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COMMENTARY

Obesity – a risk factor or a RISK factor for myocardial infarction?

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The detrimental actions of leptin on cardiovascular function are well established. Smith *et al*. report the novel finding of a reduction of infarct size by exogenous leptin when given at reperfusion. The involvement of the reperfusion injury salvage kinase (RISK) pathway in such reduction of infarct size and its relation to ischemic pre- and postconditioning are discussed and some methodological issues in its assessment are raised. Obesity has possibly opposite effects on the incidence and outcome of myocardial infarction.
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Abbreviations: Akt, protein kinase B; ERK, extracellular-regulated kinase; IP_3 kinase, inositoltrisphosphate kinase; JAK, janus kinase; MAPK, mitogen-activated kinase; MPTP, mitochondrial permeability transition pore; RISK, reperfusion injury salvage kinase; STAT, signal transducer and activator of transcription

There is an increasing awareness that obesity is not only a growing epidemic but also a serious risk factor for cardiovascular disease, notably myocardial infarction (Hawken *et al*., 2005). Obesity is associated with increased plasma leptin levels. Leptin is the 16 kDa product of the obese (*ob*) gene and is released from adipose tissue, that is, it is a adipocytokine (Zabeau *et al*., 2003; Ren, 2004). Leptin shares structural homology with other cytokines such as tumor necrosis factor-α and interleukin 6, that is, inflammatory cytokines, which have been linked to atherosclerosis and acute coronary syndromes (Plutzky, 2001). Chronic leptin infusion in rats increases heart rate and arterial pressure (Shek and Brands, 1998), leptin impairs excitation–contraction coupling and decreases contractile function in isolated adult rat and mouse cardiomyocytes (Nickola *et al*., 2000; Dong *et al*., 2006), leptin induces hypertrophy in cultured neonatal rat cardiomyocytes (Rajapurohitam *et al*., 2003) and leptin promotes arterial thrombosis in mice (Konstantinidis *et al*., 2001), all undesired effects in the setting of cardiovascular disease. There are at least five leptin receptor isoforms, and a complex intracellular signalling system has been identified in a variety of different cells and organs, which includes NO, inositoltrisphosphate (IP_3) kinase, mitogen-activated protein (MAP) kinases, Janus kinase (JAK), signal transducer and activator of transcription (STAT) and others (Zabeau *et al*., 2003; Ren, 2004). It is the involvement of the extracellular-regulated kinases (ERKs) of the MAP kinase system and the involvement of IP_3 kinase that suggest that leptin may also have beneficial actions, particularly in the setting of an acute myocardial infarction.

Timely reperfusion is mandatory to salvage myocardium from acute impending infarction. However, reperfusion comes at a price and induces additional injury, so the long debated reperfusion injury clearly exists. Modification of the reperfusion procedure can attenuate reperfusion injury. This has been known for quite some time: slow restoration of coronary blood flow and perfusion pressure, maintenance of an acidic pH in the reperfusate, temporary contractile blockade and scavenging of free oxygen radicals, all have been shown to attenuate reperfusion injury in experimental animal models, but none of these procedures have ever become clinical routine (Heusch, 2004).

More recently, two other approaches to attenuate reperfusion injury have led to renewed interest in this phenomenon. Yellon and co-workers have identified a number of substances that when given just at reperfusion reduced the final infarct size (Hausenloy *et al*., 2005). These substances have in common that they act through stimulation of myocardial receptors, activating two specific protein kinase pathways, the IP_3-kinase/Akt and the ERK pathway, and leading ultimately to the inhibition of mitochondrial permeability transition pore (MPTP) opening. Very appropriately, Yellon and co-workers have termed the protein kinase system, which is specifically activated during early reperfusion, the reperfusion injury salvage kinases (RISKs).

