Glutamate receptors involved in central sensitization in the decerebrated rabbit

John Harris, Claire Joules and Rob W. Clarke

School of Biosciences, University of Nottingham, Sutton Bonington Campus, Loughborough LE12 5RD, UK

In the decerebrated rabbit, electrical stimulation of the toes evokes reflexes in the knee flexor semitendinosus (ST) and the ankle flexor tibialis anterior (TA) that are facilitated for several minutes after application of mustard oil to the toe tips. The present experiments have investigated the roles of glutamate *N*-methyl-D-aspartate (NMDA), and group I metabotropic ($mGlu_1$ and $mGlu_5$) receptors in mediating mustard oil-induced sensitization of flexor reflexes.

Experiments were performed on rabbits decerebrated under halothane (2–3 %) nitrous oxide anaesthesia. Reflexes were evoked by electrical stimulation of the skin at the base of the toes and recorded from the ipsilateral TA and ST muscle nerves, to be averaged and integrated by computer. A total of 100 μl 20 % mustard oil in paraffin oil was applied to the tips of either the two lateral or medial toes and the effects on the reflexes recorded. At least 1 h after the mustard oil stimulus one of three drugs was given intrathecally: dizocilpine (NMDA antagonist, 1 mg, $n = 7$); 7-(hydroxylimino)cyclopropa(b)chromen-1a-carboxylate ethyl ester (CPCCOEt, $mGlu_1$ antagonist, 1–3 mg, $n = 8$); or 2-methyl-6-(phenylethynyl)pyridine (MPEP, $mGlu_5$ antagonist, 0.2–1 mg, $n = 10$). After a further 30–40 min, mustard oil was applied to the toes that had not received it previously. Dizocilpine and MPEP were dissolved in Ringer solution, whereas CPCCOEt was dissolved in DMSO. In experiments with this drug, the first mustard oil stimulus was preceded by an intrathecal injection of 100 μl DMSO. Experiments were terminated by I.V. injection of KCl solution.

In the control states before dizocilpine, CPCCOEt and MPEP respectively, mustard oil significantly (Friedman's ANOVA, $P < 0.01$) enhanced TA reflexes to median peak values of 186, 172 and 176 % and ST reflexes to medians of 163, 158 and 214 % of pre-stimulus levels. Median duration of effect was 63, 37 and 63 min for TA responses and 55, 45 and 29 min for ST reflexes. None of the drugs or vehicles had any significant effect on either reflex response *per se* (Wilcoxon tests, $P > 0.05$). After dizocilpine, mustard oil failed to increase the TA reflex (Friedman's ANOVA, $P > 0.1$) and the duration of enhancement of ST reflexes was significantly reduced, to a median of 3 min (Wilcoxon test, $P < 0.05$). After CPCCOEt, the peak facilitation of TA reflexes was reduced (Wilcoxon, $P < 0.05$) but no other significant effects were observed. After MPEP, mustard oil induced changes that were statistically indistinguishable from controls.

These data show that glutamate NMDA receptors make a major contribution to the development of central sensitization of spinal reflexes in the rabbit, but that Group I metabotropic receptors have little role to play in generating the sensitized state.

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All procedures accord with current UK legislation.

Bilateral corticomuscular coherence in the human neonate

W.K. Mitchell and S.N. Baker

Department of Anatomy, University of Cambridge, Cambridge CB2 3DY, UK

The corticospinal (CS) tract forms the major pathway for cortical control of movement. The time scale of the normal development of this pathway is controversial.

Studies in monkeys show that the CS tract continues to grow after birth, and direct corticomotoneuronal (CM) synapses form with the onset of independent finger movements at about 4 months postnatal (Kuypers, 1962; Armand *et al.* 1994). The timetable in humans may be different. Transcranial magnetic stimuli (TMS) over the motor cortex in adults excite CS cells and produce a twitch in contralateral muscles. In human babies, Eyre *et al.* (2001) showed responses in both ipsilateral and contralateral muscles to TMS, suggesting bilateral CM synapses are present at birth. Ipsilateral fibres may be 'pruned' during postnatal development.

Field potential recordings in the adult motor cortex reveal oscillations at *ca* 20 Hz, which are coherent with EMG from contralateral muscles. This study used corticomuscular coherence as an index of neural connectivity in the infant.

With local ethical committee approval, recordings were made from nine babies (3 male, age 21 ± 3 days post-due date, mean ± S.D.). We used adhesive electrodes to measure 5–15 min of EEG (two differential recordings across the central sulci) and three channels of EMG (electrodes placed on the dorsal aspect of the hand, flexor compartment of the forearm, and overlying biceps brachii). Periods of steady contraction were selected off-line for coherence analysis.

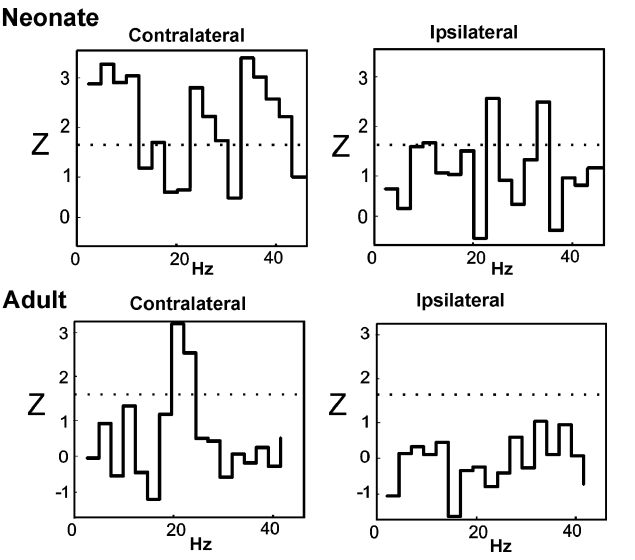

Figure 1. Bilateral corticomuscular coherence estimates in both newborns and adults. The dashed lines show significance level ($P < 0.05$).

Figure 1 shows results combined across nine babies and three EEG-EMG pairs. The ordinate is a Z-score, where coherence at a given frequency is compared with that at 100–150 Hz (a range with no known physiological relevance). The Z-score has mean zero, SD one, if there is no coherence at that frequency. Neonates had bilateral corticomuscular coherence at a range of frequencies; in comparable adult recordings ($n = 5$ subjects) coherence was only observed contralaterally and at *ca* 20–25 Hz.

These findings support previous work, suggesting CM connections are present at birth in human. There may be weak ipsilateral, as well as contralateral, connections, although we cannot rule out spread of potentials on the scalp as the source of the ipsilateral coherence seen. In monkeys, the CS terminals are not present in the vicinity of motoneurons at birth. It may be that the developmental timetables differ substantially between the two species. Alternatively, CS axons may synapse onto the distal dendrites of motoneurons, mediating the weak coherence we observed.

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All procedures accord with current local guidelines and the Declaration of Helsinki.