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Original

^{18}F–fluorodeoxyglucose accumulation in the heart, brain and skeletal muscle of rats; the influence of time after injection, depressed lipid metabolism and glucose–insulin

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Abstract

BACKGROUND: to study the effect of lipid depressing drugs on ^{18}FDG myocardial concentration. The changes of ^{18}FDG uptake in myocardium, brain and skeletal muscle of rats were compared as influenced by acipimox, tyloxapol and glucose with insulin.
MATERIAL AND METHODS: 5.55 MBq of ^{18}FDG were administered to Wistar rats. Control rats were killed 15, 30, 45 and 60 minutes following intravenous injection and the radioactivity concentration (cpm/g of tissue) in relation to injected cpm was determined in a well crystal adjusted to 511 KeV in order to check the time of maximal ^{18}FDG tissue uptake. The radioactivity in myocardium, skeletal muscle and brain in intact animals was compared with that of rats treated with tyloxapol (tritton WR 1339, 125 mg intravenously immediately before ^{18}FDG injection), acipimox (nicotinic acid derivative, 25 mg by stomach cannula 15 minutes before ^{18}FDG), or glucose with insulin (intravenous injection of 0.04 g and 0.04 UI immediately before ^{18}FDG). The animals were killed 45 minutes following ^{18}FDG injection.
RESULTS: Tyloxapol and acipimox significantly elevated myocardial ^{18}FDG concentration (tyloxapol +37% and acipimox +48%), but the increase in ^{18}FDG concentration after glucose and insulin was slight and insignificant. The changes in skeletal muscle after lipid depressing agents were quite contrasting; the decrease in ^{18}FDG concentration was –74% after tyloxapol and –44% following acipimox administration. The accumulation of ^{18}FDG in brain was not influenced markedly by the drugs used or by glucose with insulin.
CONCLUSION: The highest ^{18}FDG uptake in myocardium could be achieved by depressing the lipid metabolism and not by administration of glucose with insulin only. A marked increase in glucose accumulation in myocardium is not possible without previous shift from the utilisation of fatty acids. This finding is fully in agreement with present knowledge about energetic metabolism of myocardium.
Key words: ^{18}FDG, myocardium, acipimox, glucose, insulin

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Introduction

Free fatty acids (FFA) represent the main energetic fuel for normoxic myocardium [1], but glucose is beginning to be the main source of energetic metabolism, in the case of oxygen lack, demanding anaerobic metabolism together with stimulation of glucose uptake and gluconeogenesis [2].

Fluorodeoxyglucose labelled by positron emitter ^{18}F (^{18}FDG) has been widely used for scintigraphic imaging of normal and viable myocardium because the uptake of ^{18}FDG in myocytes is similar to endogenic glucose [3].

It seems to be essential to increase myocardial uptake of ^{18}FDG and to elevate myocardial concentration in order to achieve better PET scintigrams. There are two clinically used possibilities: either to increase the affinity for glucose by insulin or to depress the lipid metabolism of the myocardium. The first technique has some limitations, in particular in diabetic patients, and therefore an insulin-glucose clamp is practised. However preceding saturation of myocardium by glucose before ^{18}FDG application seems to be rather contradictory. The second possibility is to decrease pharmaceutically the uptake of FFA and myocardial lipid turnover and to provoke a shift of predominantly lipid utilisation to the glucose metabolism.

Most of the published data describing the influence of both techniques on ^{18}FDG uptake in the human heart have been gained by PET scintigraphy. However this procedure cannot be accurate for determination of ^{18}FDG-tissue concentration and therefore exact results could be obtained in animal experiments only.

The aim of our study was to determine the influence of antilipemic agents and glucose with insulin on ^{18}FDG concentration in the heart of rat at a time of maximal uptake after intravenous injection. Prior to this determination it was necessary to check the time of maximal tissue uptake following intravenous application of ^{18}FDG. The differences in myocardial ^{18}FDG uptake could be more evident in comparison with other tissues, in particular with brain and skeletal muscle.

