Central sympathetic outflow to skeletal muscle: the major link between non-esterified fatty acids and elevated blood pressure?

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ABSTRACT

Sympathetic nervous system activation is a hallmark of several conditions associated with an adverse prognosis, including hypertension and the metabolic syndrome. Proposed mediators of increased sympathetic drive include hyperinsulinaemia, leptin, NEFAs (non-esterified fatty acids), pro-inflammatory cytokines, baroreflex impairment and others. The role of NEFAs appears to be of particular importance given the increased levels observed in human obesity and the experimental results linking the NEFA-induced pressor response to sympathetic activation. Findings from human studies have yielded conflicting results with regards to a sympathetically mediated association between NEFAs and elevated arterial blood pressure. In the present issue of Clinical Science, Florian and Pawelczyk present some interesting results obtained from a small number of healthy normotensive lean volunteers who were exposed to NEFA infusion and cardiovascular and sympathetic monitoring using state of the art methodology that appears to be in support of such a link. However, several methodological and conceptual considerations need to be taken into account when interpreting the results from this study. Put into perspective, the case for a substantial sympathetically mediated pressor response to NEFA infusion does not appear to be very strong one.

The metabolic syndrome represents a major public health burden due to its high prevalence in the general population and its association with cardiovascular disease and Type 2 diabetes. There is now convincing evidence that the metabolic syndrome represents a state of sympathetic overactivity [1]. Although the mechanisms linking the metabolic syndrome with sympathetic activation are complex and not completely understood, factors that have been suggested to enhance sympathetic drive, either directly or indirectly, include hyperinsulinaemia, leptin, NEFAs (non-esterified fatty acids), pro-inflammatory cytokines, baroreflex impairment and others.

Abdominal obesity is linked to increased NEFA levels and turnover, which are resistant to suppression by insulin. NEFAs not only appear to contribute to the metabolic aspects of the metabolic syndrome by impairing insulin-mediated glucose disposal, but have also been associated with elevated levels of BP (blood pressure) [2]. Indeed, increased delivery of NEFAs to the portal circulation in rats mediates a pressor response [3], which appears to be sympathetically mediated [4], thereby potentially contributing to the association between increased abdominal adiposity and hypertension [5].

Unfortunately, the findings from human studies available to date are less clear cut and have failed to unambiguously demonstrate an association between NEFAs and elevated arterial BP that may be mediated by sympathetic stimulation. Within this framework, Florian and Pawelczyk [6] in the present issue of Clinical Science describe a study aimed at unravelling

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Unfortunately, the findings from human studies available to date are less clear cut and have failed to unambiguously demonstrate an association between NEFAs and elevated arterial BP that may be mediated by sympathetic stimulation. Within this framework, Florian and Pawelczyk [6] in the present issue of Clinical Science describe a study aimed at unravelling
the potential contribution of central sympathetic outflow to skeletal muscle (MSNA (muscle sympathetic nerve activity)) to the pressor response of infusion of NEFAs in young healthy normotensive lean volunteers. Similar to previous studies, the infusion of NEFAs over a 4 h period in this single blind placebo-controlled study resulted in a significant increase in both systolic and diastolic BP. This was accompanied by an increase in systemic vascular resistance and muscle sympathetic burst frequency (from $16.3 \pm 1.7$ to $21.2 \pm 1.8$ bursts/min; values are means $\pm$ S.E.M.). In their comprehensive approach, Florian and Pawelczyk [6] also measured a variety of additional haemodynamic and hormonal variables potentially involved in the BP response to NEFAs. In the given context it is of interest that, in response to NEFA infusion, plasma noradrenaline levels fell, whereas insulin, aldosterone and F2-isoprostanes rose significantly. The authors [6] conclude that central sympathetic activation contributes to the pressor response to NEFAs.

Do these results provide the ultimate proof of a relevant contribution of central sympathetic outflow to NEFA-induced elevation of arterial BP or even the role of NEFAs for insulin resistance and elevated BP commonly seen as components of the metabolic syndrome? Probably not.

As alluded to by the authors [6], there are several limitations that need to be taken into account when interpreting their results. First of all, the authors are to be commended for their efforts to study the effects of NEFA infusion on MSNA for a prolonged period of time and to comprehensively assess additional factors potentially involved in the pressor response to NEFAs. Some of the effects observed in response to NEFAs were only evident 3–4 h after NEFA infusion, such as the increase in insulin levels and, in fact, the increase in MSNA. The majority of comparable studies had shorter observation periods, which may explain some of the differences in the reported outcomes, in particular the study by Monahan et al. [7], who could not detect any changes in MSNA in a similar cohort at 2 h after NEFA infusion. However, this prolonged observation period also carries the risk of losing the recording site, which in fact could only be maintained in 13 out of 17 subjects and total MSNA was only available for analysis in eight subjects. Although the increase in mean burst frequency with NEFA infusion was statistically significant when compared with baseline (from 16.3 to 21.2 bursts/min), it is noteworthy that the baseline mean burst frequency before saline infusion of 20.5 bursts/min was not different from that before NEFA infusion. It is probably fair to say that the magnitude of the observed effect appears to be rather small and may still lie within the variability of the method despite statistical significance. Furthermore, heart rate was significantly increased with NEFA infusion, but burst incidence, expressed as bursts/100 heart beats, during acute hyperlipidaemia was not provided.

Apart from these methodological issues, there are several important conceptual considerations. First, the present results [6] only provide insights into the effect of acute hyperlipidaemia in healthy subjects. Although such hyperlipidaemia does occur after ingestion of a high-fat meal, the response both in terms of cardiovascular as well as hormonal parameters may well be different in obese subjects and those with dyslipidaemia or the metabolic syndrome. Furthermore, it is probably more chronic rather than acute hyperlipidaemia that is associated with some forms of obesity and of relevance for BP regulation via altered autonomic control.

Secondly, sympathetic outflow, although directly measured, included only efferent sympathetic outflow directed towards skeletal muscle, which cannot be extrapolated to other organs. In fact, a previous study in humans using radiotracer dilution methodology indicated that hyperlipidaemia tended to decrease rather than increase whole-body and renal noradrenaline spillover [8]. This is of particular relevance given that obesity itself is accompanied by high rates of noradrenaline spillover from the kidneys.

Thirdly, NEFA infusion resulted in increased insulin levels. With hyperinsulinaemia, activation of the sympathetic nervous outflow to the skeletal muscle vasculature is observed using microneurography [9]. This effect of insulin is mediated through the CNS (central nervous system), either as a reflex response to vasodilation or as a direct effect of insulin on forebrain areas regulating sympathetic outflow. Although fasting serum insulin concentrations are higher in the obese, serum insulin and renal noradrenaline spillover values do not appear to be quantitatively related overall, arguing against hyperinsulinaemia itself causing the elevated sympathetic nervous activity [10].

The role of sympathetic nervous system activation in mediating the pressor response to acute hyperlipidaemia is far from resolved. The complexity of the interaction between haemodynamic, metabolic and hormonal alterations in response to acute (and chronic) hyperlipidaemia remains a difficult but important challenge that can only be met by combining the most sophisticated methodology in a series of studies that adequately address the interplay between the systems involved in both human health and disease.

REFERENCES