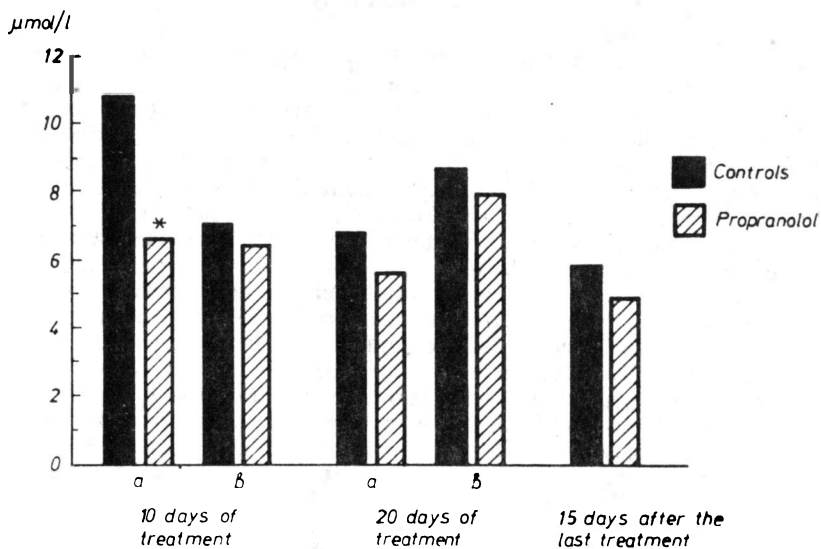


Fig. 2. Changes of serum levels of myristic acid after propranolol administration for 20 days and 15 days after cessation of treatment: a) 2 h after the last application, and b) 16 h after it. Asterisks indicate statistically significant differences

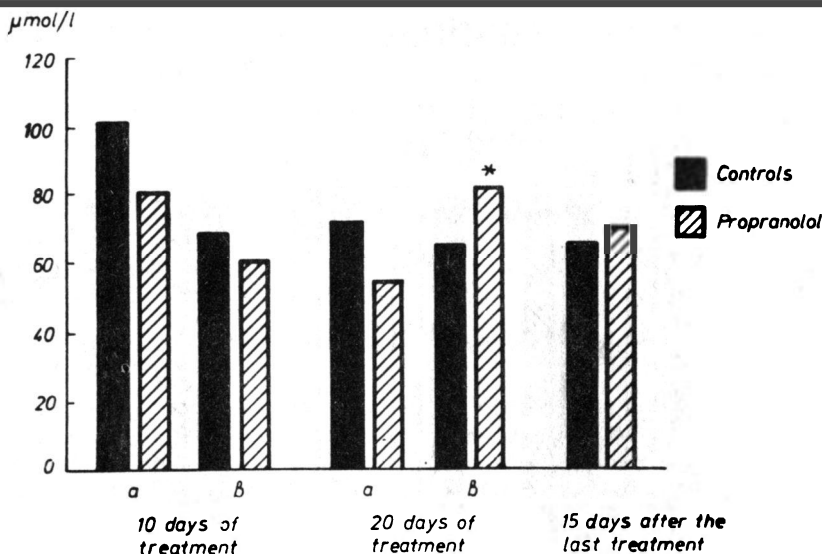


Fig. 3. Changes of serum levels of linoleic acid after propranolol administration for 20 days and 15 days after cessation of treatment: a) 2 h after the last application, and b) 16 h after it. Asterisks indicate significant differences

application. This propranolol effect reduction in the course of its long-lasting administration (i.e. on the 20th day) found out by us is similar to that one reported by Lehtonen [6] as an initial, during the first month only, FFA level decrease in patients chronically treated with a cardioselective beta-blocker. The effect of the drug is completely exhausted on the 15th day after cessation of application.

The participation of single FFAs in the total effect is quantitatively differently manifested: on the 10th day after a 2-h interval of examination there is the greatest reduction of C14:0 (by 38 per cent) followed by that of C16:1 (by 32 per cent) and C16:0 (by 24,9 per cent). However, on the 20th day the reduction of these FFAs is significantly less expressed, by 18 per cent, by 11,3 per cent and by 1,2 per cent, respectively. All changes are insignificant when a 16-h interval of examination is concerned. Similar behaviour of these three FFAs is illustrated on fig. 2 on the example of C14:0 concentration changes.

Polyunsaturated fatty acids act by a different manner. On the 10th and 20th day after a 2-h interval after the last injection C18:2 concentration remains reduced by about 20 per cent. In our previous investigation [2] we established a significant reduction of this acid even after a single propranolol administration. As C18:2 reduction in some lipid classes is considered a risk factor in ischemic heart disease [7] these data seem to be of particular importance. However, on the 20th day after a 16-h interval after drug introduction C18:2 concentration is increased (fig. 3).

