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The inhibitory effects of pro-inflammatory cytokines on LTP are attenuated by nicotine

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Nicotine has previously been shown to facilitate the induction of long-term potentiation (LTP), long-term depression (LTD) and depotentiation (Fujii *et al.* 1999; Fujii & Sumikara, 2001), as well as reversing age-related impairments of LTP in the hippocampus. However the relative contribution of nicotine to hippocampal synaptic transmission and plasticity is disputed. Previously we have shown that IL-1β and IL-18 inhibition of LTP can be reversed by selective inhibition of the p38 mitogen-activated protein kinase (O'Connor & Coogan, 1999). As nicotine has been demonstrated to facilitate the induction of LTP and to reverse age-related impairments in LTP which are associated with increased levels of pro-inflammatory cytokine production, we hypothesized that these cytokines would not affect the induction of LTP in the presence of nicotine.

Experiments were performed on slices of dentate gyrus (350 μm) of young Wistar rats (50–100 g) humanely killed. Recordings of field excitatory post-synaptic potentials (EPSPs) were made from the medial perforant path using standard methods. LTP was induced by a high frequency stimulation (HFS) consisting of eight trains of eight pulses at 200 Hz separated by 2 s intervals, at a voltage corresponding to 50 % maximum EPSP slope. Data are expressed as means ± S.E.M. and were statistically analysed using Student's paired *t* test. $P < 0.05$ was considered significant.

HFS in hippocampal slices with picrotoxin (100 μM) present gave rise to robust LTP (151.1 ± 7.0 %, $n = 9$ at 50–60 min post tetanus; $P < 0.01$ compared to baseline). In the presence of nicotine (50 μM) LTP was 197.2 ± 3.5 % of baseline levels at 50–60 min post tetanus ($P < 0.01$ compared to slices without nicotine, $n = 5$–6). LTP in the presence of picrotoxin was fully depotentiated to 109.7 ± 0.6 %, $n = 9$ at 20 min post low-frequency stimulation (LFS). However LTP in the presence of picrotoxin and nicotine was not significantly depotentiated (169.4 ± 1.4 % at 20 min post LFS; $P < 0.01$ compared to slices without nicotine). Treatment of slices with IL-1β (4 ng ml^{-1}), IL-18 (100 ng ml^{-1}) or tumour necrosis factor-α (4 ng ml^{-1}) for 20 min prior to treatment with nicotine (50 μM) led to a robust LTP when HFS was applied (206.3 ± 14.9 %, 200.9 ± 9.8 % and 208.5 ± 7.9 % of baseline respectively 50–60 min post HFS). These were all significantly different from slices treated with cytokine alone ($P < 0.05$; $n = 4$–6 for all). Application of LFS 1 h post HFS did not significantly depotentiate the LTP in all three cases ($P < 0.01$ for all).

These results report for the first time a modulatory role for nicotine on cytokine-induced inhibition of LTP. These effects of nicotine may have an important role to play in the neuro-immune effects of cytokines in the central nervous system.

Fujii S *et al.* (1999). *Brain Res* **846**, 137–143.

Fujii S & Sumikara K (2001). *Brain Res* **894**, 340–346.

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Heterotopic fetal striatal transplants ameliorate motor impairments induced by frontal cortex lesion

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Recently, we demonstrated that transplantation of the frontal cortex lesion with fetal cortical tissue can promote functional recovery of skilled forelimb use when rats were obliged to use the impaired limb (Riolobos *et al.* 2001). The present experiment was undertaken to investigate the mechanisms of this neurotransplantation-induced recovery using different types of donor materials.

Before surgery, rats were trained in a paw-reaching for food-task. All animals were anaesthetised in all stages of the subsequent procedure (Equithesin, 20 mg kg^{-1} I.P.). At the end of the experiments all animals were killed humanely. The experimental animals were unilaterally lesioned by aspiration in the sensorimotor cortex of the contralateral hemisphere to the preferred paw in the paw reaching for food task. After lesion, animals were retested in the paw reaching task to evaluate the deficit induced by the lesion. Only animals with an unequivocal impairment of the forelimb were subjected to transplantation. Four weeks later, fetal frontal cortex was placed in the lesion cavities in one group of rats; in a second group fetal striatal primordium was employed as donor tissue and adult sciatic nerve tissue in a third group. These groups were compared to a group of non-lesion rats considered as controls. Four months later, animals with homotopic or heterotopic transplants showed amelioration of the deficits caused by the lesion when animals were forced to reach with the lesion paw. By contrast, sciatic nerve transplants failed to produce any significant recovery in the reaching-for-food task. Morphological studies showed that the transplant-induced recovery was independent of the number of surviving neurons. However, it was conditioned by the size of the lesion, the transplant location as well as the nature and degree of the transplant connectivity with the host brain.

