Increased GSK-3 activity is believed to contribute to the aetiology of Alzheimer disease (AD). Accordingly, GSK-3 inhibitors such as lithium have been postulated as a potential AD therapy. Despite lithium's efficacy for treatment and prophylaxis of bipolar disorder, its clinical use is often curtailed by its frequent side-effects such as hand tremor. Accordingly, clinical trials to assess the efficacy of lithium for AD are hampered by lithium’s toxicity, particularly in the elderly. Although GSK-3 inhibition has been shown to result in neuroprotection in various models, increased apoptosis has also been documented when it is triggered by activation of death domain-containing receptors. Similarly, dominant-negative-GSK-3 transgenic mice show increased neuronal apoptosis in various brain regions, such as the striatum, and also motor-deficits. We reasoned that this may relate to the side-effects of lithium therapy. We have shown that chronic lithium administration to mice induces neuronal apoptosis in various brain regions and that GSK-3 inhibition increases nuclear translocation of NFATc3/4 leading to increased FasL levels and to Fas-receptor activation. Finally, we demonstrate that NFAT/Fas signaling mediates both lithium-induced neuronal apoptosis and lithium-induced motor deficits as these are absent when NFAT nuclear translocation is prevented by CsA administration or when the experiments are performed on Fas-deficient lpr mice. These findings may enable development of new combined therapies to counteract the drawbacks of lithium treatment for mood disorders and to extend the potential of lithium, and other GSK-3 inhibitors, to AD.
