Physical Medicine and Rehabilitation Research

Short Communication ISSN: 2398-3353

Specific intracellular Ca^{2+} signal in hepatocytes after 70% partial hepatectomy in rats

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New intracellular Ca^{2+} signal consisting of two successive peaks in hepatocytes is found during liver regeneration after 70% partial hepatectomy in rats [1,2].

1. To study the regeneration mechanism of livers in male Donryu rats were subjected to the 70% PH method of Higgins and Anderson [3] at a scheduled time during 5:00 pm and 7:00 pm in Japan time, and the intracellular Ca^{2+} $[Ca^{2+}]_i$ in hepatocytes was measured using a fluorescent Ca^{2+} indicator, fura-2 [4]. Hepatocytes (1×10^6 cells) were resuspended in 1 mL Ca^{2+}- and Mg^{2+}-free HBSS (pH 7.4) in a 10 mm quartz cuvette, and their fluorescence was measured at an emission wavelength of 500 nm and excitation of 340 or 380 nm using a spectrofluorometer. The proliferative phase restoring the liver volume after 70% PH were surrounding around a sustained increasing signal of $[Ca^{2+}]_i$ in hepatocytes, consisting of two successive peaks with the first narrow peak at one hour and the second broad peak increasing by day three and then returning to normal by day four. Then, the ratio (R_r) of the liver regeneration in rats after 70% PH was evaluated by the formula: $R_r=100 \times$ (total weight of the regenerated liver/total weight of the initially excised liver lobe pieces/0.7). Although the liver mass increased uniformly on the R_r curve after 70% PH and returned to the initial liver weight by day 10–14 except an abnormally high peak at around day four ($P<0.05$). Then, the R_r value had suddenly increased at around day four after 70% PH, temporarily exceeding 100%, and decreased steeply, followed by normal liver regeneration ($P<0.05$). Then, the R_r curve temporarily exceeded 100% and decreased steeply, followed by ordinary liver.

2. Various physiological activities after 70% PH were induced in response to promote liver regeneration. Indeed, susceptibility of hepatocytes against to cell death by intoxication switch from sensitivity to resistance between the two successive intracellular Ca^{2+} peaks, as confirmed in also low dose CCl4-induced liver injury, [5] and various physiological activities after 70% PH were induced to promote liver regeneration. Indeed, hepatocytes are resistant to intoxication for 2 days after 70% PH [6,7] and are the cytosolic Ca^{2+} increase [8]. The mRNA expression of genes encoding Ca^{2+}-binding proteins S100A4 and calpain was increased by day 4, corresponding to the increase in Ca^{2+}, and the hepatocytes proliferated synchronously. Thus, the number of cells in S phase increased strikingly with two divisions after 70% PH, hepatocytes underwent synchronous cell proliferation as the liver was restored from 30% to 70% at day four, and significant expression of VEGF mRNA at around day 4 promoted angiogenesis to remodel the sinusoidal system. After the abnormal peak in the R_r curve occurred at day 4, liver regeneration was sustained in the R_r curve by liver swelling alone, as shown previously [9] and recovered transiently to the control level at day four, returned to the decreased level, and then slowly recovered by day ten.

Conclusion

In conclusion, the increase in $[Ca^{2+}]_i$ may be critical for the abnormal increase in R_r of liver regeneration at day 4 and the termination phase to complete liver regeneration after 70% PH. Even though, further study is in progress to precisely characterize the sustained increase in $[Ca^{2+}]_i$, consisting of two successive peaks. In this study, two novel signals were found that regulate liver regeneration after 70% PH in rats. The second finding was an abnormal and transient increase in the ratio R_r curve of liver regeneration at around day 4, and the two successive peaks $[Ca^{2+}]_i$ signal.

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Key words: *partial hepatectomy, ratio of liver regeneration (Rr), intracellular Ca2+, S100A4, termination signal*

Received: February 09, 2021; **Accepted:** February 15, 2021; **Published:** February 25, 2021

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