Published in final edited form as:

J Am Soc Hypertens. 2007 August ; 1(4): 231–241.

EFFECTS OF LEPTIN ON CARDIOVASCULAR PHYSIOLOGY

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INTRODUCTION

The discovery of leptin synthesis and secretion from adipose tissue was a result of studies to understand the genetic basis for obesity in the *ob/ob* mouse (1). Shortly following the identification of leptin as a secretory product of adipose tissue a number of laboratories demonstrated that administration of the exogenous hormone resulted in inhibition of food intake and weight loss in mice (reviewed in detail in 2). The leptin receptor was then identified as a hypothalamic protein, and a point mutation within the gene implicated as the defect resulting in obesity in *db/db* mice (3,4). Taken together these observations, as well as numerous other related findings, established a central role for leptin in regulation of body weight. However, the demonstration of elevated leptin in obese humans and animals, and that the leptin receptor point mutation in the *db/db* mouse was not present in the human leptin receptor, suggested that most human obesity was not the result of single gene mutations identified in these mouse obesity models. Thus, in analogy to the concept of insulin resistance, it was suggested that obese humans were resistant to the weight-reducing effects of leptin (2,5). Further, findings from a number of laboratories suggest that the hyperleptinemia resulting from the inability of leptin to reduce adipose tissue mass in obesity may have pathologic consequences, particularly on the cardiovascular system. In this review the cellular and neural mechanisms through which the leptin signal is propagated are reviewed with respect to the development of leptin resistance. Deleterious effects of hyperleptinemia on cardiovascular physiology are then evaluated in the context of whole body physiology and with attention to differences between physiologic and pharmacologic effects.

LEPTIN RECEPTORS AND LEPTIN SIGNALLING

The leptin receptor is present in almost all tissues examined. The best-studied isoform, the hypothalamic leptin receptor Ob-Rb, is a class I cytokine receptor (6). Upon leptin binding, activation of Ob-Rb promotes janus kinase (JAK)-dependent signaling through signal transducer and activator of transcription (STAT) proteins, primarily STAT-3 (7). This leptin receptor has also been observed to activate phosphoinositol-3 kinase and phosphodiesterase 3B signaling pathways in the hypothalamus (8,9), although the role of JAK and STAT proteins in this process is not fully understood.

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Johnathan D. Tune, Ph.D. and Robert V. Considine, Ph.D. have no Conflicts of Interest to Report

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Ob-Ra (originally termed the short leptin receptor) is the best characterized of the five short leptin receptor isoforms that are derived by alternative splicing of the gene (3,10). The extracellular domain of Ob-Ra is identical to that of Ob-Rb, however the intracellular domain is truncated; thus this short leptin receptor lacks the Box 2 motif at which STAT proteins bind. Although Ob-Ra has been shown to activate JAK2 and MAPK in transiently transfected cell models, the physiologic significance of this observation is not yet understood (11). Ob-Ra is highly expressed in cerebral microvessels comprising the blood brain barrier where it functions to transport leptin from the blood to the brain (12,13).

Ob-Rb mRNA expression is greatest in the hypothalamus and strong evidence supports the concept that this leptin receptor isoform signals for leptin action within the central nervous system (14). In contrast expression of Ob-Ra, which lacks a well-defined leptin signaling mechanism, is more readily detectable in non-neural tissue than is Ob-Rb (12). This significant difference in expression levels must be taken into consideration when interpreting effects of leptin elicited by direct interaction of the hormone with tissues and cells. However, it has been suggested, based on observations in leptin receptor transfected cells, that limited expression of Ob-Rb is sufficient to provide competent leptin signaling (15).

Within the hypothalamus Ob-Rb is highly expressed in the arcuate, paraventricular, ventromedial and dorsomedial nuclei (14). The prevalent model for leptin signaling in the hypothalamus is that two leptin responsive populations of neurons are present in the arcuate nucleus (Figure 1). The first type of neuron expresses proopiomelanocortin (POMC), which is processed to α -melanocyte-stimulating hormone (α -MSH), and cocaine- and amphetamine-regulated transcript (CART). α -MSH and CART inhibit food intake and promote weight loss in a leptin responsive manner. The second population of neurons expresses both neuropeptide Y (NPY) and agouti-related peptide (AGRP). Neurons expressing NPY and AGRP stimulate feeding and are inhibited by leptin (14). The primary leptin responsive neurons present in the arcuate nucleus innervate other hypothalamic areas including the paraventricular nucleus (PVN), perifornical area (PFA) and lateral hypothalamic area (LHA), which contain secondary neurons that express different neuropeptides that regulate food intake (16). The presence of leptin receptors in the PVN, PFA AND LHA suggests that leptin may regulate food intake and other processes through mechanisms separate from those initiated in the arcuate nucleus. In support of this concept, POMC neuron specific leptin receptor knockout mice have only a modest increase in body weight (17), suggesting that leptin receptors located on neurons other than those expressing POMC in the arcuate are important in body weight homeostasis.