Changes of arachidonic acid concentration differ from these of saturated and monoenic acids (fig. 4). In the course of propranolol treatment the level of this acid does not decrease significantly concerning any intervals examined and even increases on the 20th day. Having in mind the role of this acid as a prostaglandin precursor as well as data about its concentration increase in the myocardium under conditions of experimentally induced ischemia [8] this increase established by us on the 20th day after treatment has an essential importance for the characterization of propranolol influence on serum FFA levels.

There are similar changes of C20:3 concentration which increases on the 10th and 20th day after treatment.

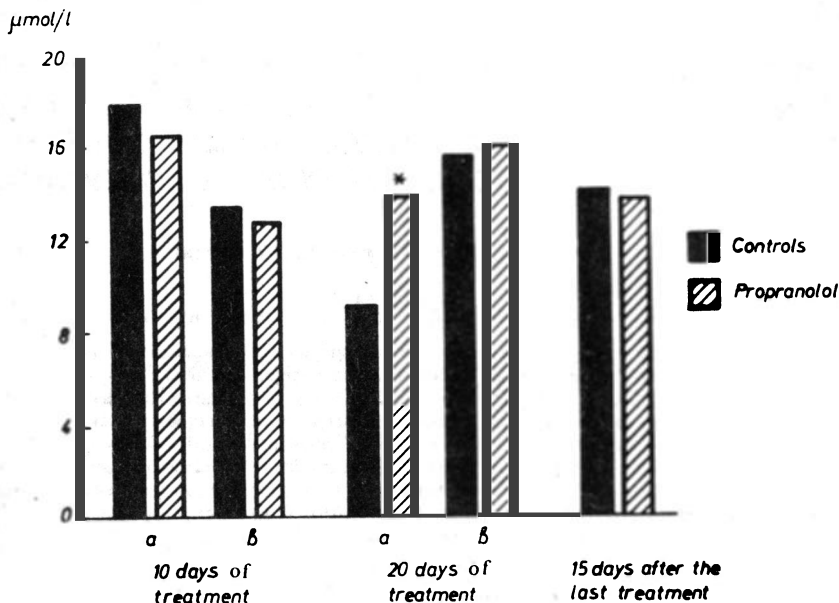


Fig. 4. Changes of serum levels of arachidonic acid after propranolol administration for 20 days and 15 days after cessation of treatment: a) 2 h after the last application, and b) 16 h after it. Asterisks indicate statistical differences

These differences in the behaviour of polyunsaturated FFAs, on the one hand, and of saturated and monounsaturated ones, on the other hand, in the course of long-lasting propranolol application enable us to suggest a different significance of the beta-adrenergic blockade for the lipolysis of these two FFA groups. Our previous studies concerning single propranolol application also direct our attention to a probably different role of beta-adrenergic control of lipolysis of individual FFAs [2]. In both cases, propranolol effect on individual FFA lipolysis is not an uniform one and thus requires its follow-up in the rest lipid classes - triacylglycerols, phospholipids, cholesterol esters, etc. It seems especially important to follow-up the concentration changes of polyenic acids, particularly of C20:4 as well as of C20:3 / C20:4 ratio being an important parameter in cases of an essential-fatty-acid deficit. Having in mind the most commonly rather long duration of beta-blocker therapy we suggest the purposefulness of the follow-up of these changes for a longer period of propranolol application.

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БЕТА АДРЕНЕРГИЧЕСКИЕ БЛОКЕРЫ И ЛИПИДНЫЙ МЕТАБОЛИЗМ. II. ВЛИЯНИЕ ПРОПРАНОЛОЛА ПРИ МНОГОКРАТНОМ ЕГО ПРИМЕНЕНИИ НА УРОВЕНЬ СЫВОРОТОЧНЫХ СВОБОДНЫХ ЖИРНЫХ КИСЛОТ

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РЕЗЮМЕ

Авторами прослеживается эффект многократного применения пропранолола на сывороточный уровень восьми свободных жирных кислот. Бета блокер применяется интраперитонеально в дозе 3 мг/кг 2 раза в день в течение 20 дней. Уровень свободных жирных кислот определялся на 10 и 20 дни с начала введения (2 и 16 часов после последнего введения) и на 15 день после остановки его введения посредством газ-жидкой хроматографии. На 10-тый день было установлено уменьшение тотального количества свободных жирных кислот. Эффект редуцирован на 20-тый день и вполне отсутствует на 15-тый день после прекращения введения. Участие индивидуальных свободных жирных кислот неодинаково в количественном отношении. Относительную стабильность показывает арахидоновая кислота, количество которой возрастает на 20-тый день. Обсуждаются различия в влиянии пропранолола на липолиз индивидуальных свободных жирных кислот.