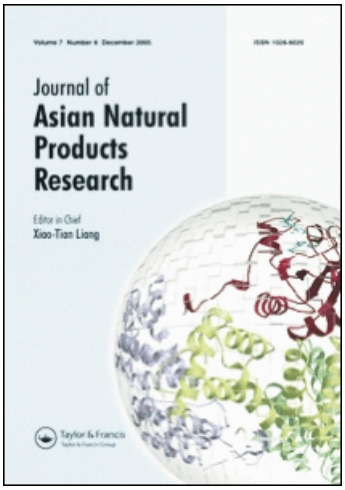

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EFFECT OF GINSENOSIDE Rb1 ON LONG-TERM POTENTIATION IN THE DENTATE GYRUS OF ANAESTHETIZED RATS

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Ginsenosides are the major principles of *Panax ginseng* and have various pharmacological actions on the central nervous system. In this report, we investigated whether ginsenoside Rb1 (10, 100 nmol l^{-1}, icv) could increase the population spike (PS) amplitude in a dose-dependent manner, and accelerate the maintenance phase of long-term potentiation (LTP) induced by high frequency stimulation (HFS) in the dentate gyrus of anaesthetized rats. However, it had no effect on basic synaptic responses evoked by test stimulation. Comparatively, ginsenoside Rb1 (10, 100 nmol l^{-1}, icv) inhibited the induction phase of LTP induced by HFS in a dose-dependent manner. This may be one of the mechanisms of action of ginsenoside Rb1 on synaptic transmission. The details of the mechanism need further investigation.

Keywords: Ginsenoside Rb1; Long-term potentiation; High frequency stimulation; Population spike

INTRODUCTION

We investigated the cognition-enhancing effects of ginsenoside Rb1. In previous studies, Rb1 improved acquisition, consolidation and retrieval of memory impaired by amnestic agents, and accelerated protein biosynthesis in the mouse brain [1,2]. Rb1 (28.6 and 56.1 mg kg^{-1}) has been found to accelerate brain development in young mice as well as facilitate memory acquisition in step down and step through avoidance response tests [3]. Mook-Jung reported similar results: mice were trained in a Morris water maze following injection (ip) of Rb1 (1 mg/kg) for 4 days. Rb1-injected mice showed enhanced spatial learning compared to control animals [4]. To further investigate the action of Rb1 on the central nervous system, we have undertaken to study the effect of Rb1 on long-term potentiation (LTP). LTP of evoked potentials in the hippocampus is a form of activity-dependent synaptic plasticity which has become widely regarded as a possible physiological substrate for some aspects of learning and memory [5].

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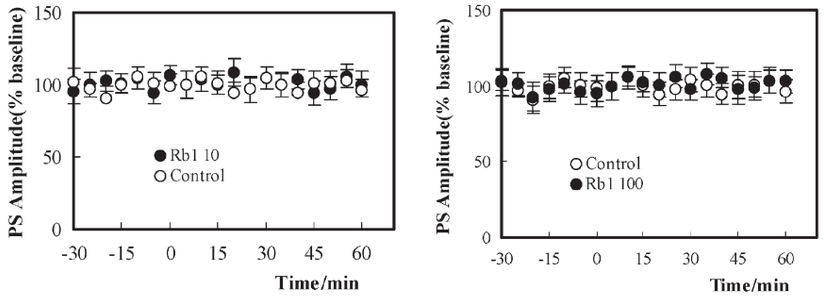

FIGURE 1 The effect of Rb1 (10, 100 nmol l^{-1}, icv) on evoked potential in dentate gyrus of anaesthetized rats. The average amplitude of the PS recorded 30 min before Rb1 injection was defined as 100%. All data are presented as mean ± SD of five observations.

