In co-cultures of embryonic rat spinal cord slices and skeletal muscle, spinal motoneurons innervate muscle fibers and drive muscle contractions. Evidence for this finding comes from multielectrode array (MEA) recordings showing that the activity in the neuronal networks and in muscle fibers in these preparations is frequently correlated. However, besides such correlated activity, muscle contractions often appear in the absence of population activity in the spinal cord networks. Such uncorrelated muscle activity remains almost unchanged when the population bursts in the neuronal networks are blocked by uncoupling the network with the glutamatergic antagonists CNQX and d-APV showing that it is not driven by the population activity in spinal networks. On the other hand, the uncorrelated muscle activity is fully blocked by the muscular nicotinic antagonist d-tubocurarine, showing that it is driven by motoneurons. Together these findings suggest that motoneurons in this preparation are intrinsically spiking in the absence of synaptic input. Analyzing the correlated muscle activity, we found that in 15% of the population bursts, muscle activity appears at the beginning or before neuronal activity, suggesting that motoneurons drive the population activity. The positive feedback from motoneurons to spinal networks involves nicotinic receptors, since both the total numbers of population bursts as well as the percentage of such bursts that are initiated by muscle activity are reduced by a block of cholinergic but not muscarinic receptors. All together these findings suggest that in organotypic spinal cord cultures, intrinsic firing of motoneurons drives part of the spontaneous population burst activity.