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Model of adipose tissue cellularity dynamics during food restriction

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HIGHLIGHTS

- Adipocytes deflate according to lipid fluxes via lipolysis.
- We show using biological data that lipolysis rate is radius squared based.
- We use longitudinal biopsies during food restriction to assess size evolution.
- We relate size distribution evolution to radius square based rate.

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ABSTRACT

Adipose tissue and adipocytes play a central role in the pathogenesis of metabolic diseases related to obesity. Size of fat cells depends on the balance of synthesis and mobilization of lipids and can undergo important variations throughout the life of the organism. These variations usually occur when storing and releasing lipids according to energy demand. In particular when confronted to severe food restriction, adipocyte releases its lipid content via a process called lipolysis. We propose a mathematical model that combines cell diameter distribution and lipolytic response to show that lipid release is a surface (radius squared) limited mechanism. Since this size-dependent rate affects the cell's shrinkage speed, we are able to predict the cell size distribution evolution when lipolysis is the only factor at work: such as during an important food restriction. Performing recurrent surgical biopsies on rats, we measured the evolution of adipose cell size distribution for the same individual throughout the duration of the food restriction protocol. We show that our microscopic model of size dependent lipid release can predict macroscopic size distribution evolution.

1. Introduction

In the past decades, obesity has emerged as an acute and increasing public health problem worldwide (Flier, 2004). Obesity is associated with several conditions, one of the most devastating being type 2 diabetes (Kahn et al., 2006; Abrams and Katz, 2011). Recent findings have put adipose tissue and adipocytes as a central hub of many interacting physiological pathways through the production of numerous adipokines such as adiponectin and leptin (Deng and Scherer, 2010).

In particular, adipocytes serve as calorie storage and are therefore well suited to regulating energy balance. Although adipocyte size results from the equilibrium between influx and efflux of lipids; size markedly alters tissue function such as adipokine production (Skurk et al., 2007; Matsubara et al., 2009). Understanding adipocytes size and number dynamics is then a crucial issue for understanding the pathophysiological basis of obesity and its related metabolic disorders.

At first glance, adipocytes are simply fat depots. Triglycerides (TG) are intracellularly stored as fat droplets (via a mechanism called lipogenesis) and are hydrolyzed (via a mechanism called lipolysis) when needed and excreted into the extracellular milieu in the form of glycerol and non-esterified fatty acids (NEFAs). Thus, the overall lipid storage in adipose tissues represents the excess energy consumption relative to energy expenditure. The size (radius) difference between adipocytes in the same population can span an order of magnitude. This reaches three orders of magnitude for the volume: such a variation is unique in the same organism. In addition, adipocytes have no unique characteristic size. Indeed adipocytes exhibit a bimodal size distribution: one peak population of small size with diameter around 15 μm and another peak for bigger adipocytes generally more than 60 μm (Mclaughlin et al., 2007).

Adipocyte size and number for instance reflect directly the volume of the lipid content. Obese subjects tend to have an increased mass of adipose tissue mainly resulting both from more

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numerous and bigger adipocytes (Drolet et al., 2008; MacKellar et al., 2010; Arner and Spalding, 2010).

Individual adipocyte size and population size distribution have attracted a lot of attention concerning their physiological impacts. Indeed, differences in size distribution are associated with a diabetic phenotype (Mclaughlin et al., 2007), hepatic steatosis (Kursawe et al., 2010) and inflammation (Mclaughlin et al., 2010; Liu et al., 2010). Several other studies have shown that an individual adipocyte's size may have an impact on its behavior such as adipokines secretion (Skurk et al., 2007), glucose metabolism (Lay et al., 2001), lipolysis (Zinder and Shapiro, 1971; Smith, 1971), lipogenesis activity (Gliemann and Vinten, 1974) and the expression of adrenoceptors (Lafontan and Berlan, 1995). Recent works have dealt with the issue of size dynamics: How adipocytes population size shifts under various dietary conditions for different mouse strains (Jo et al., 2009, 2010) or the Zucker rat (MacKellar et al., 2009, 2010).

In a previous paper (Soula et al., 2013), we showed that size dependent lipid fluxes can lead and explain bimodal distribution at equilibrium. In the present study, using biological data, we first show evidence that the efflux rate – i.e lipolysis – is indeed radius squared rate. Since lipolysis is a mechanism that affects the size of an adipocyte via the reduction of its lipid content. A given level of noradrenergic stimulation induces a change of volume proportional to the surface. Starting with a given population of adipocytes whose size (radius) distribution is known we are able to predict the evolution of this population using transport equation and we derived the evolution equation of an adipocyte population submitted to lipolysis only. We confronted our model with a longitudinal study of rats submitted to severe food restriction and used periodic biopsies to assess cell size distribution.