RESULTS AND DISCUSSION

Effect of Ginsenoside Rb1 on Basic Synaptic Transmission

Rb1 (10, 100 nmol l^{-1}, icv) was injected into the lateral cerebral ventricle. The influence of Rb1 on the population spike (PS) evoked by low-frequency test stimulation was examined. The mean baseline was obtained by averaging the PS amplitude of 6 time points within 30 min before Rb1 administration. As shown in Fig. 1, the amplitude of PS did not change after the vehicle and Rb1 over a 60 min recording period. The PS amplitude of the Rb1 10 nmol l^{-1} group at 10, 30, 60 min was 95 ± 8, 104 ± 7, 100 ± 9%, respectively, and that of the Rb1 100 nmol l^{-1} group was 106 ± 8, 98 ± 8, 103 ± 7%, respectively. Therefore, icv injection of 10, 100 nmol l^{-1} did not significantly affect the response evoked by test stimulation ($n = 5$, $P > 0.05$). In other words, ginsenoside Rb1 has no significant effect on basic synaptic transmission of dentate gyrus in anaesthetized rats. The result was in agreement with Kazuho Abe's report [6]. Therefore, ginsenoside Rb1 is unlikely to change the excitability of the postsynaptic membrane or release of neurotransmitter from presynaptic terminals under normal conditions.

Effect of Rb1 on Inductive Phase of LTP Induced by High Frequency Stimulation (HFS)

As shown in Fig. 2, the PS amplitude of control groups did not change during a 90 min recording period, the PS amplitude of HFS (100 Hz, 200 μs) group was 209 ± 20, 182 ± 19,

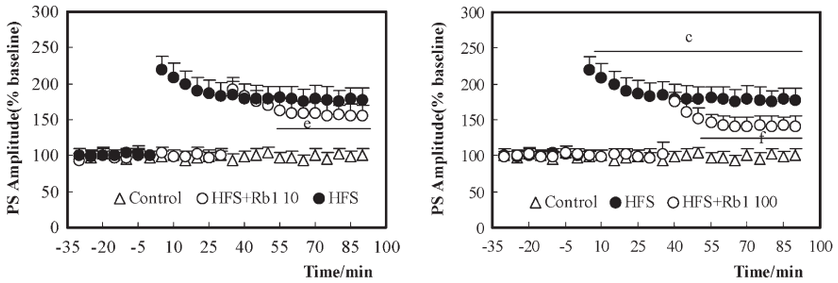

FIGURE 2 Effect of Rb1 (10, 100 nmol l^{-1}, icv) on DG LTP in anaesthetized rats. The average amplitude of the PS recorded 30 min before Rb1 injection or HFS application was defined as 100%. Rb1 was injected 30 min before tetanic stimulation (100 Hz, 200 μs) application. All data are presented as mean ± SD of six observations. $^{c}P < 0.01$ versus vehicle-injected group, $^{e}P < 0.05$, $^{f}P < 0.01$ versus HFS group.

180 ± 19 and 178 ± 17% ($n = 6$) at 10, 30, 60, 90 min, respectively. Rb1 (10, 100 nmol l^{-1}) was injected 30 min before tetanic stimulation application. The PS amplitude of the Rb1 10 nmol l^{-1} + HFS group was 183 ± 19, 157 ± 16, 156 ± 14% at 10, 30, 60 min after HFS application ($n = 6$). In comparison, the PS amplitude of the Rg1 100 nmol l^{-1} group was 176 ± 17, 142 ± 13, 141 ± 13% at 10, 30, 60 min, respectively ($n = 6$). The result suggested that Rb1 (10, 100 nmol l^{-1}, icv) decreased the PS amplitude and inhibited the efficacy of synaptic transmission in a dose-dependent manner. Kazuho has reported a similar result, Rb1 5 nmol l^{-1} icv attenuated the magnitude of LTP induced by strong tetanus (100 pulses, 100 Hz). It is of great interest that ginsenoside Rg1 and Rb1 exerted the opposite effect on hippocampus LTP [7]. Considering the fact that Rg1 showed an excitatory effect and Rb1 behaved as a sedative in the central nervous system, and injection of Rb1 did not affect the potential evoked by low-frequency test stimulation, it was probable that Rb1 selectively modulated processes activated during or following tetanic stimulation. The following effect of Rb1 on the maintenance phase of LTP demonstrates further the complex effect of Rb1 on synaptic plasticity.