Material and methods

The experiments were carried out on Wistar rats of 180 g weight (175–200 g). 5.55 MBq of ^{18}FDG produced by a cyclotron unit at the Nuclear Physics Institute was injected intravenously. Groups of control rats, consisting of 5 animals, were killed 15, 30, 45 and 60 minutes following ^{18}FDG injection. All important organs or samples of tissues were weighed and measured for radioactivity. The radioactivity concentration (cpm/g of tissue) in relation to total injected cpm was determined in a well detector adjusted to 511 KeV in order to define optimal time of maximal ^{18}FDG tissue accumulation after its intravenous injection. Tissue radioactivity concentration in myocardium, brain and skeletal muscle of control animals was compared with that of another groups of rats (consisting of at least 5 animals) treated by drugs with expected influence on ^{18}FDG accumulation in the myocardium.

For lipid metabolism depressing, the following drugs were used: a) tyloxapol (triton WR 1339), experimentally used for its blocking of superficial membranes, inhibiting lipoprotein transport into the cells and blocking hormone-sensitive lipase (intravenous injection of 125 mg immediately preceding ^{18}FDG injection), b) acipimox (Olbetam®, Pharm&Upjohn S.p.a., Italy), dissolved in water, 25 mg by stomach cannula 15 minutes prior to ^{18}FDG. Another group of animals was treated by intravenous injection of 0.04 g of glucose and 0.04 UI of insulin immediately before ^{18}FDG application.

All rats given drugs were killed 45 minutes after ^{18}FDG injection, i.e. at the time of maximal ^{18}FDG tissue accumulation.

Results

The uptake of ^{18}FDG in the heart, brain, kidney, liver, spleen, lungs and skeletal muscle with blood radioactivity related to the period after intravenous injection shows that maximal radioactivity concentration in myocardium, brain and muscle was achieved in 45 minutes (Tab. 1). Therefore this time period from ^{18}FDG injection to the killing of animals was used in all groups of rats treated by the studied drugs.

Table 1. The ^{18}FDG concentration (mean ± STD), expressed in % (cpm/g of tissue), related to the total injected cpm

	15 min.	30 min.	45 min.	60 min.
blood	0.78 ± 0.07	0.60 ± 0.07	0.26 ± 0.06	0.15 ± 0.01
myocardium	6.13 ± 0.30	6.37 ± 0.81	7.20 ± 1.38	5.39 ± 1.29
lungs	0.92 ± 0.05	1.08 ± 0.13	0.84 ± 0.14	0.46 ± 0.12
spleen	0.82 ± 0.09	1.12 ± 0.14	0.86 ± 0.09	0.73 ± 0.10
kidney	1.59 ± 0.14	1.24 ± 0.21	0.66 ± 0.11	0.62 ± 0.05
skeletal muscle	0.30 ± 0.04	0.51 ± 0.05	0.87 ± 0.22	0.35 ± 0.13
brain	2.72 ± 0.32	2.16 ± 0.14	2.74 ± 0.46	1.58 ± 0.19
liver	0.88 ± 0.07	0.58 ± 0.05	0.28 ± 0.01	0.16 ± 0.01

There are great differences in ^{18}FDG accumulation between tissues. The highest radioactivity concentration in control rats was in the heart, nearly three times higher when compared with the brain and more than seven times higher than in other organs. The concentration of ^{18}FDG in myocardium was 8 times that in spleen, 11 times in kidney and 16 times in liver. Blood background gradually decreased during the first hour. Therefore we compared the effect of the tested drugs on ^{18}FDG uptake in myocardium, brain, and also in skeletal muscle having another energetic metabolism.

Both tyloxapol and, even more, acipimox significantly increased myocardial uptake of ^{18}FDG; its concentration was, in comparison with control group of animals, 37% and 47% higher, respectively. The increase after glucose with insulin was slight and insignificant (Fig. 1)

The influence of the tested drugs on the accumulation of ^{18}FDG in skeletal muscle was quite opposite to that in the myocardium. Whereas glucose and insulin increased slightly the concentration of' ^{18}FDG, acipimox and, even more, tyloxapol markedly decreased tissue uptake of ^{18}FDG (Fig. 2).