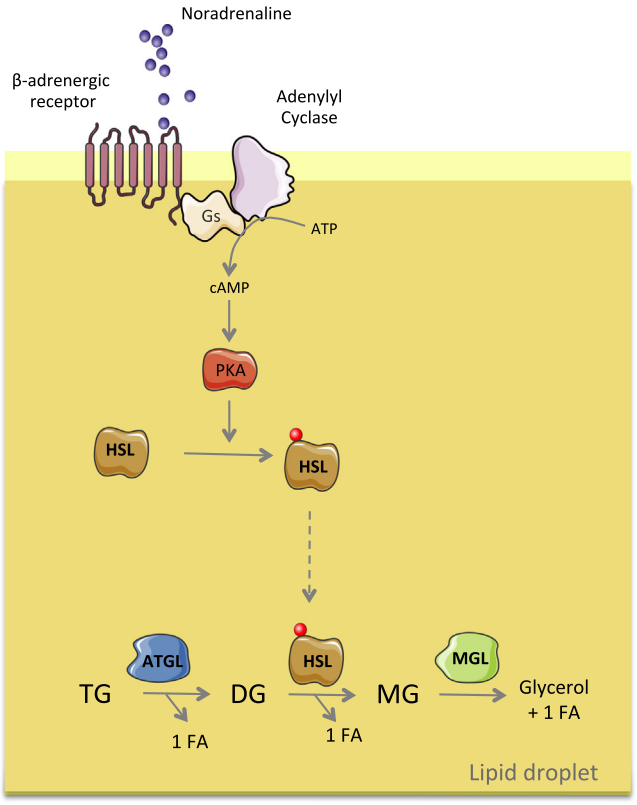

Fig. 1. Stimulation of adipocyte lipolysis by catecholamines (noradrenaline, adrenaline). Abbreviations: AC, Adenylyl Cyclase; ATGL, Adipose Triglyceride Lipase; DG, Diglyceride; HSL, Hormone Sensitive Lipase; MG, Monoglyceride; MGL, Monoglyceride Lipase; PKA, Protein Kinase A; TG, Triglyceride.

2. Mathematical model of size-dependent lipolysis

Lipolysis is the efflux of lipid that an adipocyte undergoes when submitted to catecholamines stimulation in a dose dependent manner (see Fig. 1 for a schematic description). In short, catecholamines activates β-adrenoceptors and adenylyl cyclase to increase the concentration of cAMP. This in turn will trigger a cascade that lead to the release of stored triglycerides in the form of Non-Esterified Fatty acids and glycerol. To estimate a size dependent lipolysis, we propose a simple three-parameters Michaelis–Menten like dose–response scheme to describe the Norepinephrine-induced release of glycerol. Note that it amounts to assume implicitly that this step is the limiting one.

In its simplest version and for a given cell of radius r this amount of released glycerol will be

$$g_{0,2}(r,[\mathrm{Nor}]) = b + ar^2\frac{[\mathrm{Nor}]}{\kappa+[\mathrm{Nor}]}. \tag{1}$$

with b the basal lipolysis (nmol h^{-1} cell^{-1}), a the lipolysis rate (nmol h^{-1} cell^{-1} μm^{-2}), κ the efficient concentration for Norepinephrine stimulation ([*Nor*] in mol) yielding a hourly glycerol release rate $g_{0,2}$. This model assumes radius squared dependence but a more general model can be used:

$$g_{m,n}(r,[\mathrm{Nor}]) = br^m + ar^n\frac{[\mathrm{Nor}]}{\kappa+[\mathrm{Nor}]}. \tag{2}$$

Here we used n and m are the size scaling parameters and a value of zero for either means a size-independence for the related parameter. Note that in case units are for b nmol h^{-1}cell^{-1} μm^{-m} and for a: nmol h^{-1}cell^{-1} μm^{-n}. The model is composed of three parameters b, a and κ and several models are available depending on m and n.

Having access to the cell size density function ρ, we can estimate the lipolysis hourly rate for N cells

$$L_{m,n}([\mathrm{Nor}],a,b) = \sum_{i=1}^{N_{\mathrm{bins}}}\left(br_i^m + r_i^n aN\frac{[\mathrm{Nor}]}{\kappa+[\mathrm{Nor}]}\right)\rho(r_i) \tag{3}$$

using $\rho(r_i)$ as the density histogram – the fraction of cells with radius in $[r_i, r_{i+1}]$ for $1 \le i \le N_{\mathrm{bins}}$ and N_{bins} being the number of bins.

Once the scaling parameters (m,n) set, a triplet of the free parameters a, b and κ yields a population lipolysis dose response $L_{m,n}(\mathrm{Nor}, a, b, \kappa)$.

In Soulage et al. (2008) data contained the norepinephrine dose–response alongside the corresponding adipocyte size distribution for two rat strains: Lou/C and Wistar rats. Lou/C is considered obese-resistant (Couturier et al., 2002; Perrin et al., 2003) while Wistar rats spontaneously develop obesity with age (Newby et al., 1990). The adipocytes size distribution of the two groups is displayed in the inset of Fig. 2 and shows clearly a left-shifted distribution (towards smaller adipocytes) of Lou/C compared to the Wistar. This difference allows us to compare size-dependent lipolysis models. Indeed, lipolytic responses of these two groups are depicted in Fig. 2 – plain line as the release rate of glycerol when cells are stimulated with norepinephrine. Using group size distributions (see Methods section Eq. (3)), we can use several size-dependent model to explain both groups at once. Although several models are available, we suspect a surface-limited flux of fatty acids and glycerol (Zinder and Shapiro, 1971; Gliemann and Vinten, 1974).

For a given model, we obtained the model parameters (a, b, κ) to fit to the Lou/C strain data (see Methods). The Wistar lipolytic response is then estimated by using the Wistar rat cell size