VERAPAMIL PROMOTES THE MOTOR FUNCTIONAL RECOVERY IN REPERFUSED PERIPHERAL NERVE

Yang, ZG; Qi, WN; Rizzo, M; Goldner, RD; +Chen, LE; Nunley, II, JA
+ Duke University Medical Center, Durham, NC 27710

Introduction: Calcium overload plays a vital role in mediating axonal degeneration and regeneration, and the extent of neuronal damage correlates well with the amount of calcium influx into the cell. Although the exact mechanism is not fully understood, a growing body of evidence has demonstrated the role of calcium overload in cell damage caused by ischemia-reperfusion (I/R) insult in many tissues, such as heart, brain and skeletal muscle. In view of the fact that voltage-gated calcium channels (VGCC) exist in the peripheral nervous system, we hypothesized that VGCC contributes to calcium overload in peripheral nerve I/R insult, resulting in nerve degeneration, and that the use of VGCC blocker verapamil will maintain Ca++ homeostasis and promote motor functional recovery from I/R injury. To test these hypotheses, we examined the sciatic functional index (SFI) as a quantitative means for evaluating the motor functional recovery of the sciatic nerve injury after administration of verapamil.

Methods: The handling of these animals was in accordance with the NIH Guide for the Care and Use of Laboratory Animal and the protocols for the animal experiments in this study were approved by the IACUC at Duke University. A 1-cm segment of rat sciatic nerve was compressed to establish the nerve injury model using a specially designed device. A pilot study was performed in 15 rats to determine the dose-response of verapamil (0.1, 1, 3, and 6 mg/kg), intravenously administrated 30 min before reperfusion, on nerve motor functional recovery. The remaining 32 rats were divided into 2 groups: Group 1 was subjected to a compression load of 100g for 2 h, which mimics I/R insult; Group 2 received a 1000g load for 2 h (I/R combined with mechanical insult). In each group, rats were further subdivided into experimental and control groups, receiving verapamil at the optimal dose determined in the pilot study and normal saline intravenously, respectively. Walking track testing was performed and the sciatic function index (SFI) was calculated between day 1 and day 60 postoperatively (0 indicates normal nerve function and 100 represents complete dysfunction). Data was expressed as means ± SEM. Repeated two-way ANOVA and Student’s t test were used in the statistical analysis. P < 0.05 was considered statistically significant.

Results: The pilot study showed that the optimal dose of verapamil was 1 mg/kg.

In Group 1, the motor functional recovery started in two of the verapamil-treated rats at day 7, but no recovery was seen in controls. The SFI curve in the experimental group had a 7-day left shift over the controls, and its overall SFI was significantly higher than controls (P<0.05). Post hoc analysis showed that the SFI in the experimental group was significantly higher (P<0.01) than controls from day 11 to day 25. During this period, the SFI was rapidly increased from -75.0 ± 6.6 to -6.3 ± 1.6 in the experimental group, and from -96.1 ± 2.7 to -20.4 ± 1.9 in controls. After day 28, the SFI in both groups was almost the same, ranging from -8.4 ± 1.8 to -3.8 ± 1.3.

In Group 2, there was no recovery in both subgroups until 14 days postoperatively. Thereafter, a rapid recovery was observed in both subgroups as well as an evident left shift of SFI curve in the experimental group over controls (P<0.05). The SFI in the verapamil-treated group increased from -59.6 ± 5.9 to -11.0 ± 0.9 from day 18 to day 60, and was significantly higher (P<0.05 to <0.001) than controls, in which the SFI increased from -91.5 ± 2.8 to -20.1 ± 0.6. However, the SFI in both groups did not reach to the normal at day 60, especially in controls.

Comparing with Group 1, the SFI curve of Group 2 showed an evident right shift in both experimental and control subgroups, and the recovery was significantly delayed (P<0.05).

Discussion: Calcium channel blockers, blocking the calcium entry via VGCC, have been widely used in the treatment of cardiovascular disorders during the last decades and recently used experimentally in a wider range of disorders outside the cardiovascular system, including I/R injury. Although these VGCC blockers have been shown to protect tissues from I/R injury, few studies have been performed in peripheral nerve I/R injury. Our results demonstrate that VGCC blocker verapamil promotes motor functional recovery in peripheral nerve I/R injury.

Our data demonstrated that I/R injury combined with mechanical insult leads to more severe damage to peripheral nerves than I/R injury alone and verapamil-treated animals had an earlier onset of motor functional recovery in both of these circumstances. This may have implications for the treatment of patients with peripheral nerve I/R injury in that verapamil will be beneficial to allow earlier recovery. The mechanism of its action in promoting the recovery might be due to its maintenance of calcium homeostasis in the damaged nerves and this area needs further investigation.

References:

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