Effect of Ginsenoside Rb1 on Maintenance Phase of LTP Induced by HFS

Rb1 (10, 100 nmol l^{-1}, icv) was injected 30 min after HFS application. As shown in Fig. 3, the PS amplitude of the Rb1 10 nmol l^{-1} + HFS group was 194 ± 17, 202 ± 18, 204 ± 18% at 10, 30, 60 min, respectively ($n = 6$). Comparatively, the PS amplitude of the Rb1 100 nmol l^{-1} group was 203 ± 19, 219 ± 18, 220 ± 21% at 10, 30, 60 min, respectively ($n = 6$). Ginsenoside Rb1 exhibited a positive effect on the maintenance phases of LTP, and increased LTP expression in a dose-dependent manner. It is of great interest that Rb1 showed an opposite effect on the induction and maintenance phases of dentate gyrus LTP in anaesthetized rats. Hippocampus LTP is considered to underlie certain forms of learning and memory, and it has been reported that Rb1 ameliorated learning performances of mice in passive avoidance tests [2], but inhibited the responses in conditioned avoidance tests such as a shuttle-box test [8]. It is possible that inhibition of LTP by ginsenoside Rg1 is, at least in part, involved in the effects of Rb1 on learning behaviour. However, Rb1 accelerated the maintenance phase of hippocampus LTP, therefore, as stated above, Rb1 improved acquisition, consolidation and retrieval of memory impaired by amnestic agents.

In conclusion, we have found for the first time that ginsenoside Rb1 showed opposite effects on the induction and maintenance phases of dentate gyrus LTP in anaesthetized rats.

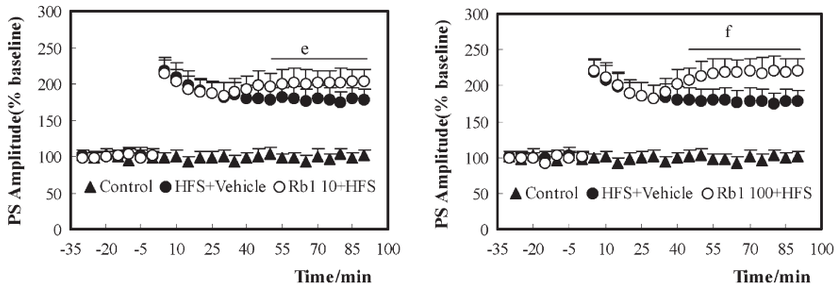

FIGURE 3 Effect of Rb1 (10, 100 nmol l^{-1}, icv) on maintenance of perforant DG LTP induced by tetanic stimulation in anaesthetized rats. The average amplitude of the PS recorded 30 min before Rb1 injection or HFS application was defined as 100%. Rb1 was injected 30 min after tetanic stimulation (100 Hz, 200 μs) was applied. All data were presented as mean ± SD of six observations. $^{e}P < 0.05$, $^{f}P < 0.01$ versus HFS group.

This finding will contribute to explaining the complex pharmacological effects of Rb1 on the central nervous system, but the detailed mechanism needs further studies.

EXPERIMENTAL SECTION

Drug Delivery [9,10]

Rb1 was supplied by the Department of Basal Organic Chemistry, Norman Bethune Medical University. Drug doses were calculated on the basis of assuming the brain volume to be approximately 2 ml and drugs theoretically achieved the brain concentrations required. The final brain concentrations of Rb1 10 and 100 nmol l^{-1} were used. The vehicle or Rb1 was injected into the lateral cerebral ventricle via a cannula inserted through the outer guide cannula that was located in the lateral cerebral ventricle, following the measurement of the baseline for 25–30 min from the DG of the same hemisphere, the cannula was left in place for 5 min after each injection.

Electrophysiological Recording

Recording of PS was carried out as described in our previous study [7,9,11,12]. Briefly, male SD rats were anaesthetized with urethane carbamate (1.5 g kg^{-1}, ip) and fixed in a stereotaxic frame. A bipolar stimulation electrode was stereotaxically placed in the left entorhinal cortex to stimulate the perforant path and the evoked potential was extracellularly recorded from the granule cell layer of DG. Electrodes were slowly lowered to a depth of 2.5 mm, the final depths were adjusted until maximal PS was obtained. A low-frequency test stimulation (0.033 Hz, 200 μs) was applied at intervals of 30 s and the stimulus intensity was set at a level which evoked a PS of 30–50% of the maximum. The theta-like HFS induced LTP consisted of 10 bursts of 5 pulses (100 Hz, 200 μs), and the brief tetanic stimulation was applied at the same intensity through the same stimulation electrode as that used for test stimulation.

The evoked responses were averaged every five measurements, and the mean baseline was obtained by averaging the PS amplitude of 6 time points obtained within 30 min before injection of Rb1 or HFS application. The data were expressed as a mean percentage of the mean baseline; the statistically significant difference between means was estimated using the Student's *t*-test.

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