Mechanism of action of the cardiovascular drug levosimendan in the management of amyotrophic lateral sclerosis

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BACKGROUND
Levosimendan is a calcium sensitizer that promotes myocyte contractility through its calcium-dependent interaction with cardiac troponin C, also found in skeletal muscle. It has been used for nearly two decades as i.v. treatment in acute heart failure. During that time many additional pharmacological actions of levosimendan have been described. Effects of levosimendan increasing diaphragm function suggested a possible new application in the treatment of patients with amyotrophic lateral sclerosis (ALS).

OBJECTIVES
As levosimendan has been linked to a range of pleiotropic actions we reviewed the mode of actions that may be of relevance in the treatment of ALS.

METHODS
Systematic literature review was conducted to collect all evidence on the different pharmacological effects of levosimendan. A special focus was given to effects relevant to the pathophysiology of ALS and to the therapeutic needs of patients with ALS.

RESULTS
Table 1. Pharmacological mode of actions of levosimendan in various models potentially relevant to ALS

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<tr>
<th>Pharmacological effect</th>
<th>Outcome</th>
<th>Refs</th>
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<tr>
<td>Improved respiratory muscle contractility</td>
<td>In vitro levosimendan enhances calcium sensitivity (pCa50) of isolated diaphragm muscle fibres by 20-30% (p&lt;0.01). In healthy volunteers, levosimendan improves neuromechanical efficiency by 25% (p&lt;0.05) and contractile function of the human diaphragm</td>
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<td>Improved brain circulation</td>
<td>Increased blood volume of the cerebral microvessels (ΔR2) of the cortex (ΔR=3.5±0.15 vs. 2.7±0.17ml in vehicle; P=0.001) and hemisphere (ΔR=3.2±0.23 vs. 2.6±0.14ml in vehicle; P=0.018) in vivo stroke model in Dahl salt-sensitive rats</td>
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<td>Endoplasmic reticulum stress (ERS) relief</td>
<td>Levosimendan significantly reduced apoptotic cardiomyocytes from 27.6±2.4% to 8.2±2.1% (P&lt;0.05) in anoxia-reperfusion model in hCPCs</td>
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<td>Prevention of programmed cell death</td>
<td>Levosimendan reduced apoptosis 0.02 ± 0.017% vs. 0.06 ± 0.044% in control (p&lt;0.03) in in vivo myocardial ischemia-reperfusion model in pigs</td>
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<td>Anti-oxidative and anti-inflammatory effects</td>
<td>Levosimendan dose-dependently maximally reduced ΔpO2 (p&lt;0.001) of paw oedema (-84%) and suppressed cytokines (TNFα, IL-1, and IL-6 by 68%, 66%, and 76%, respectively) and increased superoxide dismutase (SOD) activity by 76% as well as GSH by 230% and decreased ß-isoenprostilglandin F2α by 74% in in vivo carrageenan-induced inflammatory paw oedema rat model</td>
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<td>Mitochondria-protective effects</td>
<td>Levosimendan opens mitochondrial KATP channels in mitochondria isolated from rat heart. Levosimendan prior to reperfusion decreased infarct size (28 ± 3% vs. control) in Dahl salt-sensitive rats. The mitochondrial KATP-channel blocker 5-HD and the P38 kinase inhibitor wortmannin completely abolished the protection by levosimendan (50 ± 2 and 52 ± 3%, respectively)</td>
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REFERENCES

CONCLUSION
While the direct activity of levosimendan on skeletal muscle is clearly the main effect of interest in relation to ALS, a number of other pleiotropic effects of the drug raise some intriguing possibilities in the context of this disease. These effects should be confirmed in models more relevant to ALS.

Figure 1. The dysfunction and death of motor neurons that is the core feature of ALS is believed to arise from multiple underlying pathophysiological processes. Pharmacological mechanisms of action of levosimendan may suggest a relevance for anti-inflammatory effects to attenuate neuroinflammation, autophagy activation to reduce proteasome impairment, ER stress alleviation to reduce endoplasmic reticulum stress, anti-apoptotic effects to prevent excitotoxicity, and improved mitochondrial function to prevent mitochondrial dysfunction and oxidative stress. These effects should be confirmed in models relevant to ALS. Adapted from Al-Chalabi et al 2019.

Figure 2. Scheme of the mode of actions and pharmacologic effects of levosimendan. The actions in the grey boxes underlie the cardiovascular effects of the drug. In the violet boxes are pharmacologic effects of levosimendan that may be considered of primary relevance in ALS. Grey dotted lines identify interplays that are still not fully elucidated. Abbreviations: cTnC and sTnC, cardiac and skeletal isoforms of troponin C, respectively; PDE III and IV, phosphodiesterase isoforms in cardiac tissue; PCWP, pulmonary capillary wedge pressure. Adapted from Al-Chalabi et al 2019.