MECHANISMS CAUSING PLATEAU POTENTIALS IN SPINAL MOTONEURONES

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ABSTRACT

Plateau potentials are generated by a voltage sensitive persistent inward current. In spinal motoneurones this current is predominantly mediated by influx of Ca^{2+} through L-type Ca^{2+} channels of the $Ca_V1.3$ subtype. Depolarisation-induced facilitation of L-type Ca^{2+} channels is thought to be the mechanism for delayed activation (wind-up and warm-up) of the plateau potential and for the hysteresis in firing frequency and I-V relation during triangular depolarisation. L-type Ca^{2+} channels and plateau potentials in spinal motoneurones are facilitated by activation of metabotropic receptors for glutamate, acetylcholine, noradrenaline and serotonin and down regulated by activation of $GABA_B$ receptors. The facilitation has been shown to depend on activated calmodulin.

PLATEAU POTENTIALS IN SPINAL MOTONEURONES

Plateau potentials were originally observed in motoneurones during experimentally induced spinal seizures (Kao and Crill, 1972) and later shown to be an intrinsic property mediated by a persistent inward current, I_i (Schwindt and Crill, 1977; Schwindt and Crill, 1980a; Schwindt and Crill, 1984). The potential for a physiological role emerged from two observations. First it was shown that plateau properties were induced in spinal motoneurones by activation of a range of metabotropic transmitter receptors (Hounsgaard et al., 1984; Hounsgaard and Kiehn, 1985; Hounsgaard et al., 1988; Hounsgaard and Kiehn, 1989; Conway et al., 1988; Lee and Heckman, 1996; Svirskis and Hounsgaard, 1998). Secondly, although plateau potentials were only directly observable in reduced preparations, recordings of unit activity and force development from muscles in the intact organism provide strong evidence that plateau potentials are part of the normal physiological repertoire of spinal motoneurones (Eken and Kiehn, 1989; Kiehn and Eken, 1997; Kiehn and Eken, 1998; Gorassini et al., 1998; Gorassini et al., 1999; Collins et al., 2001, 2002). The fact that the ability to generate plateau potentials is a highly conserved intrinsic property of spinal motoneurones in mature terrestrial vertebrates (Perrier and

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Hounsgaard, 2000) suggests a fundamental role in motor behaviour. This is supported by the finding that maturation of motor behaviour and plateau potentials evolves in parallel during development (Jiang et al., 1999; Perrier and Hounsgaard, 2000).

ION CHANNELS MEDIATING PLATEAU POTENTIALS IN SPINAL MOTONEURONES

Plateau potentials in spinal motoneurones (Fig. 1A) are mediated by a persistent inward current, I_i (Schwindt and Crill, 1984; Svirskis and Hounsgaard, 1997) and associated with a conductance increase (Hounsgaard and Kiehn, 1989). The nature of I_i was first explored by Schwindt and Crill (1977, 1980a, 1984). In the cat *in vivo* they found that I_i was sensitive to iontophoretically applied Ba^{2+} and therefore concluded that at least part of I_i was mediated by Ca^{2+} channels. They also found that I_i was insensitive to QX314, excluding a contribution from voltage sensitive Na^+ channels. This was confirmed more directly in a slice preparation of the spinal cord of the turtle. In this preparation plateau potentials in motoneurones persisted in the presence of TTX and were blocked by Co^{2+} (Hounsgaard and Kiehn, 1985). Moreover, removal of Na^+ ions from the extracellular medium did not affect plateau potentials (Perrier and Hounsgaard, 1999).

Dihydropyridine sensitivity being the hallmark of L-type Ca^{2+} channels (Bean, 1985) established this channel as the main contributor since both plateau potentials and the underlying I_i were blocked by nifedipine (Hounsgaard and Mintz, 1988; Svirskis and Hounsgaard, 1997; Svirskis and Hounsgaard, 1998). Key properties of plateau potentials can be related directly to the properties of I_i and L-type Ca^{2+} channels.

Activation Range. In spinal motoneurones, plateau potentials are activated near the threshold for action potentials (Fig. 1A). Activation of I_i and plateau potentials occur in the same voltage range, 10-30 mV depolarised from the resting membrane potential, in the spinal and decerebrate cat *in vivo* (Schwindt and Crill, 1984; Hounsgaard et al., 1988; Lee and Heckman, 1998) and in the turtle spinal cord *in vitro* (Hounsgaard and Mintz, 1988; Svirskis and Hounsgaard, 1998). $Ca_V1.3$, the subtype of L-channels expressing the α1D subunit, has a similar activation range and is expressed in dendrites of adult motoneurones in mouse (Carlin et al., 2000) and turtle (Simon, Perrier and Hounsgaard, article in preparation). Also in favour of $Ca_V1.3$ being the channel mediating plateau potentials in spinal motoneurones, is the shared 10 fold lower sensitivity to dihydropyridines compared to other L-channel subtypes (Koschak et al., 2001; Xu and Lipscombe, 2001).

Delayed activation. The slow or delayed activation of plateau potentials and I_i can be related to the properties of a population of L-type Ca^{2+} channels (Perrier et al., 2001). The opening of L-type Ca^{2+} channels in response to depolarisation is facilitated by preceding depolarisation (Dolphin, 1996). In motoneurones and plateau generating interneurons in the spinal cord, depolarisation induced facilitation of L-type Ca^{2+} channels is the mechanism for wind-up of the response to repeated depolarisations (Fig. 1B) and for the gradually reduced threshold for activating plateau potentials during a maintained, initially subthreshold depolarisation (Russo and Hounsgaard, 1994; Russo and Hounsgaard, 1996; Delgado-Lezama and Hounsgaard, 1999). It has also been found that an increased intracellular calcium concentration facilitates opening of L-type Ca^{2+} channels via calmodulin activation (Zuhlke et al., 1999; Zuhlke et al., 2000) and activation of plateau potentials in motoneurones (Perrier et al., 2000). For this reason it was proposed that the depolarisation induced transition of closed Ca^{2+} channels from a reluctant to a willing