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Why May Allopregnanolone Help Alleviate Loneliness?

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Abstract

Impaired biosynthesis of Allopregnanolone (ALLO), a brain endogenous neurosteroid, has been associated with numerous behavioral dysfunctions, which range from anxiety- and depressive-like behaviors to aggressive behavior and changes in responses to contextual fear conditioning in rodent models of emotional dysfunction. Recent animal research also demonstrates a critical role of ALLO in social isolation. Although there are likely aspects of perceived social isolation that are uniquely human, there is also continuity across species. Both human and animal research show that perceived social isolation (which can be defined behaviorally in animals and humans) has detrimental effects on physical health, such as increased hypothalamic pituitary adrenal (HPA) activity, decreased brain-derived neurotrophic factor (BDNF) expression, and increased depressive behavior. The similarities between animal and human research suggest that *perceived* social isolation (loneliness) may also be associated with a reduction in the synthesis of ALLO, potentially by reducing BDNF regulation and increasing HPA activity through the hippocampus, amygdala, and bed nucleus of the stria terminalis (BNST), especially during social threat processing. Accordingly, exogenous administration of ALLO (or ALLO precursor, such as pregnenolone), in humans may help alleviate loneliness. Congruent with our hypothesis, exogenous administration of ALLO (or ALLO precursors) in humans has been shown to improve various stress-related disorders that show similarities between animals and humans i.e., post-traumatic stress disorders, traumatic brain injuries. Because a growing body of evidence demonstrates the benefits of ALLO in socially isolated animals, we believe our ALLO hypothesis can be applied to loneliness in humans, as well.

Keywords

Social neuroscience; Allopregnanolone; Pharmacological treatment; Social pain; Loneliness; Social Pain; Perceived Social Isolation

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Introduction

Evolutionary model of loneliness

People often think about humans as unique compared to other species and ourselves as unique and independent relative to those around us. At first glance, other individuals certainly look distinct, independent, self-sufficient with no forces binding them together. We are, however, connected across our lifespan to one another, through a myriad of invisible forces that, like gravity, are ubiquitous and powerful [1-2]. Like other social species, we, humans, create emergent structures that extend beyond our own organism -- structures that range from couples and families to schools and nations and cultures. For our species to survive, infants must, for instance, instantly engage their parents in protective behavior, and the parents must care enough about these offspring to protect and nurture them. Even once grown, our survival depends on our collective abilities, not our individual might [3].

The superorganismal structures and processes that define social species are varied [4] but all have evolved hand in hand with neural, hormonal, and genetic mechanisms to support them because the consequent social behavior helps these organisms survive, reproduce and leave a genetic legacy. For a social species, including humans, to become an adult is not to become autonomous and solitary -- it is to become a conspecific on whom others can depend [3]. Whether we are aware of it or not, our brain and biology have been shaped to favor this outcome. Across our biological heritage [5], our brain and biology have been sculpted to incline us to certain ways of feeling and behaving. For instance, we have a number of biological mechanisms that capitalize on aversive signals to motivate us to act in ways that are essential for our survival [3, 5-6]. Hunger, for instance, is triggered by low blood sugar, an important early and automatic warning signal that motivates you to eat. Similarly, thirst is an aversive signal that motivates you to search for drinkable water prior to fall victim to dehydration. Like hunger and thirst, loneliness (the aversive feeling of loneliness) is an aversive signal that motivates us to maintain, repair, or replace our social body, which members of a social species need to survive, prosper, and leave a genetic legacy [3, 5-9].

According to this evolutionary model of loneliness [5, 10-11], being on the social perimeter is not only sad it is dangerous. Accordingly, loneliness increases both an explicit motivation to connect with others and an implicit motivation for self-preservation. Loneliness increases an automatic (non-conscious) hyper-vigilance for social threats, which then can introduce attentional, confirmatory, and memory biases, impulse control, and poor sleep salubrity [5, 10-14]. Given the effects of attention and expectation on anticipated social interactions, behavioral confirmation processes then can incline an individual who feels isolated to have or to place more import on negative social interactions, which if unchecked can reinforce withdrawal, negativity, and feelings of loneliness [10-12] (See Figure 1).