LEPTIN RESISTANCE

The concept of leptin resistance was originally proposed to explain the observation that elevated levels of the hormone did not reduce food intake or prevent body weight gain in obese humans (5,18). Subsequently several molecular possibilities have been put forth to explain the mechanism of leptin resistance. Feeding a high fat diet decreases the effectiveness of peripherally injected leptin to induce weight loss in rodents (19,20). As described above, Ob-Ra is present on cerebral microvessels of the blood brain barrier where it functions to transport leptin from the blood to the brain and high fat feeding impairs Ob-Rb mediated transport of leptin across the blood brain barrier. Although defective leptin transport with high fat feeding may occur, the extent to which this defect contributes to leptin resistance is not clear, considering that the arcuate nucleus is located very near the median eminence in which the blood brain barrier is more porous. A second mechanism for leptin resistance centers on suppressors of cytokine signaling (SOCS), a group of early genes activated by the JAK/STAT signal transduction pathway which act in a negative feedback loop to limit cytokine signaling. SOCS-3 is a potent inhibitor of leptin receptor initiated JAK/STAT signaling in cultured cell lines, and leptin induces SOCS-3 mRNA in the hypothalamus (21). SOCS-3 mRNA is

increased in leptin responsive arcuate neurons in Agouti mice, and these mice are resistant to central leptin administration suggesting that the increased SOCS-3 expression is a cause of leptin resistance in these animals (21). It is important to note that leptin resistance can also have an anatomic distribution. The arcuate nucleus can demonstrate defective leptin-stimulated STAT3 phosphorylation while other hypothalamic and extrahypothalamic sites (see Figure 1) remain leptin sensitive (22). The anatomic distribution of leptin resistance may be of particular importance in understanding effects of leptin on blood pressure as discussed below.

EFFECTS OF LEPTIN ON CARDIOVASCULAR PHYSIOLOGY

Elevated serum leptin has been associated with cardiovascular disease including stroke, chronic heart failure, acute myocardial infarction, coronary heart disease and left cardiac hypertrophy (reviewed in 23,24). Many of these studies suggest that the effect of leptin is independent of adiposity, although correction for measures of adiposity may not be sufficient if body fat distribution is not also taken into account. For example, a recent report adjusting for body fat distribution and insulin levels suggests that leptin may actually have a cardioprotective effect in coronary heart disease for subjects with type 2 diabetes (25). In support of the epidemiologic studies implicating leptin as a link between obesity and cardiovascular disease, testing of leptin in various experimental models suggests that the hormone can have direct, non-CNS mediated adverse effects on cardiovascular function. These deleterious effects of leptin may occur in vivo because leptin resistance in the CNS results in circulating hyperleptinemia, and leptin signaling in peripheral tissues remains intact in obese individuals. It also appears that central leptin resistance may be “selective” and that certain centrally mediated effects of the hormone, such as sympathetic responses, remain intact (26). The role of selective leptin resistance in obesity related hypertension is discussed in detail below.