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Another, only recently described, approach to attenuate reperfusion injury is by ischemic postconditioning, where infarct size is reduced by a few cycles of re-occlusion/reperfusion in the immediate-early phase of reperfusion (Zhao *et al*., 2003). Interestingly, ischemic postconditioning is also associated with RISK activation (Tsang *et al*., 2004). And finally, it appears that ischemic preconditioning, which has attracted the interest of experimental researchers for 20 years but has so far received only indirect support with surrogate end points in clinical settings (Heusch, 2001), is also associated with RISK activation (Hausenloy *et al*., 2005). Therefore, Downey and Cohen (2005) have sensibly proposed that those substances identified by Yellon and co-workers, ischemic preconditioning and ischemic postconditioning, all share RISK activation as a common denominator of signal transduction. At this point, it remains unclear how ischemic postconditioning relates to the long-established procedures of modified reperfusion (slow restoration of coronary blood flow and perfusion pressure, acidic reperfusate, temporary contractile blockade) and whether or not these procedures are also associated with RISK activation (Heusch, 2004).

In this issue of the *British Journal of Pharmacology*, Smith *et al*. (2006) report that exogenous leptin when given at early reperfusion in an isolated mouse heart model reduces infarct size, that this cardioprotective action of leptin is associated with RISK activation, and that leptin also inhibits MPTP opening in isolated rat cardiomyocytes. The observation of cardioprotection by acute administration of leptin at reperfusion is entirely novel and based on the most robust end point, reduced infarct size assessed by quantitative histochemistry. It remains to be seen whether such beneficial effect of leptin holds also true for obesity when there is chronic endogenous hyperleptinemia or whether leptin's signal transduction might then be downregulated.

The observed RISK activation brings up a number of methodological and biological questions. A delicate methodological point which Smith *et al*. (2006) explicitly acknowledge is the timing and location of tissue sampling for Western blot analysis to assess RISK activation. The most appropriate time point can only be ascertained in tedious time control series in any given model and it may vary for different kinases, rendering any single time point a compromise. With respect to location, it is impossible to determine whether a given sample was taken from infarcted or salvaged myocardium, unless infarct size is delineated in the same individual heart and the site of tissue sampling can be clearly assigned to either infarcted or salvaged tissue. This approach will require large animal studies. Apart from time and location of sampling, it remains unclear to what extent phosphorylation of a given kinase truly reflects its activity. Related to this, and apart from the issue of specificity of a given pharmacological inhibitor at any single dose, it is important to know whether this inhibitor interferes with the phosphorylation or the catalytic site of a given kinase.

A major biological question is whether RISK activation is a rigid program that is, in an all-or-nothing mode, a prerequisite for any protection from reperfusion injury, or whether it is more plastic, being mandatory for protection but still subject to modification in response to a specific stimulus. Yellon and co-workers have previously provided evidence for cross-talk between the IP_3 kinase/Akt and the ERK pathway of RISK activation (Hausenloy *et al*., 2004). The present study by Smith *et al*. (2006) further supports a certain plasticity of the RISK program. There is solid evidence in their study from both increased ERK phosphorylation and loss of the infarct size reduction with the ERK inhibitor, for the causal involvement of the ERK pathway in leptin's cardioprotection. The evidence for the involvement of the IP_3 kinase/Akt pathway is weaker; inhibition of IP_3 kinase abolished the infarct size reduction, but there was no increase of either Akt phosphorylation or of one of its downstream targets, endothelial NO synthase. On the other hand, there was also increased phosphorylation of p38 MAP kinase and reduced content and phosphorylation of STAT3 and AMP-dependent kinase. Collectively, these data support the view that there is RISK activation along with other more specific signal pathways for a specific stimulus, that the specific pathways cross-talk with RISK, and that the final kinase activation pattern is variable, with some common denominators of RISK activation and other more specific elements.

In conclusion and in answer to the question in the title of this Commentary, obesity is a risk factor for myocardial infarction. However, the present study suggests the possibility that obesity through increased leptin levels might also be a RISK factor. Indeed, there is clinical evidence that patients with a higher body mass index have a better outcome once they experience an acute coronary syndrome or a percutaneous coronary intervention (Kennedy *et al*., 2005; Nikolsky *et al*., 2006).

Conflict of interest

The authors state no conflict of interest.

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