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Rapid communication

Long-term potentiation in rat prefrontal slices facilitated by phased application of dopamine

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Abstract

We have previously shown that coupling bath application of dopamine with 50 Hz tetani induces long-term depression in rat prefrontal slices [Neuroscience 85 (1998) 669]. Here, we report a reliable protocol for inducing long-term potentiation in the same preparation. Long-term potentiation was induced by the same dopamine–tetani coupling protocol when the coupling was preceded (~ 30 min) by a single bath application of dopamine. We suggest that metaplastic processes triggered by the first application of dopamine might underlie the LTP induction. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Long-term potentiation; Dopamine; Cortex, prefrontal

The rat prelimbic area may be functionally analogous to the primate dorsolateral prefrontal cortex (Birrell and Brown, 2000). Normal prefrontal cortex function requires an optimal dopamine concentration in the PFC (Sawaguchi and Goldman-Rakic, 1994; Zhart et al., 1997), and we showed in rat prelimbic (rat prefrontal cortex) slices that tetanic stimuli to layer I–II afferents in the presence of dopamine (100 μM) induce long-term depression of layer I–II to layer V pyramidal neuron glutamatergic synapses (Otani et al., 1998, 1999). Although we theorised that long-term neuronal traces are important for the executive cognitive function carried by the prefrontal cortex (Otani, submitted), our dopamine-tetanic stimulation protocol never induced long-term potentiation. Interestingly, in anaesthetised preparations, LTP facilitation was seen after afferent tetani were coupled with ventral tegmental stimulation, which releases dopamine in prefrontal cortex (Gurden et al., 1999). One possible explanation for the apparent discrepancy is that, under anaesthetised conditions, dopamine receptors are tonically stimulated by baseline dopaminergic activity, perhaps triggering metaplastic processes. We manipulated this factor in this investigation.

Methods were as described elsewhere (Otani et al., 1999). Coronal brain slices including prelimbic area were prepared from 23- to 30-day-old male Sprague–Dawley rats and maintained in oxygenated (95% O_2–5% CO_2), phosphate-buffered saline (in mM; NaCl 124, KCl 2, $NaHCO_3$ 26, KH_2PO_4 1.15, $MgCl_2$ 1, $CaCl_2$ 2, and D-glucose 11) at 28 °C. A bipolar stimulating electrode was placed on layer I–II. Monosynaptic excitatory postsynaptic potentials (EPSP) were evoked at 0.033 Hz and recorded from the soma of layer V pyramidal neurons by glass micro-pipettes containing 3 M K-acetate. Tetani consisted of 50 Hz stimuli (100 pulses), repeated four times every 10 s. Bicuculline methiodide (1 μM) was present in the bath.

Dopamine (100 μM) was first bath-applied for 10–15 min without tetani ($n=8$). Changes in the EPSP slope during application were monitored in the majority of cases ($n=6$), and as shown previously (Otani et al., 1998, 1999), dopamine transiently depressed the responses ($-33 \pm 5.2\%$), which fully recovered within 30 min (Fig. 1). When the EPSP became stable (i.e. about 30 min after the beginning of dopamine washout), dopamine was bath-applied for a second time. The acute depression induced by the second application of dopamine ($-4.3 \pm 4.6\%$, $n=8$) was significantly smaller than that induced by the first application of dopamine ($P<0.0025$, paired t-test, $n=6$), suggesting desensitisation of the receptors. Delivery of 50 Hz tetani at the end of the second application of dopamine induced long-term potentiation (Fig. 1). No long-term depression was observed. The mean EPSP slope increase 40 min after the second dopamine–tetani coupling was $19 \pm 3.6\%$ ($n=8$). In one case,

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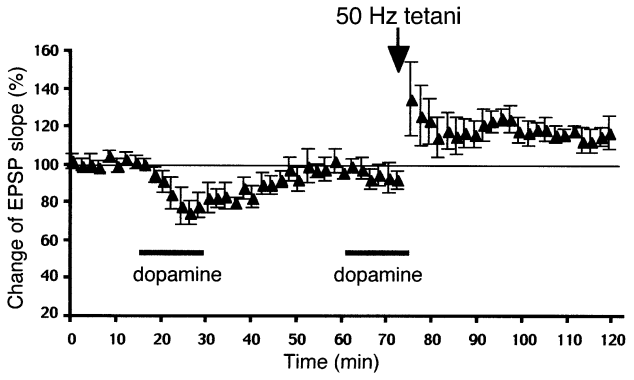

Fig. 1. Coupling a second bath application of dopamine with 50 Hz tetani induced long-term potentiation of layer I–II to layer V pyramidal neuron glutamatergic synapses in rat prefrontal slices ($19 \pm 3.6\%$ increase in the EPSP slope 40 min after tetani, $n = 8$). The first application of dopamine (without tetani) was made about 30 min before the second application of dopamine (coupled with tetani). The acute response depression after the first application of dopamine ($-33 \pm 5.2\%$) fully recovered by the time of the second dopamine–tetani coupling. Acute depression induced by the second application of dopamine was only $-4.3 \pm 4.6\%$ ($P < 0.0025$), suggesting desensitisation of dopamine receptors.

long-term potentiation was monitored for 90 min following coupling (23% at 90 min). Three control conditions were created. First, long-term potentiation induction might depend solely on pre-exposure to dopamine. Therefore, we pre-exposed slices to dopamine 30–40 min before delivering tetani with dopamine already washed out ($n = 6$). In this case, tetani did not induce long-term potentiation ($4.2 \pm 4.0\%$ 40 min after tetani, $P < 0.025$). Second, the successive dopamine application alone might induce long-term potentiation. Thus, in three cells, we applied dopamine twice without tetani, with the identical inter-application interval as in the long-term potentiation group. There was no long-term potentiation after the second sole application of dopamine ($0.5 \pm 13\%$). Third, long-term potentiation induction might depend on the size of the response at the time of tetani, because the responses were largely undepressed during the second dopamine application. Therefore, in five cells, we increased the stimulus intensity to increase the EPSP size to approximately the baseline level before delivering tetani at the end of a first application of dopamine. Three cells showed long-term depression ($-16 \pm 2.2\%$) and two showed long-term potentiation (14% and 55%). Thus, increasing postsynaptic cooperativity converted dopamine-facilitated long-term depression to potentiation in some cases. This conversion was not seen by Law-Tho et al. (1995), but there may have been slight differences in the experimental conditions used. Interestingly, analysis of the postsynaptic depolarisation during tetani showed that the depolarisation was not enhanced in the second dopamine–tetani condition, while it was enhanced in the first dopamine/response-increased condition ($P < 0.05$). Thus, the facilitation of long-term potentiation by phased dopamine application does not involve increased postsynaptic depolarisation during tetanic stimuli (cf. Otani et al., 1998). We suggest that metaplastic modifications in cellular biochemistry might underlie this long-term potentiation.

Herry and Garcia (2002) recently showed long-term potentiation induction in the rat prefrontal cortex during learning of conditioned-fear extinction. Further work is required to determine the exact physiological role of prefrontal long-term potentiation in cognition and behaviour.

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