COMMENT

Coupling of metabolism and cardiovascular response represents normal physiology

ABSTRACT

In this issue of Clinical Science, Fugmann and co-workers demonstrate a highly integrated cardiovascular response to changes in plasma concentrations of glucose, triacylglycerols (triglycerides), fatty acids and insulin. Since the different substrates, alone and combined, evoked these changes, this response is likely to be a physiological one and directed towards minimizing the extent and duration of substrate elevations that could cause vascular dysfunction.

The article by Fugmann and co-workers [1] in this issue of Clinical Science addresses an important, although still somewhat controversial [2], issue. The authors [1] studied changes in haemodynamic patterns in response to a variety of metabolic states that occur after food ingestion. This deserves consideration. It is the first study that systematically investigates the effects of the different metabolic components of a meal on cardiac output, blood pressure, heart rate and peripheral skeletal muscle blood flow. The collected results allow the interested reader and researcher to find reference values for changes in haemodynamic parameters in response to metabolic changes.

Importantly, all interventions, despite differences in serum triacylglycerol (triglyceride), fatty acid, glucose and insulin levels, caused changes in skeletal muscle blood flow. Thus increments in skeletal muscle blood flow are not exclusively dependent on insulin, although it appears that appropriate elevations of insulin result in higher rates of blood flow than that achieved without insulin. This finding strongly indicates that a connection exists between metabolism and cardiovascular function. It also indicates that substrate delivery is not a random process, but a highly integrated response involving all components of the vascular system from the heart to the capillaries. The mechanism(s) by which substrates (nutrients) modulate tissue blood flow are not well understood.

Interestingly, it appears that the response to the metabolic interventions caused differential responses at the level of the heart as well as other organs. The most impressive difference is observed between the response to hyperglycaemia (without concomitant increased insulin levels) and the mixed meal. The fact that heart rate and cardiac index decrease in spite of increased metabolism during hyperglycaemia might be attributable to acute glucose toxicity or due to the lack of appropriate hyperinsulinaemia with its vascular protective effects. Since insulin also directly stimulates the sympathetic nervous system, which can modulate heart rate and cardiac output, the fall in heart rate may be attributable to relative insulin deficiency.

Taken together, the changes in haemodynamic patterns are driven, at least in part, by an interaction between glucose, triacylglycerol and insulin levels. Furthermore, the patterns suggest that the response is not only due to local effects, but also reflect a central component that integrates the different stimuli. Clearly more work is needed to identify the mechanisms that mediate the different response patterns at the tissue level as well as at the level of the whole organism.

The reported size of the change in the haemodynamic patterns needs to be taken with a pinch of salt. First, increments in skeletal muscle blood flow are related to metabolic rate [3]. In other words, the observed differences in the cardiovascular response are, in part, due to differences in metabolic rates. Since glucose infusion rates are not provided, one cannot exclude the possibility that the differences in the response might have been smaller if metabolic rates were matched. Secondly, the size of the change in the haemodynamic pattern is partially determined by variables that are related to the specific study subjects and these variables are largely unknown. In other words, subjects matched for all known predictors of vascular function will still differ in their responses to identical stimuli. Since different study groups were used to define the effects of metabolic perturbations on changes in haemodynamic patterns, one cannot rule out that the size of some effects was underestimated. The only way to circumvent this problem would have been, as pointed out by the authors [1], to study each subject five times, which is hard to achieve. Thus a
comparison between the cardiovascular responses with the different metabolic stimuli should be more qualitative than quantitative.

Finally, it needs to be emphasized that the conclusions hold up only for young, lean, normotensive and normolipaemic subjects. It is highly likely that the haemodynamic responses to the different metabolic conditions would be different in older, obese or Type II diabetic subjects [4,5] as well as in subjects with cardiovascular disease.

In summary, metabolism of nutrients irrespective of type or route of administration elicits an integrated cardiovascular response. Insulin appears to be one of the major contributors of this response. It is possible that incretins, such as glucagon-like peptide or ghrelin, in addition to insulin may modulate the cardiovascular response to food intake to optimize the delivery of glucose, triacylglycerols and fatty acids to the target organs. This would minimize changes in substrate concentration which, if left unopposed, could injure the vasculature and promote the development of vascular disease. Thus the results of the study [1] presented in this issue of *Clinical Science* indicate that the integrated cardiovascular response to nutrient intake and metabolism represents normal physiology.

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REFERENCES

2 Steinberg, H. O. and Baron, A. D. (1999) Insulin-mediated vasodilation: why one's physiology could be the other's pharmacology. Diabetologia 42, 493–495