British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2011.01788.x
www.brjpharmacol.org

Themed Section: Fat and Vascular Responsiveness

EDITORIAL

Obesity and vascular dysfunction: the fat-e of rich and poor

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Received
15 November 2011
Accepted
15 November 2011

Linked Articles
This article is part of a themed section on Fat and Vascular Responsiveness. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2012.165.issue-3

Obesity, defined as excess accumulation of body fat, is due to a chronic imbalance between a too plentiful supply of dietary calories and a limited level of physical activity, often on a background of genetic susceptibility (Woodhouse, 2008).The beginning of the 21st century has witnessed an alarming, almost explosive increase in the number of obese people (e.g. Haslam and James, 2005; Bloom *et al.*, 2008; Bays, 2011). This, albeit for very different reasons, has been evident both in the Western world and in emerging countries, in particular in China. In Western countries, since the days of Pieter Bruegel and until the beginning of last century, being fat was rather associated with being rich, and being 'Rubenesque' was beautiful. As the concept of physical beauty evolved to almost anorexic silhouettes, the well-to-do became more and more weight conscious as they could afford the more expensive, balanced 'healthy' food and the access to gymnasia. By contrast, the not-so-well-to-do turned increasingly to cheaper fast-foods and snacks while they became extremely sedentary as machines replaced real labour, automobiles made walking redundant and watching television became the focal activity. In the emerging countries where the majority of the population was/is lean, the access to sudden wealth (permitting food intake *ad libitum*) combined with the broad availability of Western products (provided by the invasion of the fast-food chains) has triggered a real epidemic of obesity among the new rich, in particular among children. For example, this is very obvious in China, the land of the happy smiling but very obese Buddha, where the one-child policy favours leniency and thus exaggerated food intake in the very young. In addition, both the 'new poor' in the West and the 'new rich' in the East often belong to ethnic groups that for generations have survived hunger and famine and thus are genetically rather better prepared to fight limitation than abundance. From an evolutionary point of view, fat and adipocytes are no villains, as they prepare our organism to resist rainy, or rather, snowy days. However, too many adipocytes and too much fat, for too long, obviously are deleterious for health as they predispose to the continuum of metabolic syndrome, type 2 diabetes and cardiovascular disorders, not to mention other diseases (e.g. Wild *et al.*, 2004; Haslam and James, 2005; Bays, 2011). Key to the understanding of the progression of this continuum is the recognition that adipocytes affect the function of the vascular wall, both at distance and locally. The purpose of this themed issue is to summarize the current knowledge about the complex interactions between fat and vascular cells.

Fifty years ago, the vision of vascular control was rather simple: besides local metabolites directly governing the opening of arterioles in function of the needs of the tissues, daily vascular regulation was pretty much the affair of the omnipotent sympathetic adrenergic nervous system, with its partner the adrenal medulla, and that of the kidney, with the production of renin and thus angiotensin II (see Shepherd and Vanhoutte, 1979). A first glimpse of the importance of local modulation of the control of vascular tone came with the realization that a number of factors could impinge on the adrenergic nerve endings and reduce or augment the amount of noradrenaline released per nerve impulse reaching the adrenergic varicosities (Vanhoutte, 1974; Vanhoutte *et al.*, 1981). A further fundamental breakthrough was the discovery that endothelial cells could initiate relaxations (Furchgott and Zawadzki, 1980) or contractions (De Mey and Vanhoutte, 1982) of the underlying vascular smooth muscle, permitting the concept of endothelium-dependent control of vascular tone (Vanhoutte, 1988; Furchgott and Vanhoutte, 1989). Thirty years later we know a lot about nitric oxide, endothelium-dependent hyperpolarization, endothelins and endothelium-derived vasoconstrictor prostaglandins but we still do not understand all the complexities of endothelial control (e.g. Félétou and Vanhoutte 2009; Vanhoutte, 2009, 2011; Vanhoutte *et al.*, 2009; Garland and Weston, 2011; Rodriguez-Pascual *et al.*, 2011; Rubanyi, 2011). However, we are (or at least I am) convinced that endothelial dysfunction, with reduced release of relaxing signals and augmented production of vasoconstrictor mediators, is the first step that permits the inflammatory reaction that leads to atherosclerosis (Vanhoutte *et al.*, 2009). It will become clear to the reader of this themed issue that, both in the animal and in humans,

obesity results in progressive endothelial dysfunction, not only in large arteries, but also at the level of the microcirculation, which then helps us to understand why it is a major risk factor for cardiovascular disease (Bagi *et al.*, 2012; Barton *et al.*, 2012; Campia *et al.*, 2012; Hui *et al.*, 2012).

The question of importance of course is how exaggerated accumulation of fat cells could bring about such dysfunction at a distance. The answer is provided by the evidence that adipocytes produce chemokines (adipokines) that are secreted in the blood stream and modify the release of NO and vasoconstrictor prostaglandins in opposite directions, in a good or a bad sense depending on the state of the fat cells and thus of the adipokines that they release (e.g. Furuhashi and Hotamisligil, 2008; Zhu *et al.*, 2008; Lee *et al.*, 2009; Shibata *et al.*, 2009). This is exemplified in this themed issue for the lack of adiponectin and the emergence of both adipocyte fatty acid binding protein and lipocalin-2, respectively (Hui *et al.*, 2012; Wang, 2012). The impact of adipokines on the vascular wall is not limited to moment-to-moment changes is the release of endothelium-derived vasoactive factors, but some of them also can profoundly affect local inflammation, growth and remodelling (Lee *et al.*, 2009; Miao and Li, 2012; Hui *et al.*, 2012; Jamaluddin *et al.*, 2012). Obviously, these adipokines have become precious biomarkers and predictors, and their study provides exciting possibilities to identify novel targets for the treatment of obesity and its related cardiovascular complications (Bagi *et al.*, 2012; Barton *et al.*, 2012; Campia *et al.*, 2012; Gollasch, 2012; Hui *et al.*, 2012; Jamaluddin *et al.*, 2012; Miao and Li, 2012; Payne *et al.*, 2012; Wang, 2012).

The generation of adipokines by fat cells can be regarded as an endocrine function and one can even pretend that, based on weight, fat is the largest endocrine organ of the body. But the concept is also emerging that adipocytes of the perivascular tissue also may exert a more direct, local effect on the vascular wall (e.g. Auger *et al.*, 2007; Brandes, 2007; Ichiki, 2010). This themed issue reviews how perivascular adipose tissue does so by generating relaxing mediators, not to mention inflammatory mediators and growth factors (Miao and Li, 2012; Aghamohammadzadeh *et al.*, 2012; Barton *et al.*, 2012; Gollasch, 2012; Payne *et al.*, 2012). The exact nature of some of those adipocyte-derived vasoactive factors remains elusive and we do not know how to interrupt their effect specifically. Thus we do not know whether or not those signals from outer space actually contribute to the regulation of vascular tone in the intact organism. But since Furchgott's at first unbelievable observation (Furchgott and Zawadzki, 1980) we have learnt never to say: 'This is not possible'.

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