The following letters are in response to Point:Counterpoint: “Interleukin-6 does/do not have a beneficial role in insulin sensitivity and glucose homeostasis” that appears in this issue.

To the Editor: In our learned wisdom, the word “inflammation” almost always leads to bad connotations in human physiology; however, proteins often considered inflammatory in nature (i.e., cytokines) can also have positive effects on tissue (5). This Point:Counterpoint provides a perfect vehicle to examine why environmental context of the tissue is a critical point when considering this topic. The majority of total glucose disposal is regulated by skeletal muscle, with smaller contributions coming from the liver and adipose tissue (2). Dr. Mooney (3) provides evidence for IL-6’s contribution to insulin resistance in the liver, and Drs. Pedersen and Febbraio (4) counter that IL-6 has minimal effects on insulin sensitivity. Because the majority of glucose homeostasis discussion focused on glucose uptake and not release, then shouldn’t the effect IL-6 has on skeletal muscle be the most critical issue to discuss? The same can be said for SOCS-3, the predicted downstream mediator of IL-6 in the liver (3). We demonstrated that SOCS-3 expression increases with exercise in skeletal muscle (6), which presents us with the same conundrum encountered by IL-6. Why would physical activity, a mechanism that prevents insulin resistance, upregulate the expression of proteins that induce insulin resistance? Perhaps context is critical here; if we evolved to be active as suggested by Booth et al. (1), then IL-6 induced by exercise in lean individuals is beneficial; however, in the face of society’s inactive lifestyle perhaps elevated IL-6 levels seen in sedentary obese patients result in inappropriate gene expression leading to an overt pathology.

REFERENCES


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To the Editor: The Point:Counterpoint by Mooney on one side and Pedersen and Febbraio (2, 3) on the other debates the “IL-6 paradox.” While they argue that IL-6 is either good or bad, in nearly all cases evolution requires that genes and encoded proteins do something “good,” or they would have been selected against long ago. And despite the focus of this debate on skeletal muscle production and improved insulin sensitivity (good guy) vs. obesity- and hepatic steatosis-induced inflammation and exacerbation of insulin resistance (bad guy), the major function of IL-6 is a proinflammatory cytokine required for normal immune function.

Why is IL-6 chronically elevated in obesity and raised acutely during exercise? Given the growing evidence for an inflammatory state in obesity with pathogenic consequences on insulin resistance, diabetes, and atherosclerosis (1, 4), an elevation of IL-6 is not surprising. IL-6 could directly impact insulin resistance, but more likely works in conjunction with other inflammatory substances to modulate immune function and the systemic inflammatory milieu that promotes these disorders. One of several fascinating but unanswered questions is why muscle produces this particular cytokine and not others.

I do not agree that IL-6 is beneficial in humans as an insulin sensitizer but detrimental in mice. There are too many similarities between these species for this to be likely. Both rely on IL-6 for normal immune function, overproduce IL-6 in muscle in response to vigorous exercise, and have more circulating IL-6 in obese states. Because the IL-6 paradox remains unresolved after this debate, carefully crafted research must continue!

REFERENCES


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To the Editor: To improve our understanding of the controversy discussing the role of IL-6 in insulin signal transduction (2, 5), we should visualize a physiological situation where local IL-6 concentrations, and to a lesser extent IL-6 plasma levels, are substantially upregulated. This is the case in skeletal muscle during and after exercise. The challenge for the organism in this situation is to supply the working muscle with energy substrates. In fact, IL-6 improves the uptake and the degradation of energy fuels and supports the refill of energy stores in skeletal muscle (3, 5). Moreover, IL-6 has lipolytic properties and could increase hepatic glucose output (1, 4). Thus IL-6 exerts anabolic, insulin-like effects in muscle and catabolic effects in liver and fat, which is antagonistic to insulin. This is supported by our data on a tissue-specific regulation of insulin signaling molecules by IL-6 (5, 6).

But when do we have relevant local IL-6 and insulin concentrations? During exercise, only low insulin levels are present. A local cross-talk of IL-6 and insulin signaling pathways may occur in muscle in the recovery phase. Furthermore this cross-talk is conceivable in adipose tissue, which is a permanent producer of IL-6 (11). Whether the chronic increases in circulating IL-6 concentrations caused by obesity, which are usually within the reference range, have functional importance is at least questionable.

