

Optimizing Progesterone – A Clinical Tool For Managing the Effects of Social Isolation

It is well established that progesterone plays a role in the stress response, in motivation for affiliation/social contact, and in mediating anxiety and depression. With large numbers of patients at home and out of touch with their normal social circles, there is increasing concern for the impacts of isolation on mental health and the feeling of wellness. Patients who have been getting by with sub optimal hormone levels may find that present circumstances make that sub optimal level more of a challenge than previously felt. Kajarin has experienced a surge in demand for progesterone creams coinciding with the second wave of the COVID-19 pandemic. Optimizing progesterone levels is a simple, natural, and affordable clinical tool that can be utilized during this time of challenge and uncertainty.

Progesterone is best known for its functions in mammalian reproduction. However, progesterone and its metabolites including allopregnanolone, have actions on neurons, causing effects that are relevant for stress, emotion, and behavior. Allopregnanolone, a metabolite of progesterone, belongs to a subset of steroid hormones called neuroactive steroids, which are produced in the brain and change neuronal excitation via membrane-bound receptors. This action is in contrast to actions of steroid hormones on classical steroid receptors, which reside inside the cytoplasm and initiate changes in gene transcription, leading to slower and more prolonged responses. Allopregnanolone is synthesized from progesterone in a two-step pathway requiring the enzymes 5-reductase and 3-hydroxysteroid dehydrogenase both of which are found in the adrenals, gonads, cerebral cortex, hippocampus and hypothalamus.¹ Progesterone by itself, and/or via conversion to allopregnanolone may play in stress reduction and promote social affiliation or bonding.² One connection between allopregnanolone and depression may involve social support and isolation. Lower allopregnanolone levels are connected with depressed individuals' social isolation, a feature of depression which puts individuals at greater risk for worsened mental and physical health. Malfunctioning of the progesterone allopregnanolone system could therefore decrease propensity to affiliate with others and thereby exacerbate depression.³

The physiological stress response is essential for life, but can be maladaptive if prolonged.^{4,5} Fortunately there are feedback loops that turn off production of corticotropin-releasing hormone and adrenocorticotrophic hormone released during stress. GABA-active neurosteroid levels increase during stress and these elevated levels suggest involvement with down-regulation of the stress response.^{6, 7} Interestingly, a 2018 study established that PTSD in women is associated with a block in conversion of progesterone to the GABAergic neurosteroids allopregnanolone and pregnanolone measured in plasma⁸.

The anti-stress and anxiolytic effects of progesterone are thought to be mediated by the conversion of progesterone to allopregnanolone, and allopregnanolone's actions at GABA-A receptors, rather than by effects on intracellular progesterone receptors.

Gabaergic neurotransmission through interneurons is known to modulate local neuronal circuits via, for example, activation of dopaminergic⁹ and serotonergic neurons¹⁰. While estrogen appears to suppress GABA inhibitory input¹¹, progesterone and allopregnanolone seems to increase GABAergic transmission.¹²

Research in multiple fields has documented the positive or protective health effects of social contact and support in humans, and, conversely, the detrimental effects of isolation or lack of affiliation on mental and physical health. Elevated levels of progesterone and allopregnanolone that accompanies stress may function in two ways. First to inhibit anxiety on a cellular level by reducing neuronal activity, and second by promoting behavioral strategies to cope with stress, including seeking out social contact and social bonds. Progesterone and allopregnanolone have been observed to influence the expression of social-affiliative behaviors in rodents.¹³ There is evidence that supports a connection between progesterone and pro-social (helping) behavior, including evidence that progesterone is involved in the beneficial effects of helping behavior on cardiovascular recovery from stress.^{14,15}

So, what does this mean with respect to clinical tools? It is possible that allopregnanolone release during stress, while down-regulating stress in the short term by its actions at GABA-A receptors, also ameliorates stress by promoting affiliation and social bonding as a coping strategy.¹⁶ A 2020 study found that sub-acute progesterone treatment reduced depression-like behavior through actions on GABA-A receptors in a rat model of surgical menopause.¹⁶ When connecting with patients – either in practice or through your social media outreach, ask about new stress levels, ask about feelings of social isolation on a scale of 1-10. For those patient's beginning to exhibit higher levels of stress, especially those who thrive on in-person contact, live alone, or are working from home, evaluate current progesterone levels and consider what support you can provide by optimizing progesterone levels.

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