In turn, loneliness can contribute to a constellation of health issues [e.g., 6-8, 11, 12, 15-26]. Human and animal research provides significant evidence that social species do not fare well when there is a discrepancy between the presence of a preferred and an actual conspecific -- i.e., when perceived social isolation is relatively high (for reviews across phylogeny see [7, 8, 15]). The isolation from significant others has long been recognized as a risk factor for broad based morbidity and mortality. Although the focus has been on objective social roles

and health behavior, the brain is the key organ for forming, monitoring, maintaining, repairing, and replacing salutary connections with others. Accordingly, population-based longitudinal research indicates that loneliness (*perceived* social isolation) is a risk factor for morbidity and mortality independent of objective social isolation and health behavior.

In humans, loneliness contributes to a broad variety of physical and mental disorders that mirror those observed in animals [7]. These disorders include depressive symptomatology [27-29], aggressive behaviors, social anxiety, and impulsivity [7, 8, 15, 17, 19]. In addition, loneliness is a risk factor for recurrent stroke [15], obesity [18], increased vascular resistance [16], elevated blood pressure [16], an under-expression of genes bearing anti-inflammatory glucocorticoid response elements and an upregulation of pro-inflammatory gene transcripts [20-21], abnormal ratios of circulating white blood cells (e.g., neutrophils, lymphocytes, and monocytes; [30], premature mortality [22], decreased sleep salubrity [23-24], diminished immunity [24], and increased hypothalamic pituitary adrenocortical (HPA) activity [8, 25]. As the prevalence of loneliness rises, evidence accrues that loneliness is a major risk factor for poor physical and mental health outcomes. Therefore, there is a crucial need to find a therapy against loneliness. To date, however, there is no pharmacological treatment for loneliness. Animal research may shed promising light on this issue, however, and it is the evidence from this animal literature that constitutes the rationale for the proposed medical hypothesis.

Loneliness and HPA axis

To the extent that the brain is the central organ for evaluating relationships with others, the neuroendocrine system becomes an important system through which perceived social isolation may operate, at least in part, to affect morbidity and mortality. Research suggests that loneliness and social threats are associated most consistently with activity of the HPA axis [8 for review]. Human and animal investigations of social isolation and the neuroendocrine system suggest that: (a) chronic social isolation increases the activation of the HPA axis, and (b) these effects are more dependent on the disruption of a social bond between a significant pair than objective isolation per se [8 for review]. A cascade of signals travels from the prefrontal cortex and limbic regions (e.g., amygdala, bed nucleus of the stria terminalis or BNST) to the brainstem (e.g., locus coeruleus) and to the paraventricular nucleus of the hypothalamus. The sympathetic nervous system includes both sympathetic nerve fibers that directly innervate most major organ systems and locally release the catecholamine neurotransmitter norepinephrine, as well as an adrenal-medullary (SAM) component. The direct innervation of the adrenal medulla by the sympathetic nervous system permits rapid neuroendocrine responses to acute stressors. On the other hand, the HPA axis is sensitive to the interpretation by the brain of threats and stressors, as well, and influences a wide range of physiological, behavioral, and health outcomes [8]. Schematics of the SAM and HPA axes are depicted in Figure 2. Unlike the adrenal medulla of the SAM axis, the adrenal cortex of the HPA axis is necessary for survival and the HPA axis includes a negative feedback mechanism to limit its circulating hormonal outputs.

The limbic system permits the modulation of HPA activity by the resulting environmental appraisals, including appraisals of the quality of companionship and mutual assistance

available in the social environment – a strong determinant of perceived social isolation [8]. Within the limbic system, the central and medial nuclei of the amygdala and the BNST are connected by cells throughout the stria terminalis, and both the amygdala and the BNST project to hypothalamic and brainstem areas that mediate autonomic, neuroendocrine, and behavioral responses to aversive or threatening stimuli [8, 31]. The BNST, which receives inputs from the hypothalamus and amygdala, is associated with anger-related emotional processing [32], is comprised of multiple distinct subnuclei (like the amygdala), which differentially regulate HPA activation [33–34]. The amygdala and the BNST are involved in fear and anxiety conditioning, respectively [35] – two acquired behaviors that permit anticipatory responses to a potentially threatening situation. The amygdala appears to be especially important for rapid-onset, short-duration behaviors which occur in response to specific threats, whereas the BNST appears to mediate slower-onset, longer-lasting responses that frequently accompany sustained threats (or the surveillance for threats) and that may persist even after threat termination [8, 36].