In summary, we have a tissue-specific cross-talk of IL-6 and insulin-dependent pathways, which appears to be of some local relevance. In our understanding, this apparently oppositional cross-talk mirrors the activation of both anabolic and catabolic pathways during and after exercise.

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To the Editor: There has been considerable debate regarding the effects of IL-6 on insulin sensitivity and risk of diabetes, as reflected in this issue of the Journal of Applied Physiology (3, 4). This debate has been fueled by data largely obtained from incubation of cells with IL-6 in vitro, associations in clinical materials, or, more seldom, pharmacological treatment with IL-6 in vivo. However, to investigate the physiological role of IL-6, it might be fruitful to apply the classic method of endocrinology: to remove the substance in vivo.

Our studies in mice with IL-6 gene knockout indicate that the overall effect of long-term lack of IL-6 is decreased insulin sensitivity, presumably due to obesity (5). The effect on fat mass probably is exerted inside the blood-brain barrier in the central nervous system, and it can not be seen after systemic treatment with IL-6 (5). Instead, long-term systemic IL-6 treatment in some, but not all, cases results in insulin resistance (3, 4). Nevertheless, obesity-associated insulin resistance due to lack of central nervous IL-6 seems to overrule the possible increase in insulin sensitivity caused by the removal of an insulin antagonizing effect by peripheral IL-6 in mice (5).

As usual, the clinical setting is more difficult to assess. A weak variant of the IL-6 promoter, that should cause decreased IL-6 production also in the brain, is associated with increased obesity (6) and decreased energy expenditure (2), but its relation to glucose metabolism is not finally determined (1).

REFERENCES
To the Editor: Clearly, much of the controversy regarding IL-6 and insulin sensitivity can be ascribed to species-specific differences, tissue-specific differences, acute versus chronic exposure to IL-6, different doses of IL-6, or discrepancies between experimental and epidemiological studies (5). In liver, IL-6 may have no effect or an opposing effect to that of insulin by enhancing the hepatic glucose output (4). Data suggesting that IL-6 may augment hepatic insulin sensitivity are lacking. In adipose tissue, increased lipolysis has been reported consistently (4), suggesting that IL-6 does not increase insulin sensitivity in this tissue. Rather, IL-6 possesses substrate-mobilizing properties. In skeletal muscle, however, the effect of IL-6 may be different. In the first study combining moderate dose IL-6 with a euglycemic hyperinsulinemic clamp in humans (3), no effect of IL-6 on glucose metabolism was observed, whereas Carey et al (2) found increased insulin sensitivity in the skeletal muscle using supraphysiological levels of IL-6. In vitro, chronic IL-6 exposure enhances myotube formation and GLUT4 mRNA expression, suggesting improved muscle differentiation and glucose metabolism (1). Thus IL-6 may affect insulin sensitivity differently in different tissues.

IL-6 is strongly associated with obesity, but it is not established to what extent IL-6 per se plays a role in the pathogenesis of insulin resistance. Although changes in body weight and plasma lipids have been observed in patients treated with anti-IL-6 antibodies (reviewed in Ref. 6), there are yet no studies reporting long-term effects of treatment with either IL-6 or anti-IL-6 antibodies on insulin sensitivity in humans. Until these data exist, the controversy regarding IL-6 and insulin sensitivity will probably continue.

REFERENCES


To the Editor: Drs. Pedersen and Febbraio argue that mice respond to IL-6 differently than humans (5, 6). The data to support their premise are not convincing. IL-6 unambiguously impairs hepatic insulin action in mice (2). The one study in humans did not detect an impairment in hepatic insulin action because it was not designed to do so (1). The dose of insulin used in that study was so high that it would have masked any underlying hepatic insulin resistance. With regard to muscle, the data in mice are once again unambiguous. IL-6 has little or no effect on insulin action at doses that are relevant to pathophysiological settings (2, 3). In humans, two studies have examined the impact of IL-6 on muscle insulin action. In one study, IL-6 was shown to have no effect on insulin action (4). In a second study, IL-6 augmented glucose uptake in the presence of insulin stimulation (1). IL-6 may have augmented glucose uptake via a parallel pathway separate to that of insulin. Consistent with that theory, IL-6 augmented glucose oxidation rather than glucose storage (i.e., glycogen synthesis), which is the major fate of insulin-stimulated glucose uptake in muscle.

In summary, there is no basis for invoking qualitative species differences with regard to the effects of IL-6 on insulin action.

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