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**A DEVELOPMENTAL COMPARISON OF VOLTAGE-  
ACTIVATED Ca<sup>2+</sup> CHANNELS AND GROUP I  
METABOTROPIC GLUTAMATE RECEPTORS IN  
OCULOMOTOR AND HYPOGLOSSAL MOTONEURONS**

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## ABSTRACT

Voltage-activated  $\text{Ca}^{2+}$  channels and group I metabotropic glutamate receptors (mGluRs) are important determinants of neuronal excitability and repetitive discharge behaviour. They are also implicated in perinatal developmental processes and  $\text{Ca}^{2+}$ -dependent excitotoxic cascades thought to contribute to neurodegeneration. To understand the role that these channels/receptor systems play in the physiology, ontogeny and pathophysiology of MNs, it is necessary to characterise them, during development, in MNs that differ functionally in the behaviours they control, the firing behaviour they produce, their rate of maturation, and their vulnerability to degeneration in ALS. Surprisingly few studies, however, have characterised these channels/receptor systems in MNs, particularly beyond early postnatal stages. I therefore compared voltage-activated  $\text{Ca}^{2+}$  channels and group I mGluRs in brain slices from neonate (P1–5) and juvenile (P14–19) rat, in oculomotor (III) and hypoglossal (XII) MNs using whole-cell patch-clamp recording and immunohistochemical techniques. III MNs innervate extraocular muscles, control eye movements that are not fully functional in rat until 2 weeks postnatal, fire at high frequency for sustained periods, and are resistant in ALS. In contrast, XII MNs innervate tongue muscles, control behaviours that are functional at birth, fire bursts of low frequency action potentials, and are vulnerable to degeneration in ALS.

In neonates, low voltage-activated (LVA)  $\text{Ca}^{2+}$  current densities are similar in III and XII MNs but high voltage-activated (HVA)  $\text{Ca}^{2+}$  current densities are ~2-fold higher in XII MNs. While N- and P/Q-type HVA  $\text{Ca}^{2+}$  channels are present in both MN pools, greater expression of P/Q-type channels in XII MNs accounts for their greater HVA  $\text{Ca}^{2+}$  currents. Developmentally, LVA and HVA  $\text{Ca}^{2+}$  current densities decrease ~2-fold by P14–19 in III MNs, but remain unchanged in XII MNs. Thus, in juveniles the HVA  $\text{Ca}^{2+}$  current density is ~3-fold greater and the LVA  $\text{Ca}^{2+}$  current density ~2-fold greater in XII compared to III MNs.

The group I mGluR agonist, DHPG, induces inward currents in III and XII MNs of neonatal and juvenile rat, which are mediated by the reduction of a resting  $K^+$  conductance. Antagonism of these currents by the mGluR1 antagonist LY367385, but not the mGluR5 antagonist MPEP, and immunohistochemical labelling for mGluR1a but not mGluR5 protein on III and XII MNs, suggest that currents primarily result from the activation of mGluR1. In neonatal rat the current density of DHPG-induced currents is similar between III and XII MNs. However, in juvenile rat DHPG-induced current density is ~3-fold greater in XII compared with III MNs.

Differential expression of LVA and HVA  $Ca^{2+}$  currents and varying effects of group I mGluR activation in III and XII MNs during development supports a role for these channels and receptor systems in determining the distinct firing patterns of these two different classes of MNs. The greater voltage-activated  $Ca^{2+}$  currents and group I mGluR-mediated effects in XII MNs, particularly in juvenile MNs, may also contribute to the greater sensitivity of XII MNs to pathophysiological processes, predisposing them to degeneration as seen in ALS.

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A handwritten signature in cursive script that reads "Gareth". The signature is written in black ink and is centered on the page.

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