Allopregnanolone and HPA axis

Allopregnanolone, also known as 3 α , 5 α tetrahydroprogesterone (THP) is (as its name applies) a neuroactive steroid derived from progesterone, and specific enzymes in the brain are involved in the biosynthesis of allopregnanolone (ALLO; [37, 38 for reviews]). Produced in both sexes (males and females) by the adrenal glands [39], ALLO is synthesized within the nervous system from progesterone by two sequential enzymatic reactions: First, progesterone is converted into 5 α -dihydroprogesterone (5 α -DHP) by the enzyme 5 α -reductase. 5 α -DHP is then converted into ALLO by NADPH-dependent cytosolic aldoketo reductases (AKR, including one of its isoforms 3 α -hydroxysteroid dehydrogenase, 3 α -HSD [37–40]). In contrast to progesterone and 5 α -DHP, ALLO does not bind to progesterone receptors, but is rather a positive modulator of γ -aminobutyric acid (GABA)_A receptors [39]. Accordingly, ALLO can play a dual role in the nervous system.

First, like progesterone (via classical steroid receptors) from which it is derived, ALLO can exert a protective and regenerative role on the brain and the spinal cord [37 for review, 41–45]. For instance, both progesterone and ALLO have beneficial effects in the recovery of traumatic brain injury, in reducing inflammation, and increasing antioxidant activity [35 for review]. Interestingly, ALLO is more effective than progesterone in reducing cortical infarct volume, apoptosis, and in reducing neuron loss [46, see also 37 for review].

Second, unlike progesterone, ALLO¹ can reduce neuroendocrine stress responses [8, 37, 47–48]. In turn, the down regulation of ALLO biosynthesis in the serum/plasma has been described as a potential contributor to various emotional and psychiatric disorders, such as major depression, anxiety disorders, post-traumatic stress disorder, premenstrual dysphoric disorder, post-partum depression, negative symptoms in schizophrenia, or impulsive aggression [38, 49]. The role of ALLO in psychiatric disorders has been mainly driven by a growing body of evidence that demonstrates that some (not all²) antidepressants, such as

¹Similar effects have been reported with 3 α , 5 β tetrahydroprogesterone, also known as pregnanolone, which is another 3 α -reduced progesterone metabolite and a precursor of ALLO.

²The tricyclic antidepressant imipramine has no effect on the formation of ALLO [36, 45].

selective serotonin re-uptake inhibitors (SSRIs) fluoxetine, paroxetine, and sertraline [49] as well as some antipsychotic drugs (e.g., olanzapine), or mood stabilizers (e.g., carbamazepine) may enhance the formation of ALLO through increased efficiency of conversion of DHP to ALLO [38, 49]. Over the past 15 years, two mechanisms of action for this specific role of ALLO on emotion regulation and stress reduction have been suggested:

1. ALLO enhances the inhibitory signals of the neurotransmitter GABA via a prolonged opening time of chloride channels within GABA_A receptors [37, 41-45, 48] – receptors that are widely distributed in the glutamatergic neurons of brain areas that are involved in emotion and stress responses (e.g. limbic areas, such as the hippocampus, the amygdala, and the BNST). As a potent positive allosteric modulator of GABA_A receptor complex, ALLO is a powerful anxiolytic, anesthetic, and anticonvulsivant agent [38, 48, 49]. Interestingly, this ALLO-related GABAergic mechanism differs from other GABAergic effects observed with standard psychoactive drugs, as the GABA_A binding sites of ALLO are distinct from the GABA sites of benzodiazepines and barbiturates [38, 48].
2. ALLO has specific regulatory effects on the HPA axis functions [38, 47]. While acute stress increases ALLO levels, which negatively modulates the stress-induced HPA axis activation and facilitates the recovery post-stressful events, repeated or chronic [physical or emotional] stress leads to a significant reduction in serum concentration of ALLO [37-38 for reviews]. This suggests that chronic stress alters ALLO synthesis, which in turn leads to the hyperactivation of the HPA axis [38, 50].

