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COMMENTARY

The Role of Insulin in Hepatic Regeneration: A New Frontier in Liver Function. An Invited Brief Commentary on "Insulin Metabolism and Assessment of Hepatic Insulin Extraction During Liver Regeneration. A Study in a Rat Model"

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Liver regeneration (LR) is a complex, fascinating process, and there are a lot of factors that contribute to and influence the development such as tumor necrosis factor (TNF-α), interleukin-6 (IL-6), hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF) and recently also micro-RNA [1, 2].

However, despite the advances in molecular techniques as well as the publication of many studies over the last 50 years, the mechanisms underlying LR in pathological situations are not yet well described.

In fact, an improved understanding of LR in cases of compromised livers, which sometimes require liver transplantation, could be useful to avoid the clinical consequences of liver failure.

Several animal models have been used to understand LR, with the first rodent model of two-thirds hepatectomy (the median and left lateral lobes) described by Higgins and Anderson in 1931 [3].

According to this model, the adult liver is in a quiescent state until a so-called 70% hepatectomy triggers a proliferative reaction.

Unfortunately, when the 90% threshold is exceeded, the regenerative capacity of the remaining hepatocytes decreases with the risk of liver failure. The causes of this reduction are still misunderstood, although vascular shear stress in the liver's sinusoids [4] as well as octreotide [5] seem to play a major role.

In "Insulin Metabolism and Assessment of Hepatic Insulin Extraction During Liver Regeneration. A Study in a Rat Model", the authors evaluate the role of insulin in rat hepatic regeneration after major hepatectomy using an Isolated Perfused Rat Liver (IPRL) model to extract insulin from the liver [6].

This model allows for an accurate calculation of insulin levels retained by the liver after major hepatectomy with injection of a stable, standardized concentration of insulin (450 uU/ml).

Insulin has been shown to be a regulatory growth factor for hepatotrophic regeneration in animal models. In fact, LR, depending on mitochondrial metabolism, is strongly linked to insulin levels to maintain a high ketone body ratio (KBR) [7], the latter being a good indicator of graft function.

The authors included 86 male Wistar rats with a mean weight of 220 g in the study. The rats were submitted to a randomization process based on the execution of laparotomy with or without hepatectomy and subdivided in nine groups.

The first group (control, $n = 20$) was used to evaluate normal values of insulin extraction and the effect on liver tissue. Meanwhile in the second group (sham, $n = 10$), the rats were subjected to blood and liver tissue sampling after laparotomy to determine reference values (glucose, endogenous insulin, alanine transferase, aspartate transferase, albumin, lactic acid, total bilirubin, prothrombin time and activated partial thromboplastin time) for the other groups. Groups 3–8 ($n = 8$) and Group 9 ($n = 8$) were subjected to 70% hepatectomy.

Groups 3–8 were the main experimental cohorts being evaluated on post-operative day (POD) 1, 2, 3, 5, 7 and 14, respectively.

The authors demonstrated a reduction in the liver's biochemical activities on the first POD with a recovery of the normal values at POD 5.

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Among the many interesting results, the most important finding of the current study relates to the increase in the endogenous insulin concentration on POD 1 and POD 2 with the reduction in insulin extraction by the liver on the first POD. These results were consistent with those already described in the literature with the exception of less retention of insulin by the liver, possibly due to an attempt to maintain euglycaemia.

The greatest strength of this study is the standardization of the IPRL model that in the future, together with translational research, will surely lead to new knowledge of the issue.

Unfortunately, despite many efforts concerning the use of new animal models (i.e., zebrafish [8]) and the implementation of new technologies [9], a gap between animal models and humans still remains.

DECLARATION OF INTEREST

The author declares that no conflicts of interest exist. The author declares that he has no competing interests. The author alone is responsible for the content and writing of the article. The author declares that this commentary has not been published elsewhere and that it has not been submitted previously for publication elsewhere.

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