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β-amyloid-(1–40) increases long-term potentiation in rat hippocampus in vitro

Jianqun Wu [a], Roger Anwyl [b], Michael J. Rowan [a,*]

[a] *Department of Pharmacology and Therapeutics, Trinity College, Dublin 2, Ireland*
[b] *Department of Physiology, Trinity College, Duline 2, Ireland*

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Abstract

The effect of β-amyloid-(1–40) was investigated on long-term potentiation of glutamatergic excitatory postsynaptic field potentials recorded in the inner molecular layer in the rat dentate gyrus in vitro. In the presence of 200 nM β-amyloid-(1–40) there was an increase in long-term potentiation of 51%. Basal synaptic transmission was not affected. These results provide direct evidence that a relatively low concentration of β-amyloid-(1–40) increases synaptic plasticity.

Keywords: β-Amyloid-(1–40); Long-term potentiation; Glutamatergic synaptic transmission

The production, processing and mechanism of action of the 39–43 amino acid β-amyloid peptide has become the focus of intense pharmacological research in view of its potential role in the pathogenesis and pathophysiology of Alzheimer's disease (Selkoe, 1994). One form of β-amyloid, the 1–40 sequence, is continuously released from neurones and glial cells resulting in extracellular concentrations in the pico- to nanomolar range (Selkoe, 1994). When injected acutely into the hippocampus β-amyloid-(1–40) selectively impaired footshock avoidance learning, probably as a result of interacting with a novel peptide receptor which recognises the Val-Phe-Phe sequence (Flood et al., 1994; McDonald et al., 1994). Since long-term potentiation of synaptic transmission in hippocampal glutamatergic pathways is believed to mediate certain forms of learning and memory (Bliss and Collingridge, 1993) we have investigated the effects of β-amyloid-(1–40) on this form of synaptic plasticity.

Experiments were carried out on transverse slices (350 μm) of the hippocampus of male Wistar rats (weight 70–120 g) which were continuously superfused at a rate of 5 ml/min with oxygenated (95% O_2, 5% CO_2) media at 30–32°C. The control media contained: (mM) NaCl, 120; KCl, 2.5; NaH_2PO_4, 1.25; $NaHCO_3$, 26; $MgSO_4$, 2.0; $CaCl_2$, 1.5; D-glucose, 10. All solutions contained 100 μM picrotoxin (Sigma) to block $GABA_A$ mediated transmission. β-Amyloid-(1–40, Bachem) was stored as a 0.5 mM stock water solution at −20°C in small aliquots which were freshly prepared for each experiment. Presynaptic stimulation was applied using wire electrodes in the commissural/associational pathway of the dentate gyrus at a distance of 50 μm from the cell body layer of the granule cells. Recordings of population field excitatory postsynaptic potentials (e.p.s.p.s) were made using glass microelectrodes (1–2 MΩ) containing the extracellular medium and were placed in the same layer as the stimulating electrodes. Test stimuli were applied at a rate of 0.025 Hz and at a voltage level which evoked responses of approximately 1.5 mV in amplitude. Long-term potentiation was induced using a tetanus (8 trains of 8 pulses at 200 Hz with an inter-train interval of 2 s) at a stimulation level which evoked responses of approximately 2.5 mV in amplitude. The values of long-term potentiation are expressed as the mean percentage increase above the

* Corresponding author. Tel.: +353 1 6081567; fax: +353 1 6713507; e-mail: mrowan@mail.tcd.ie.

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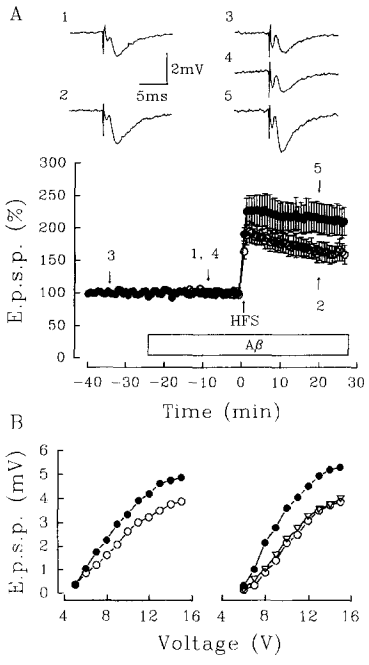

