Progesterone and Rehabilitation of Head Injury, Stroke and Addictions

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Background: Brain function is fundamental to improving human functional capacity. Research has focussed on estrogen as the important gonadal neuro-steroid; not all research confirms beneficial effects. Progesterone, the second ovarian steroid that is present in high concentrations during the menstrual cycle's luteal phase and during pregnancy, is also neurally active. There is far less basic science, animal and human randomized controlled trial (RCT) research on progesterone's psychoneuroendocrinology. Endogenous progesterone long has been known to increase core temperature [1], metabolic rate and minute ventilation through central actions and more recently was shown effective in treating hot flushes (vasomotor symptoms, VMS) [2]. The purpose of this review is to highlight what is currently known about potential beneficial effects of progesterone in three common problems that rehabilitation experts face: traumatic brain injury, stroke and addictions.
Methods and Results: This is an overview of human data. Progesterone is converted into allopregnanolone that acts through the GABA pathway to increase deep sleep in a controlled trial in men [3]. This sleep-improving effect of oral micronized progesterone (300 mg at bedtime) has now been proven in three further trials [2,4,5], one of which showed no impairment of morning executive, cognitive or fine motor functions. Progesterone may also be anxiolytic [6]. Progesterone appears to protect the brain by acting in several different ways [7]: 1) as an anti-inflammatory; 2) in decreasing edema; 3) decreasing excitoneurotoxicity; 4) decreasing apoptosis while increasing DNA repair; and 5) in decreasing lipid peroxidation. All of these actions may be beneficial for human diseases.
Traumatic Brain Injury (TBI)—Parenteral pharmacological dose progesterone shows positive pilot data in closed head trauma in 77 people—the ones on progesterone experienced improved function and a 60% reduction in 30-day mortality (Wright 2007). TBI-progesterone treatment is now being tested in large multicentre RCTs.
Stroke—Progesterone given alone or with transdermal estradiol does not increase clotting, or significantly raise D-dimer based on unpublished data from our recent VMS RCT [2]. A review of controlled trials of progesterone for experimental stroke in animals shows that in 16 of 17 RCTs, progesterone causes a significant benefit over placebo.
Addictions—The best animal model of VMS is the opioid-addicted rat. Progesterone is effective for VMS treatment [2] probably by widening the narrowed thermoneutral zone [8]. Evidence suggests beneficial effects in recovery from addictions to nicotine, cocaine [9,10], estradiol and other substances, especially in women [11].
Summary: Progesterone possesses neural protective actions that appear to be beneficial for the rehabilitation of women and men after traumatic brain injury and stroke (although data are still limited) and in recovery from addictions. More human RCT research is needed, especially in the field of rehabilitation.

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