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Boldine improves behavioral and histological outcomes following traumatic brain injury in mice

Traumatic brain injury (TBI) represents a major public health burden due to the lack of available treatments and its contribution to the development of neurological conditions. Boldine is a naturally occurring alkaloid found in various plant species, including the Chilean boldo tree. Its safety and therapeutic properties have been demonstrated in rodent models of human disease, and it is widely used as a nutraceutical. We evaluated the effects of boldine treatment on behavioral and histological outcomes using a clinically relevant murine closed-head injury (CHI) model of TBI. Eight hours post-injury, mice were treated with either saline/DMSO or boldine/DMSO, followed by two daily injections for 3 days. At 7 days post-injury (DPI), mice underwent four days of Barnes maze training to assess spatial learning, followed by a probe trial at 12 DPI for memory recall. Boldine/DMSO-treated injured mice performed similarly to saline/DMSO-treated shams in latency, errors, and time spent in the correct quadrant, indicating that boldine treatment improved Barnes maze acquisition and retention to sham levels. NeuN+ and glial acidic fibrillary protein staining were used to assess neuronal density and astrocyte activation, respectively. At 14 DPI, injury lowered CA3 neuronal density in injured saline/DMSO-treated mice, while injured boldine/DMSO-treated mice maintained densities comparable to shams. These data showed that boldine prevents neuronal loss. Surprisingly, boldine treatment increased astrocyte activation in the contralesional hippocampus compared with injured saline/DMSO-treated mice. These findings suggest that boldine reversed CHI-induced spatial learning and memory deficits on Barnes maze due to its neuroprotective action. The increased astrocyte activation by boldine may also be beneficial for the large improvement in brain function following CHI.