Reviewer's report

Title: Regulation of vascular tone by adipocytes

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Reviewer: Maik Gollasch

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This is an interesting and timely written review on an extremely important topic in medicine. The review summarizes current knowledge on the role of adipokins in the regulation of vascular tone in health and cardiovascular diseases, with major focus on obesity. I would suggest Minor Essential Revisions:

1) The authors might more clearly indicate that H2S is a novel, important candidate of “adipocyte-derived relaxing factor”, which produces endothelium-independent relaxations. There are two reports on H2S as important candidate of ADRF (Fang et al, Schleifenbaum et al., both in J. Hypertens.). It is also clear that removed endothelium had no effects (Fang et al., 2009).

2) The authors state that “it has been postulated that epoxyeicosatrienoic acids (EETs)/EDHF-dependent vasorelaxation might act as a back-up plan in case of reduced NO availability in vivo [36]”. To introduce a balanced discussion, it might be appropriate to discuss that EETs can also cause NO release to influence vascular tone (Hercule et al., ATVB, 2009).

3) P. 8. Fesüs et al. have studied adiponectin gene-deficient mice, but not adiponectin receptor 1 knock out mice.

4) P. 8: At this place, the reference of Gao YJ, Lu C, Su LY, Sharma AM, Lee RM is misleading. Gao et al did not study adiponectin gene deficient mice. ADRF effects are endothelium-independent (see ad 1). Therefore, it is unlikely that hydrogen peroxide plays a role in the effects. Instead, it is possible that Gao’s work is more related to other adipokins, for example TNFalpha, which “impairs endothelium-dependent vasorelaxation in various vascular beds as a result of a decrease in endothelial NO release or an increase in NO-scavengers (ROS) [65]”. Of note, you also mentioned a recent study, which “has shown a reduced vasorelaxing effect of perivascular adipose tissue in response to TNF# and interleukin-6 (IL-6), which upregulate ROS [54]”.

5) How is it possible that IL-6 produces vasorelaxation, but genetic deletion of IL-6 attenuates angiotensin II-induced hypertension in mice [87]. Please, provide a more critical discussion.

6) P. 12: “The angiotensinogen-deficient mice were normotensive, due to angiotensinogen expression.” What do you mean?

7) The authors state: “However, hydrogen sulfide generation and CSE expression in perivascular adipose tissue (but not in aorta) are shown to be increased in hypertensive rats [143], while the vasorelaxing effect of perivascular
adipose tissue is shown to be impaired in hypertension [144].” This statement seems to be too broad and incorrect since different models of hypertension have been used. Please, note that hypertension in [143] has been induced by abdominal aortic banding. In this report, H2S generation and CSE protein expression were significantly increased in PAT of stenotic aortas but not in aortic tissues. Transplanting PAT into periadventitia of stenotic aortas ameliorated the elevated arterial blood pressure (Fang et al., J Hypertens 2009). In my view the data show that there seems to be a compensatory up-regulation of CSE in PAT of stenotic aortas, which could have been develop independently of hypertension? Please, note that CSE knockout mice are hypertensive (Yang et al., Science 2008). Please, also note that SHR rats have been used in [144] as model of hypertension, which is different to aortic banding.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.