Leptin and obesity-related hypertension

Leptin promotes weight loss in rodents via sympathetic activation of brown adipose tissue and oxidation of fatty acids (27). Leptin binding in the CNS also increases sympathetic outflow in renal, lumbar, hindlimb and adrenal gland sympathetic nerves (28,29). Such sympathoactivation following either intracerebroventricular or chronic intravenous leptin administration has been shown to increase mean arterial blood pressure and heart rate in a number of studies in rodents (23). Further arterial blood pressure in leptin-deficient *ob/ob* mice is lower than in wild-type littermates, and is substantially increased with exogenous leptin administration (30). In contrast Agouti mice, which are obese and hyperleptinemic, and transgenic skinny hepatic-leptin overexpressing mice, both have elevated blood pressure (30). Leptin inhibition of food intake is impaired in obese Agouti mice, but the increase in renal sympathetic nerve activity in response to leptin is not different in Agouti mice compared to lean littermates (31,32). Finally in mice fed a high fat diet for 10 weeks, the effect of intraperitoneal or intracerebroventricular leptin to decrease food intake and body weight was impaired, but leptin-induced renal sympathetic nerve activity was preserved (33). Taken together these observations demonstrate in several different rodent models that leptin regulates blood pressure via sympathetic activation, and that hyperleptinemia in obesity can result in hypertension. Further, the mechanisms through which leptin regulates blood pressure, via stimulation of renal sympathetic nerve activity, appear to be intact in the presence of resistance to the weight reducing effects of the hormone, supporting the concept of selective central leptin resistance in obesity.

Leptin regulates sympathetic nerve activity via α -MSH and melanocortin-4 receptor (MC4R) activation. Intracerebroventricular administration of the MC4R receptor antagonist SHU-9119 blocks both acute and chronic effects of leptin to stimulate renal sympathetic nerve activity and heart rate (34-37). MC4R antagonism has also been shown to block the effects of leptin on food intake and body weight (34,38), implying that the same neural pathway mediates both

the metabolic and sympathetic effects of leptin. How can such an observation be reconciled with the finding of leptin resistance in metabolic pathways but leptin sensitivity in sympathetic pathways? One possibility is that resistance to the metabolic effects of leptin is not mediated by melanocortin signaling. As discussed above, POMC neuron specific leptin receptor knockout only results in mild obesity, implicating other neural pathways in leptin regulation of food intake, possibly where leptin resistance could be focused. Alternatively, it is possible that leptin engages MC4R signaling for both metabolic and sympathetic effects, but that the location of the neurons mediating each response is anatomically different. With administration of SHU-9119 into the third ventricle it is not possible to determine if antagonism of MC4R function blocks the sympathetic or metabolic responses to leptin via the same hypothalamic nuclei. In support of the idea that other hypothalamic nuclei may be engaged by leptin, a recent study has shown that injection of leptin into the ventromedial and dorsomedial hypothalamus can increase renal sympathetic activity, arterial pressure and heart rate (39). These hypothalamic nuclei have previously been shown to express normal leptin sensitivity in the presence of leptin resistance in the arcuate nucleus (22). Evidence against the hypothesis of separate nuclei for the metabolic and sympathetic effects of leptin is provided by a recent report demonstrating that injection of leptin directly into the arcuate nucleus of normal rats increased renal sympathetic nerve activity (40). While illustrating the central role of the arcuate nucleus in the metabolic and sympathetic effects of leptin, this study did not directly address the contribution of other nuclei in mediating the sympathetic effects of leptin in obese leptin-resistant animals. Thus the exact mechanism(s) that provide for selective leptin resistance and maintenance of leptin-derived sympathetic effects remain to be fully elucidated.

In contrast to the postulate that selective leptin resistance in the CNS results in hyperleptinemia driven hypertension, other investigators have suggested that development of a leptin-resistant vasculature is the cause of hypertension. This hypothesis is based on observations suggesting leptin has direct vasodilatory effects on the vasculature. Leptin stimulates nitric oxide release from cultured endothelial cells and induces relaxation of aortic ring preparations (41-43). Intravenous leptin has also been observed to increase serum nitrite/nitrate, and in the presence of sympathetic blockade, decrease arterial blood pressure (44,45). Thus leptin-induced vasodilation, via a direct interaction with the endothelium to stimulate nitric oxide release, has been hypothesized to oppose the sympathetic-mediated increase in blood pressure induced by the hormone. With such a balancing mechanism, hypertension would result if the vasculature becomes leptin-resistant, allowing the sympathetic pressor effects of the hormone to take precedence (45). In support of this hypothesis, intravenous leptin increased blood pressure in the presence of nitric oxide inhibition (45). However, a number of rodent studies using intravenous leptin at concentrations sufficient to increase sympathetic nerve activity, failed to demonstrate a direct vasodilatory action of leptin on mesenteric, lower aortic, renal and iliac artery (46-49). Thus, unequivocal evidence for a physiologically relevant direct vasodilatory effect of leptin, and the development of vascular leptin resistance resulting in elevated blood pressure, remain to be provided.