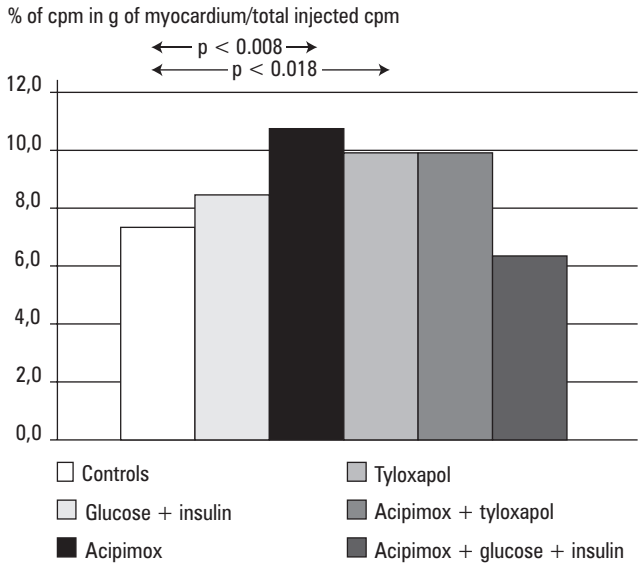

Figure 1. Accumulation of ^{18}FDG in myocardium.

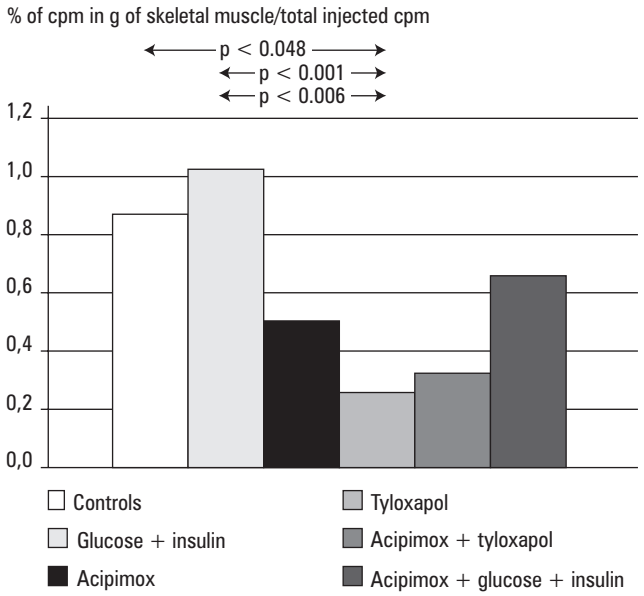

Figure 2. Accumulation of ^{18}FDG in skeletal muscle.

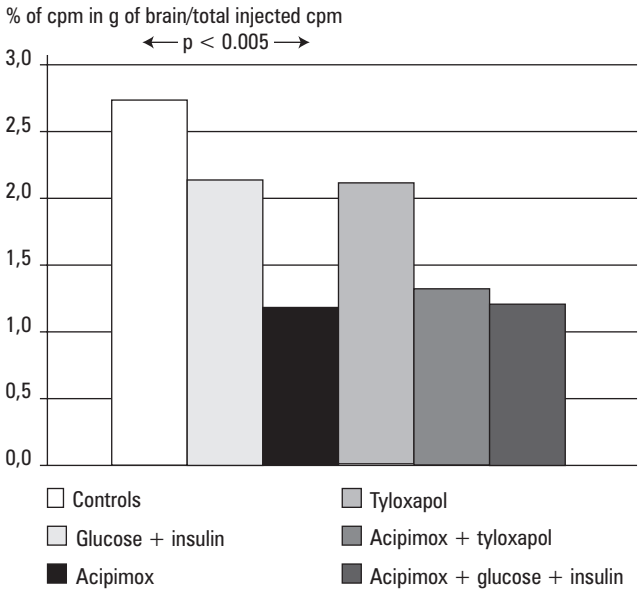

Figure 3. The ^{18}FDG accumulation in brain.

The ^{18}FDG accumulation in brain was not significantly influenced by the tested drugs; all drugs decreased slightly its concentration (most significantly after acipimox) in comparison with control animals (Fig. 3).

Discussion

The utilisation of FFA as a main fuel source for intact myocardium has been known for some years [3–5]. Usually the glucose metabolism in myocardium is inhibited by fatty acids oxidation. The shift to glucose metabolism is performed at an important level of ischaemia and lack of oxygen, or when the blood level of FFA is too low [6]. Similarly, the preference for glucose uptake begins when the blood level of fatty acids is too low but simultaneously blood concentration of glucose and insulin is high [7]. Regarding the ischaemia, the shift to predominant glucose uptake begins at a very deep reduction of coronary flow, by more than 75%, as has been demonstrated by experimental data [8].