Riolobos AS *et al.* (2001). *Neurobiol Learn Mem* **75**, 274–292.

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An *in vivo* study of motor learning and memory capabilities of wild and transgenic mice with Alzheimer-like deficits

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Functional properties of the CNS (mostly with reference to learning and memory capabilities) should be studied in awake, freely moving animals. An attempt was made in our laboratory to study motor learning and memory capabilities of wild and transgenic mice with deficits in those functions (demential states,

experimental models of Alzheimer's disease, etc.). The classical conditioning of the eyelid response in mice was used for this aim. Reproducible surgical and implantation procedures were developed in order to standardize this preparation.

Experiments were carried out following EU and Spanish guidelines and, at the end of them, animals were humanely killed. A total of four 50 μm stainless-steel wires (wholly isolated except at the very tip) were implanted in the upper lid under deep anaesthesia (ketamine, 50 mg kg^{-1}, I.P.) and soldered to a 4-pin connector. Two of the electrodes were directed to the supraorbitary branch of the trigeminal nerve and the other two to the orbicularis oculi muscle. Conditioning sessions consisted of 60 paired presentation of a conditioned stimulus (CS, a 50 μs square, cathodic pulse, 1.5 × threshold) followed, 250 ms later, by an unconditioned stimulus (US, a 0.5 ms square, cathodic pulse, 3 × threshold). The CS–US pair of stimuli was presented every 30 ± 5 s. At the end of each session, five CS were presented alone. Also, CS was presented alone for whole habituation and extinction sessions. Until now, we have used C57 and Swiss mice. We did two habituation, ten conditioning and four extinction sessions. Also, we have carried out both fast (an extinction session per day) and slow (and extinction session every ten days) extinctions.

The results for control animals were as follows. (i) The EMG of the orbicularis oculi muscle proved to be a good parameter to identify the presence of true conditioned responses. (ii) Maximum percentage of responses (70–80 %) was reached for both strains by the 7th conditioning session. (iii) The learning curve (determined as mean percent of conditioned responses per session) for C57 rose faster than for Swiss mice, but both reached a similar learning asymptote after a few conditioning sessions. Differences between both learning curves were not statistically significant.

At present we are repeating the same experimental procedure on different transgenic mice that model Alzheimer's disease. Thus C57BL76J adult male mice are being used to evaluate the effects of the overexpression of amyloid precursor protein (APP) and presenilin-1 (PS-1) on the acquisition of classically conditioned eyelid responses.

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Early development of the thalamic reticular and perireticular nuclei in the human brain

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Growing axons of the nervous system often contact cellular groups, which are thought to play a part in their guidance to their ultimate targets. In several species, thalamic fibres have been shown to associate with cells of the thalamic reticular nucleus (TRN) and perireticular nucleus (PRN) as they leave the diencephalon and negotiate towards and through the internal capsule (Metin & Godement 1996; Earle & Mitrofanis 1996). Although equivalent transient neuronal groups have been described in the human embryonic forebrain (Letinic & Kostovic, 1996; Ulfig *et al.* 1998), little is known about their early development and their relationship with thalamocortical fibres. By means of the carbocyanine fluorescent dye DiI and antibodies against microtubule-associated protein MAP2, calretinin (CR) and calbindin (CB), we studied neuronal populations along the path of developing thalamocortical and corticofugal axons in humans.

Embryos and early fetuses from Carnegie stages 16–23 (37–56 days post-fertilization) were obtained after legal abortions, following national guidelines in Russia. Retrograde tracing of axons from the dorsal thalamus at stage 17 revealed back-labelled cells in the ventral thalamus, hypothalamus and a region presumed to be the primordium of the TRN, which contained CR-, CB- and MAP2-immunopositive cells. We also found a distinct group of cells projecting to the thalamus in the mantle zone of the medial part of the basal telencephalon at stage 16–17, prior to the formation of the internal capsule. They showed a strong resemblance to the PRN described in other mammalian species. At stage 18, few thalamocortical axons have reached the ventral telencephalon, although numerous axons of the putative reticular and perireticular nuclei have entered the dorsal thalamus. By stage 21, thalamocortical axons have increased in density and have reached the lateral ganglionic eminence, and by stage 23 they have invaded the intermediate zone beneath the ventrolateral cortex. It seems, then, that, as thalamic fibres arrive at each cell group along their path, axonal projections from that region have already reached the dorsal thalamus. It is conceivable that these thalamopetal projections, and the cell groups from which they arise, play a part in the navigation of thalamocortical fibres.

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