Changes in Sensitivity of Rat Front Cortex Neurons to Acetylcholine (ACh) after α-Amino-3-Hydroxy-4-Isoxazole Propionic Acid (AMPA) Lesions of Nucleus Basalis Magnocellularis and After Embryonic Basal Forebrain Transplants

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The effects of unilateral S-AMPA lesions of nucleus basalis magnocellularis (nbm) and of subsequent ipsilateral embryonic basal forebrain transplants on the sensitivity of pyramidal cells in the frontal cortex to iontophoresed acetylcholine (ACh) and carbachol were studied in anaesthetized rats. Each drug was applied with an ejection current of 30 nA for 20 s and the average response of 3 applications (separated by 1 min recovery periods) was obtained. Neurons were considered to be sensitive when their firing rate increased or decreased (Wilcoxon, P<0.05), either during or within 20 s of drug application.

Neuronal firing rates were significantly reduced in the frontal cortex 8-10 weeks post-lesion, when acetylcholinesterase (AChE)-positive fibre staining was almost completely absent, but the percentage of ACh-sensitive neurons increased (68/82 neurons from 7 rats compared with 72/144 neurons from 12 control rats, P<0.0001); the duration of ACh's action also significantly increased. Comparison with controls showed that this enhanced sensitivity to ACh after lesion could be explained solely by an increase in the proportion of neurons excited by ACh (Table 1). The modulatory effects of ACh were also studied on responses of cortical neurons evoked by afferent electrical stimulation (single square wave pulses, 5 ms duration, 1-3 mA, were delivered at intervals of not less than 10 s and 10 stimulations used for each procedure). ACh modulation of neuronal responses evoked by sensory stimulation was not significantly changed after the lesion. Sensitivity to carbachol and glutamate was unchanged after lesion.

In normal rats, acute administration of an AChE-inhibitor, di-isopropyl fluorophosphate (DFP) significantly increased the frontal cortex neurons' responsiveness to ACh from 50% in the control group to 87.4% in the DFP treated group (P<0.0001). DFP also decreased the latency and increased the duration of ACh action without changing the frontal cortex firing rate. The sensitivity of frontal cortex to carbachol and glutamate was not changed after DFP. Chronic administration of scopolamine (10 mg/kg s.c. in 0.9% NaCl daily for 16 days) significantly increased the sensitivity of frontal cortex neurons to both ACh and carbachol. It also significantly increased the neuronal firing rate, prolonged the duration of ACh and carbachol action and decreased the latency of action of both drugs. In contrast, chronic administration of oxotremorine (0.5 mg/kg s.c. in 0.9% NaCl twice daily for 11 days and 10 mg/kg in sesame oil for 9 days) significantly decreased the frontal cortex neurons' sensitivity to both ACh and carbachol. It also significantly decreased the neuronal firing rate, decreased the duration and increased the latency of ACh and carbachol action.

Cholinergic-rich transplants to the frontal cortex normalised neuronal sensitivity to ACh and its duration of action but did not restore the firing rate. Non-cholinergic transplants or cholinergic-rich transplants to the somatosensory cortex were ineffective. Histological examination showed a sprouting of ChAT and AChE from the transplant into the neocortex of transplanted animals.
TABLE 1
Responses of frontal cortex neurones to Ach under different conditions (AMPA lesion of nbm followed by embryonic foetal transplants).

| Condition                      | No of neurones responded | Excitation | Inhibition | Biphasic |
|--------------------------------|--------------------------|------------|------------|----------|
| Control (144)                  | 72                       | 24         | 37         | 11       |
| Lesion (82)                    | 68                       | 40         | 22         | 6        |
| Non-cholinergic transplant (75)| 61                       | 32         | 20         | 9        |
| Cholinergic transplant (SC) (37)| 30                       | 19         | 9          | 2        |
| Cholinergic transplant (FC) (39)| 21                       | 14         | 6          | 1        |

The numbers in parentheses indicate the total number of neurones studied in each group. SC=somatosensory Cortex, FC=frontal cortex.

The results suggest that the increased sensitivity to ACh seen in lesioned rats was probably due to loss of AChE because similar effects were seen after DFP. The distance of the implant from the frontal cortex appeared crucial to normalizing sensitivity of frontal cortical neurones to ACh.