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Commentary

Do We Have a Channel Solution for ALS?

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Amyotrophic lateral sclerosis (ALS) is a dreadful degenerative disorder, characterized by rapidly progressing weakness causing respiratory impairment and death, in spite of moderate benefits from non-invasive ventilation, gastrostomy, riluzole treatment and multidisciplinary care (Andersen et al., 2012). Over the years a large of number of drugs have been tested to deal with this disorder, but all trials have been negative except for riluzole. We can observe that different strategies have been explored in the past, from immunosuppression to neuroprotection, from nerve growth factors to antiglutamatergic compounds (de Carvalho et al., 2005). Threshold tracking has been used to investigate axonal excitability in peripheral nerve motor axons in ALS (Vucic and Kiernan, 2006). Increased persistent Na^+ conductance and reduced K^+ conductance have been described (Vucic and Kiernan, 2006), which tend to become more marked with disease duration and may be a predictor of survival (Cheah et al., 2012). More recently, it has been suggested that motor neurons have an abnormal function of the membrane ion channels, in ALS (Devlin et al., 2015). These observations have opened a new window of opportunity in clinical trials for ALS, for testing drugs that modulate ion channels in order to stabilize membranes.

In this issue of *EBioMedicine*, Park et al. reported the first trial of flecainide (200 mg/day for 32 weeks) in ALS (Park et al., 2015). This drug is a class Ic antiarrhythmic agent that was synthesized in 1972, its clinical efficacy has been confirmed in the past, currently mostly used to in the management of atrial fibrillation and supraventricular tachycardia. Flecainide is a blocker of the persistent sodium current, then promoting membrane stabilization. Although this drug has not been tested in the animal model of ALS, the authors decided to test it in a group of 54 ALS patients, following a randomized, placebo-controlled, double-blind design. Primary outcome was the rate of decline of ALSFRS-R, adjusted for the functional change in the initial 12-weeks lead-in period. Secondary outcomes were quality-of-life, 6-meter walking time, grip strength, forced vital capacity, sniff nasal inspiratory pressure, threshold tracking of the median nerve, neurophysiological index (NI) and cortical excitability measurements. Regarding the aimed recruitment rate the trial was unsuccessful, consequently it was underpowered for the primary outcome evaluation, which was negative. Importantly, the drug was well tolerated. The secondary outcomes were generally negative, except for the NI that had a significantly slower decline in the treated than the placebo-arm ($p = 0.02$), this difference was not observed when comparing the same two groups during the lead-in period. It should be stressed that peripheral excitability remained stable after flecainide treatment, but in the placebo group it was observed a reduction of the hyperpolarizing threshold electrotonus.

Although this may be considered a negative trial by simply regarding the primary outcome assessment, it is interesting to observe that NI declined less in the active-arm. NI is a simple, reproducible and easily standardized measurement of the lower motor neuron pool, which declines faster than ALSFRS and motor response amplitude (de Carvalho and Swash, 2006). Its behavior over disease progression makes appropriate to use linear mixed models to evaluate its change in clinical trials for ALS (Cheah et al., 2011). Indeed, this outcome was used in another clinical trial before (de Carvalho et al., 2010). Threshold tracking to test excitability of the peripheral axon was not used before in clinical trials, but it is a very suitable technique to evaluate drugs that could act on the ion channels to promote neuroprotection in ALS. In this trial, the progressively increased hyperpolarization observed in the control arm was not disclosed in the group of patients taking the drug, suggesting membrane stabilization, which is a meaningful result (Park et al., 2015). Furthermore, such membrane stabilization and reduction in excitability did not exert a deleterious effect on ALS patients, opening up the landscape for future trials in this area.

These results have a number of implications for future studies. More trials are recommended with drugs acting as membrane stabilizers, currently the antiepileptic drug retigabine (a potassium channel opener) is being tested (https://clinicaltrials.gov/ct2/show/NCT02450552, n.d.); flecainide should be further investigated in a larger trial; a number of safe drugs that are available for other clinical conditions should be considered as targets for clinical trials in ALS, since their properties are relevant for this disorder; NI should be applied in future trials as a measurement of the lower motor neuron degeneration; a lead-in period to select homogenous group of ALS patients could increase the chances of finding positive results (de Carvalho and Swash, 2006).

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Our increasing knowledge of both drugs and the biology of ALS has resulted in new treatment strategies. The most promising approach is to develop compounds acting on the pathogenic process, since causal treatment is a more demanding alternative that will require more time to be fruitful. Although other pathogenic pathways are worthwhile to be considered, as RNA dysmetabolism, autophagy impairment, neuroinflammation, glutamatergic excitoxicity and axonal transport disturbance, the possibility to stabilize motor neuron and axonal membranes is an exciting new avenue that deserves more intensive work.

Disclosure

The author declared no conflicts of interest.

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