Interestingly for the present hypothesis on the potential role of ALLO on perceived social isolation (loneliness), social stressors can also modulate ALLO. For instance, studies in adult mice socially isolated for at least four weeks, compared to group housed male mice, show reductions in levels of ALLO in hippocampal CA3 pyramidal neurons and glutamatergic granular cells of the dentate gyrus, cortical pyramidal neurons (layers V-VI), and neurons in the basolateral amygdala –reductions that are attributable to the effects of social isolation on a specific enzyme involved in the biosynthesis of ALLO [46-48]. Pre-clinical studies indicates that: i) the exaggerated contextual fear response expressed by socially-isolated mice can be normalized with a single injection of ALLO [49]; ii) HPA dysfunction and impairment of hippocampal neurogenesis respectively can be normalized or prevented with the administration of exogenous ALLO (or ALLO precursors) either during or following a period of chronic stress; iii) contextual fear conditioning and aggression can be regulated with ALLO [50]; iv) socially isolated animals exhibited reduced HPA responsiveness, which was either prevented or normalized with ALLO treatment [42]; v) the establishment of depressive/anxiety-like behaviors in rats can be precluded also with administration of exogenous ALLO [8, 15, 45, 48, 50].

Combined, these results in animals indicate that administration of exogenous ALLO (or ALLO precursors) either during or following a period of chronic stress can prevent or normalize HPA dysfunction and impairment of hippocampal neurogenesis respectively, precluding the establishment of depressive/anxiety-like behaviors. In line with this, clinical studies show that decreases in the serum, plasma, and cerebrospinal fluid content of ALLO

are associated with several psychiatric disorders such as depression, anxiety spectrum disorders, posttraumatic stress disorders, premenstrual dysphoric disorder, schizophrenia, and impulsive aggression [37-38, 51-61]. Together, these findings provide a strong rationale for our ALLO hypothesis of loneliness.

Our Hypothesis

Based on the above animal literature, we hypothesize that ALLO plays a crucial role in loneliness in humans. The similarities between animal and human research suggest that *perceived* social isolation (loneliness) may be associated with a reduction in the synthesis of ALLO, potentially by reducing BDNF regulation and increasing HPA activity through the hippocampus, amygdala, and bed nucleus of the stria terminalis (BNST), especially during social threat processing. Even if of course it is clear that animal literature does not address the loneliness (subjective social isolation) *per se* (but rather objective social isolation), there is a large literature in which social animals are randomly assigned either to normal social living conditions or to socially isolated living conditions. Select studies of mammals also have contrasted the effects of social isolation from a preferred partner and social isolation from a non-preferred conspecific, which permits parsing the effects of perceived from objective social isolation ([7, 8 for reviews]). Mechanistic animal studies in which adult animals are experimentally assigned to normal or socially isolated housing conditions are important for evaluating the causal effects of an individual being deprived of mutual assistance and companionship on the role of ALLO on HPA activity.

We, therefore, hypothesize that *perceived* social isolation in humans shares with social isolation in animals/humans a common mechanism i.e., a block in the synthesis of ALLO, potentially by increasing the HPA activity through the hippocampus, BNST, and the amygdala, especially during social threat processing. We also posit that these low ALLO levels then reduce BDNF expression.

This ALLO hypothesis of loneliness is in line with the hypothesis that ALLO and its “precursors” (such as pregnenolone) can affect brain circuits involved in emotion regulation and depression [37-38]. It is, however, noteworthy that depression and loneliness are distinct (yet related) phenomena [27-29]. For instance, despite a correlation between loneliness and depression ranging from .38 to .71 [27], there is now considerable evidence that loneliness and depression are separable and that loneliness increases the risk for depression [27-29]. Compared to lonely individuals, depressed patients show a more complex disequilibrium of neuroactive steroids with decreased levels of ALLO *and* increased levels of similar substances (isopregnanolone) [38]. Based on recent studies suggesting that the effects of some SSRIs (e.g., fluoxetine) that can improve the behavioral effects of social isolation do not occur through the inhibition of selective serotonin reuptake (as in it is the case in depression), but rather through elevated cortico-limbic levels of ALLO and BDNF mRNA expression [47], we hypothesize that administration of ALLO precursors can normalize ALLO regulation in chronically lonely individuals, which in turns may provide a novel therapeutic target for the treatment of loneliness. Moreover, based on the premise that loneliness leads to depression [27-29], we further hypothesize that early administration of ALLO precursors in the early stages of loneliness could mitigate its effects on depression.