Fig. 1. Effect of β-amyloid (1–40, Aβ) on long-term potentiation of excitatory synaptic transmission in the rat hippocampus. (A) Field excitatory postsynaptic potentials (e.p.s.p.s) were recorded in the inner molecular layer of the dentate gyrus in response to stimulation of the commissural/associational pathway. In control slices (open circles) high frequency stimulation (HFS) evoked a long-term potentiation of 59% at 25–28 min post-stimulation. Whereas treatment with 200 nM β-amyloid-(1–40) for 25 min had no effect on baseline responses there was an increase in the level of long-term potentiation (110%). Values are the mean ± S.E.M., $n = 7$. Insets show traces corresponding to the different points marked on the control (1, 2) or β-amyloid-(1–40) (3, 4, 5) graphs. (B) Input-output curves (stimulation voltage versus field e.p.s.p. amplitude) before (open circles) and 20–30 min after (filled circles) high frequency stimulation in a control slice (left hand graph) and in an experimental slice from the same animal which had been exposed to 200 nM β-amyloid-(1–40) for 25 min (right-hand graph). The level of long-term potentiation was increased at all stimulus intensities. β-Amyloid-(1–40) had no effect on the baseline input-output curve (open triangles).

basal (= pre-tetanus) values ± S.E.M. and were compared using paired, two-tailed, Student's t-tests.

In order to study the effect of β-amyloid-(1–40) on long-term potentiation a series of experiments was carried out on pairs of slices from the same animal. In control slices the average short-term potentiation and long-term potentiation, measured 2 and 25–28 min after the tetanus, was 91.4 ± 17.1 and 59.2 ± 15.2% above the baseline (100%), respectively (number of animals, $n = 7$, Fig. 1A). In the other slice of the pair bath application of 200 nM β-amyloid-(1–40) for 25 min had no significant effect on the baseline field e.p.s.p. amplitude (97 ± 3.3% pre-β-amyloid values, $n = 7$). Tetanic stimulation 25 min after commencing perfusion of β-amyloid-(1–40) induced short-term potentiation and long-term potentiation of 124.9 ± 22.7 and 110.3 ± 23.5%, at 2 and 25–28 min post-tetanus, respectively ($n = 7$, $P < 0.05$ compared to controls). Of the 7 pairs of slices studied, 6 showed an increase in long-term potentiation in the presence of β-amyloid (range 16–114% increase). The increase in the level of long-term potentiation in the presence of β-amyloid-(1–40) was observed throughout the whole range of the input-output curve of the synapses (stimulus intensity versus amplitude of the field e.p.s.p., Fig. 1B) with no effect on the basal input-output curve.

The finding that β-amyloid-(1–40) produced an increase in long-term potentiation indicates that it can regulate synaptic plasticity when the extracellular concentration reaches about 200 nM. Since there was an enhancement of the synaptic responses even immediately after the tetanus, the observed increase is probably due to a facilitation of the induction stage of long-term potentiation. Although acute β-amyloid-(1–40) treatment does not appear to affect basal, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated, glutamatergic transmission in the hippocampus (the present data and Dutar et al., 1994), we have recently found that 200 nM β-amyloid-(1–40) selectively increased the *N*-methyl-D-aspartate (NMDA) receptor-mediated component of transmission (Wu et al., submitted). Since long-term potentiation induction in the associational/commissural pathway is NMDA receptor-dependent (O'Connor et al., 1995), it seems likely that the increase in long-term potentiation may be the result of an augmentation of NMDA receptor-mediated synaptic currents. Finally, it may seem somewhat paradoxical that an agent which can produce a deficit in learning after intrahippocampal injection (McDonald et al., 1994) was found to increase long-term potentiation. However, if a similar facilitation of synaptic plasticity occurred inappropriately at the time of training it would be expected to impair rather than to improve learning and memory.

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