Coronary Vascular Effects of Leptin

As just described, leptin can directly mediate vasodilation, although it is not clear that such effects alter blood pressure in vivo. To further complicate understanding of the direct effect of leptin on the vasculature, the hormone has been observed to induce vasodilation in both an endothelial-dependent (41,43) and endothelial-independent (44,50) manner. Therefore, it is unclear whether leptin affects vasomotor tone via direct actions on the endothelium and/or smooth muscle, or by central activation of the autonomic nervous system.

Matsuda *et al.* was the first to examine the direct effect of leptin on the coronary circulation (51). They reported that leptin increased coronary blood flow ~40% in patients undergoing

cardiac catheterization and that this vasodilation was unaffected by inhibition of nitric oxide (NO) synthase; i.e. leptin-induced endothelial-independent coronary vasodilation. In another study, Sundell *et al.* reported high serum leptin concentrations correlated inversely with adenosine-mediated coronary vasodilation in obese and non-obese humans (52). These studies suggest leptin affects regulation of coronary vascular resistance; however, the results should be interpreted with caution as the patients in these studies had coronary disease, which significantly affects coronary endothelial function as well as pharmacological flow reserve.

To more definitely assess the coronary vascular effects of leptin, our laboratory recently conducted studies in isolated coronary arterioles and in anesthetized open-chest dogs (53,54). We demonstrated that leptin receptors are expressed in human coronary endothelial cells and in canine coronary arteries, and that these receptors are associated with endothelium-dependent vasodilation. This was evidenced by the fact that leptin induced dose-dependent coronary arteriolar vasodilation that was inhibited by NO synthase inhibition or endothelial denudation (Figure 2). However, it is critical to recognize that this leptin-induced vasodilation occurred only at leptin concentrations far exceeding those observed in morbidly obese patients (≥ 160 ng/ml). In support of the likelihood that coronary vasodilation was the result of pharmacologic concentrations of leptin, our *in vivo* experiments in anesthetized dogs demonstrated that leptin has no effect on coronary blood flow at physiologic or pathophysiologic relevant concentrations (Figure 2). Therefore, leptin receptors are functionally expressed in the coronary circulation and couple to known signal transduction pathways; however, leptin-induced endothelial-dependent vasodilation is a purely pharmacological phenomenon.

Leptin, Coronary Endothelial Function and Atherosclerotic Disease

Endothelial dysfunction is believed to be the inciting event in the pathogenesis of atherosclerosis (55-56). Thus, identification of factors that significantly affect endothelial function is critical in understanding mechanisms contributing to the initiation and development of coronary disease. Knudson *et al.* recently demonstrated that increasing plasma leptin concentrations to levels similar to those observed in obese subjects significantly impaired paracrine regulation of the coronary circulation (53). Specifically, acute administration of leptin (10-90 ng/ml) substantially attenuated acetylcholine-mediated vasodilation *in vitro* (Figure 3A) and *in vivo* (Figure 3B). In contrast, normal concentrations of leptin (4 ng/ml) do not affect vasodilation to acetylcholine (Figure 3A). This effect of leptin is not due to altered vascular smooth muscle responsiveness to NO as leptin does not significantly alter coronary dilation to the endothelial-independent vasodilator sodium nitroprusside (53). These novel findings suggest hyperleptinemia as a potential mechanism by which obesity and the metabolic syndrome leads to significant coronary dysfunction and potentially coronary artery disease. The mechanism of leptin-induced endothelial dysfunction has not been directly examined but could be related to inhibition of NO synthase by PKC (57,58), augmented superoxide production (59,60) and/or increases in release of endothelin-1 (61).

Taken together these findings introduce a “leptin paradox” as this adipokine is associated with both the activation and inhibition of NO-dependent vasodilation. This paradox is nicely explained by data that show leptin-induced vasodilation occurred only *in vitro* at concentrations exceeding 160 ng/ml while leptin-induced endothelial dysfunction was found *in vitro* and *in vivo* at concentrations ranging from 10–90 ng/ml. These data also support the hypothesis of two independent leptin receptor binding sites in vascular endothelium; one a high affinity site (5 nM or 80 ng/ml) that couples to pathways which impair coronary endothelial function and the other a low affinity site (740 nM or 11,000 ng/ml) that couples to NO-dependent vasodilation (61-63). Additional studies are needed to directly examine this intriguing hypothesis.