Testing the Hypothesis

Our ALLO hypothesis of loneliness suggests that low corticolimbic ALLO levels and diminished ALLO regulation play a crucial role in loneliness. Even if it is of course clear that feeling lonely is not a prerequisite to de-activate the ALLO system, we postulate the existence of a shared mechanism for both loneliness and the ALLO system. If this hypothesis is correct, one would expect that the exogenous administration of ALLO (or ALLO precursors) in lonely individuals to increase cortico-limbic levels of ALLO and BDNF mRNA expression and to decrease subjective feelings of loneliness and the associated deleterious physiological effects (e.g., elevated HPA activation, impaired sleep salubrity) in comparison with a placebo.

The subjective character of loneliness can make it difficult to assess definitively. The tools of social neuroscience make it possible to approach loneliness not only by the analysis of subjective self-reports (e.g., UCLA loneliness scale), but also by approaching the automatic (non-conscious) self-preservation mechanisms of loneliness, for instance, using high performance electrical neuroimaging and evoked microstate analyses [13-14]. In lonely individuals, recent studies have shown that the perception of social threat (compared to non-social threat) activates the para-hippocampal and amygdala regions during the early (non-conscious) period (between 116 ms and 136 ms) of information processing [13-14], and the amygdala region (including BNST) modulates the neural responses to social stimuli in the temporo-parietal junction [14]. In turn, loneliness is known to be inversely related to the level of activation of the temporo-parietal region bilaterally in response to social threat (compared to non-social threat notably between 116 ms and 124 ms post-stimulus onset; [14]), possibly reflecting a disorder in reading others' intentions, feelings, and others' behaviours or a less focus on others and more on one's own self-preservation in negative social contexts [5, 14, 92].

Based on these neural findings, exogenous administration of ALLO (or an ALLO precursor that can cross the blood brain barrier i.e., pregnenolone), with event-related functional and/or electrical neuroimaging in a double-blind, placebo-controlled, crossover design in lonely individuals should make it possible to observe a modulation of this cascade of activation and deactivation in the amygdala region and temporo-parietal junction observed in response to social threat. Based on a recent fMRI study showing the modulation of the amygdala and the dorsal medial prefrontal cortex (two regions rich in GABA_A receptors) two hours after a single dose of 400 mg pregnenolone in healthy subjects while they were performing an attention emotion appraisal task [63], we expect the exogenous administration of a single dose of 400 mg pregnenolone to reduce [and normalize] the amplitude response of the amygdala that is known to be increased in lonely individuals. In turns, the reduction of amygdala activity should lead to an increased response of (and an increased connectivity with) the dorsal medial prefrontal cortex and the temporo-parietal junction in the early stages of information processing.

Because of some pharmacokinetic limitations, such as bioavailability [37-38], and the uncertainty of the long-term effects of such exogenous administration on loneliness, longitudinal studies would need to be performed. The systematic study of the ALLO

hypothesis in individuals who are chronically lonely will provide critical insights on the role of ALLO on social threat processing and on how to reduce loneliness and its related behaviors, such as hypervigilance for social threat impulse control, and poor sleep salubrity.

Conclusion

We hypothesize here that ALLO reduction is involved in loneliness in humans, notably through its corresponding reductions in its facilitative effects on GABA and its modulating effects on HPA activity and BDNF expression. Recent meta-analysis and reviews suggest that cognitive behavioral therapies (CBT) designed to modify maladaptive social cognition associated with loneliness in humans may be especially worth pursuing [11 for review]. Such interventions can, however, be expensive and time-consuming, and the client's lack of openness to changing their thoughts about and interactions with others can be an obstacle to effective treatment focusing on the subjective, conscious aspects of loneliness [11]. While CBT alone might be sufficient to treat acute loneliness, the use of CBT in the case of chronic loneliness might be more effective (or effective for a greater proportion of individuals) if an appropriate ALLO pharmacological treatment acting on the HPA axis and the BDNF expression and reducing hypervigilance to social threat associated with loneliness within the non-conscious (within the first 140 ms) stages of information processing is used in parallel and in the early stages of CBT after diagnostic.

Although the neurobiology of loneliness is now well admitted, the systematic study of our new and potentially testable explanation of loneliness might provide an adjunctive therapeutic target early in CBT interventions to help alleviate chronic loneliness, which in turns might open a new avenue towards understanding the social brain.

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Figure 1.
Evolutionary model of loneliness, From [11].

Figure 2.
Schematics of the SAM and HPA axes, From [8].