^{18}FDG is accumulated by myocardium from the blood like glucose but is not completely metabolised by the glucose cycle [3]. Therefore it does not depict accurately the fate of glucose degradation but the grade of its accumulation expresses the ability of the working myocardium to accumulate glucose for further utilisation as an energetic source. PET scanning routinely uses ^{18}FDG for demonstration of well-perfused and viable myocardium, though the myocardial tissue prefers fatty acids. As mentioned, glucose uptake and metabolism of myocardium are inhibited by oxidation of fatty acids [7], and begin to prevail till deep myocardial ischemia [8]. The preferred uptake and utilisation of fatty acids must be therefore depressed in order to increase the demand for glucose. It has been described by Fuccella et al. [9] that the nicotinic acid and, even much more, acipimox markedly inhibits lipolysis and therefore this drug was originally recommended for treatment of hyperlipidemia. Further, acipimox became the centre of attention for its depressive effect on lipid metabolism in connection with PET scintigraphy of the heart and ^{18}FDG. This drug markedly decreases oxidative degradation of fat and plasmatic level of fatty acids in healthy men [10] and increases glucose utilisation [11]. Another mechanism with a similar effect in experiments on animals is tyloxapol (triton WR 1339), a potent surface detergent but not suitable for human administration, which induces reduction in heart lipase activity due to the inhibitory effect of free fatty acids [12]. The increase of ^{18}FDG accumulation in the heart after acipimox, as well as after insulin clamp, was described in myocardial PET scintigraphies [13, 14].

As mentioned, all studies regarding myocardial ^{18}FDG accumulation and PET scintigraphy carried out till now have not been able to inform exactly about actual tissue ^{18}FDG concentration and therefore this problem remains to be solved experimentally. Our results showed that both lipid-depressing agents significantly increased the myocardial ^{18}FDG concentration 45 minutes after intravenous injection. In contrast, the increase of ^{18}FDG concentration in myocardium was slight and insignificant after glucose with insulin. This experimental finding correlates well with scintigraphic results in humans, when the accumulation of ^{18}FDG in normal or abnormal myocardium did not differ after a small or great dose of insulin, only the image was better due to the lower blood background [15]. The combination of acipimox and glucose with insulin did not elevate the myocardial ^{18}FDG concentration as observed in PET scintigraphy by Schröder et al. [16].

Acipimox and tyloxapol markedly decreased ^{18}FDG concentration in non-working skeletal muscle of the rat in contrast to the myocardium, whereas glucose and insulin increased ^{18}FDG accumulation. Our finding is quite in agreement with similar behaviour of glucose uptake described by Jenkins et al. [17]. They studied the non-labelled glucose utilisation index in skeletal muscle and myocardium in rats after administration of long-chain fatty acid oxidation blocking methyl palmoxyrate and glucose clamp. As in our experiments, lipid-depressing agent significantly increased glucose utilisation in the myocardium and simultaneously it was decreased

in red skeletal muscle. These results are in accordance with the fact that the energetic metabolism of myocardium and skeletal muscle substantially differs. This finding is corroborated by results of a clinical PET study, published by Nuutila et al. [18]; they observed significantly lower ^{18}FDG accumulation in the heart of endurance athletes and increased uptake in femoral muscle.

^{18}FDG concentration in the brain was not markedly influenced either by acipimox and tyloxapol, or glucose with insulin. Clearly brain metabolism is not based on free fatty acids; also insulin does not increase glucose transport through blood-brain barrier, as was demonstrated under normal circumstances by PET scintigraphy on healthy volunteers [19].

In order to achieve maximal ^{18}FDG accumulation for PET scintigraphy of the heart, it seems to be rather contradictory from the physiological point of view „to feed" the myocardium with glucose and insulin before ^{18}FDG administration, because myocardial muscle prefers fatty acids as a fuel. Therefore it is more reasonable to reduce lipid metabolism of the myocardium by lipid depressing agent such as acipimox and to shift substantially myocardial metabolism to glucose utilisation and in this way to augment simultaneously ^{18}FDG accumulation in the heart.

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