While recent studies implicate leptin with the initiation of coronary endothelial dysfunction (53,59-61), other investigations strongly support its role in additional key aspects of atherogenesis. The topic is nicely outlined in the recent reviews of Lau et al (64) and Beltowski (65). Leptin increases the accumulation of cholesterol esters in foam cells (66) and serum leptin inversely correlates with plasma HDL-cholesterol and apolipoprotein AI (67,68). Leptin may also contribute to the “pro-inflammatory” state associated with obesity in that it correlates strongly with acute phase reactants such as C-reactive protein and serum amyloid A (69,70). Leptin also increases oxidative modification of plasma lipoproteins (oxidized LDL) (71) and increases DNA-binding activity of proinflammatory transcription factors AP-1 and NFkB as well as increases expression of monocyte chemoattractant protein-1 (59). Therefore, leptin may be a key mediator of augmented inflammatory/oxidative stress environment associated with obesity.

In vivo studies in rodents also suggest that leptin is involved in atherosclerosis. *Ob/ob* and *db/db* mice develop only small arterial lesions following injury despite being on a pro-atherogenic diet; i.e. mutation of leptin signaling appears to protect rodents against atherogenesis (72). Other studies suggest that exogenous leptin administration augments spontaneous atherosclerotic lesions in apo E-/- mice (73). However, rodents are normally resistant to atherosclerosis and thus not entirely ideal for these studies. Although coronary atherosclerosis was not examined in these studies, they do agree with clinical evidence suggesting a causal role of leptin in coronary artery disease. These clinical investigations have documented that plasma leptin levels correlate with coronary artery calcification in type 2 diabetics (74,75) and intima-media thickness of common carotid artery (76). Increased expression of Ob-R (not differentiating between Ob-Rb and Ob-Ra) also co-localizes with MMP expression in the intima of human atherosclerotic plaques (77,78).

In contrast, it must be recognized that effects of leptin on atherogenesis remain extremely controversial since contradictory studies have found little/no effect of leptin on markers of inflammation (79), oxidative stress (80), intima-media thickness (81,82) or development of atherosclerotic disease (83,84). In addition, there is evidence of “resistance” to the vascular effects of leptin (54). Our laboratory found that obese, insulin resistant chronically high-fat-fed dogs were resistant to leptin-induced coronary endothelial dysfunction. This resistance may represent an early protective adaptive change in the pathogenesis of atherosclerosis that should be further explored. Therefore, although many studies suggest a causative role for leptin in coronary atherogenesis, this hypothesis remains controversial, as no study has demonstrated a direct role of leptin in the pathogenesis of atherosclerotic disease.

Prothrombotic effects of leptin

The long form of the leptin receptor is present on platelets and *in vitro* exposure to high concentrations of leptin enhances ADP-induced aggregation of platelet enriched human plasma (85). Leptin enhanced ADP-induced platelet aggregation has also been observed for plasma from wild-type mice (86). In contrast, leptin has no effect on aggregation of platelets from *db/db* mice, suggesting that leptin effects on platelet aggregation require the functional long form of the leptin receptor. In *ob/ob* mice the thrombotic response to vascular injury is slower than in wild-type mice and results in unstable thrombi, a condition that is corrected with leptin administration (86). In contrast, reducing serum leptin with anti-leptin antibody in wild-type mice prolongs the time to thrombotic occlusion in response to vascular injury, mimicking that seen in the *ob/ob* mice (87). These observations have been interpreted to suggest that leptin may contribute to increased risk of thrombosis in obese subjects due to a potential effect of the hormone to stabilize thrombi after they are formed (86,87). However, the effect of leptin to enhance the *in vitro* aggregation of human platelets from obese subjects is significantly attenuated (88) compared to the response in platelets from lean subjects, a finding that argues

against a physiologically significant prothrombotic effect of leptin in obese humans. Recently this issue has become much more complex in that platelets from some humans (~40% of those tested) demonstrate leptin-enhanced ADP-mediated aggregation but that many other preparations do not (89). In this study there was no relationship of the non-responding platelet preparations to adiposity, age or gender. Therefore, although studies suggest that leptin can promote or potentiate thrombosis in animal models, a direct prothrombotic effect of leptin in obese humans remains to be definitively demonstrated. Of interest in this regard, leptin has recently been reported to be a positive determinant of PAI-1 activity, independent of body fat content and distribution, in overweight and obese humans (90). Thus it is possible that leptin could contribute to a prothrombotic state in obese humans via effects on other factors.

Direct Effects of Leptin on Cardiomyocytes

Within the past several years a number of studies have addressed the potential for direct effects of leptin on cardiomyocyte function. Leptin induces hypertrophy of neonatal rat ventricular myocytes (91,92) and proliferation of both primary pediatric human cardiomyocytes and murine cardiomyocyte HL-1 cells (93). Leptin inhibits the contractile function of ventricular myocytes through several intracellular signaling mechanisms including activation of the endothelin-1 receptor (94,95). Finally, leptin stimulates matrix metalloproteinase-2 expression and alters the collagen profile of human pediatric ventricular myocytes (96). Taken together, these findings suggest that hyperleptinemia in obesity may have a direct negative effect on myocardial function promoting heart failure. However, administration of leptin during reperfusion of ischemic mouse hearts significantly reduced infarct size, and in oxidatively stressed rat cardiomyocytes, delayed opening of the mitochondrial permeability transition pore (97). Further, hyperleptinemia appears to protect the heart from ectopic lipid deposition, which is negatively correlated with systolic function (98). Therefore additional work will be required to determine if leptin has positive or negative effects on cardiac function in vivo under physiologically relevant conditions.

CONCLUSIONS

The discovery of leptin fourteen years ago (1) began a new era of research that recognized adipose tissue as an active endocrine organ rather than just a passive reservoir for storage of fatty acids. An extensive amount of work since that time has established that leptin influences many physiological processes in addition to body weight homeostasis. However, hyperleptinemia resulting from resistance to the weight reducing effects of leptin can result in pathology. In particular the evidence is fairly strong that hyperleptinemia in obesity contributes to hypertension. However, additional work will be needed to determine if the effects of leptin on other aspects of cardiovascular function are relevant at concentrations present in human obesity, and in the context of counter-regulation by other processes. Further, it is important to keep in mind that adipose tissue secretes a number of hormones and cytokines in addition to leptin. Although adiponectin appears to have positive effects on vascular function (99), many other secretory products of the adipose tissue are likely to have deleterious effects on the cardiovascular physiology. Thus an integrated approach will be required to fully understand the mechanism(s) through which excess adipose tissue contributes to cardiovascular disease.

Acknowledgements

Work of the authors mentioned in this review has been supported by National Institutes of Health grants DK51140 (RVC) and HL67804 (JDT) and a grant from the American Diabetes Association (RVC).

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Figure 1.

Schematic drawing of the hypothalamus in sagittal section illustrating leptin signal pathways. Leptin enters the hypothalamus through the median eminence (ME) but can also access other areas of the brain via transport across the blood brain barrier. In the arcuate nucleus (ARC) leptin activates neurons containing α -MSH and CART, which inhibit feeding. Leptin also binds to arcuate neurons expressing NPY and AGRP and inhibits release of these orexigenic peptide neurotransmitters. Leptin responsive neurons in the arcuate nucleus project to the paraventricular nucleus (PVN) and the lateral hypothalamic area (LHA) for integration with other neural signals. The effects of leptin signaling in the hypothalamus are then relayed to the body via parasympathetic and sympathetic neurons. Leptin receptors (black semicircle) are also present in the dorsomedial (DMH) and ventromedial (VMH) nuclei, PVN, and LHA. Leptin receptors in nuclei other than the arcuate may be important in selective leptin resistance as discussed in the text. Figure modified from Elmquist et al (100).

Figure 2.

(A) Leptin induces dose-dependent vasodilation of isolated canine coronary arterioles that is inhibited by nitric oxide synthase inhibition with N-nitro-L-arginine methyl ester (L-NAME). Importantly, this dilation was observed only at concentrations far exceeding those observed in morbidly obese patients (≥ 10 $\mu\text{mol/L}$). (B) Leptin has no effect on coronary blood flow at physiologic or pathophysiologic relevant concentrations in anesthetized open-chest dogs. Data taken from Knudson et al (53).

Figure 3.

Leptin impairs coronary endothelial-dependent vasodilation to acetylcholine in isolated coronary artery rings (A) and in anesthetized open-chest dogs (B). Normal concentrations of leptin (4 ng/ml) do not significantly affect acetylcholine-mediated vasodilation in isolated coronary arteries (A). Data taken from Knudson et al (53).