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Contents

Monthly Volume 11 Number 9 September 19, 2021

EDITORIAL

- 507 Future of processing and facilitating change and learning
Löffler-Stastka H, Steinmair D

REVIEW

- 517 Binge eating and psychostimulant addiction
Blanco-Gandia MC, Montagud-Romero S, Rodríguez-Arias M

MINIREVIEWS

- 530 Genetics of adult attachment: An updated review of the literature
Erkoreka L, Zumarraga M, Arrue A, Zamalloa MI, Arnaiz A, Olivas O, Moreno-Calle T, Saez E, Garcia J, Marin E, Varela N, Gonzalez-Pinto A, Basterreche N
- 543 Recent advances in the treatment of opioid use disorders-focus on long-acting buprenorphine formulations
Soyka M, Franke AG
- 553 Is there a place for cellular therapy in depression?
do Prado-Lima PAS, Costa-Ferro ZSM, Souza BSF, da Cruz IBM, Lab B
- 568 Antiglutamatergic agents for obsessive-compulsive disorder: Where are we now and what are possible future prospects?
Maraone A, Tarsitani L, Pinucci I, Pasquini M
- 581 The renin-angiotensin system, mood, and suicide: Are there associations?
Sanchez M, Teixeira AL
- 589 Cognitive attentional syndrome and metacognitive beliefs as potential treatment targets for metacognitive therapy in bipolar disorder
Batmaz S, Altinoz AE, Sonkurt HO
- 605 Gastrointestinal disease in children with autism spectrum disorders: Etiology or consequence?
Krigsman A, Walker SJ

ORIGINAL ARTICLE

Observational Study

- 619 Evaluating the emotion regulation of positive mood states among people with bipolar disorder using hierarchical clustering
Chan SHW, Yu CH, Liu KHK, Lau C, Fung AOY, Tse S

SYSTEMATIC REVIEWS

- 635** Thinking about worry: A systematic review and meta-analysis on the assessment of metacognitions in children and adolescents
Köcher LM, Schneider K, Christiansen H
- 659** Deep brain stimulation for obsessive-compulsive disorder: A systematic review of worldwide experience after 20 years
Mar-Barrutia L, Real E, Segalás C, Bertolin S, Menchón JM, Alonso P

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The renin-angiotensin system, mood, and suicide: Are there associations?

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Abstract

Available evidence points to a possible role of the renin-angiotensin system (RAS) in the pathophysiology of mood disorders and suicide. We carried out a critical analysis of literature data regarding this role, with a focus on the proposed association between RAS dysfunction and suicidal behavior. Epidemiological, genetic, and biochemical findings are described, and the pathophysiological hypothesis aiming at explaining the possible relationship between RAS and suicide are discussed. Available findings do support the involvement of the RAS in the neurobiology of suicide, although the exact mechanisms underlying this involvement are still unknown.

Key Words: Renin-angiotensin system; Suicide; Mood disorders; Depression; Bipolar disorder

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INTRODUCTION

Despite the large amount of research aiming at understanding its clinical, epidemiological, and neurobiological correlates, suicide remains a leading cause of death worldwide[1,2]. Data from the World Health Organization indicate that, during 2015, 800000 suicides took place worldwide, corresponding to 1.4% of premature deaths[3]. Suicide represents the second leading cause of death during the second and third decades of life, with more than 45000 deaths by suicide reported in the United States alone during 2016[4]. From a psychiatric and epidemiological standpoint, there is a strong association between suicidal behavior and psychiatric disorders, particularly mood disorders (unipolar depression and bipolar disorder). Approximately 50% of all completed suicides are associated with mood disorders, with a 20-fold increase in the risk of suicide among individuals suffering from depression or other mood disorders compared to healthy individuals[5-7].

In order to characterize the pathophysiology of suicide, most authors adopt a stress-diathesis model, according to which certain individuals with genetic vulnerability exhibit increased risk of suicidal behavior when exposed to external stressors or life events[8,9]. A large amount of evidence supports the involvement of neurobiological factors in the pathogenesis of suicidal behavior, although the search for suicide biomarkers has not yet produced consistent findings. In addition to abnormalities in the serotonergic system, the most consistent neurobiological findings associated with suicide are related to dysregulation in stress response and its downstream effects[10, 11].

Over the last several years, the renin-angiotensin system (RAS) has been the object of great interest due to its possible involvement in the pathophysiology of mood disorders and suicide[12,13]. At a systemic level, the RAS plays an important role in blood pressure regulation and in the maintenance of body homeostasis. Furthermore, the existence of a brain RAS is well-established, with angiotensin-II receptors being found in brain areas involved in the processing of emotions, including the amygdala, the hippocampus, and the prefrontal cortex[14,15]. Evidence points to associations between increased RAS activity and depression, with angiotensin conversion enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) having been hypothesized as having protective and possibly therapeutic effects against mood disorders[12,16, 17]. On the other hand, some epidemiological studies have raised concerns about possible associations between the use of medications targeting the RAS and increased risk of suicide. In particular, the results of a recent study pointing to the association between the use of angiotensin receptor blockers and suicide[18] have been discussed not only by the specialized literature but also in the mass media due to the potential implications and the widespread use of these medications in the treatment of hypertension and other cardiovascular conditions[19,20].

The current mini-review critically analyzes the putative relationships between the RAS, mood disorders, and suicide, in light of available evidence. Clinical and epidemiological data are discussed, in addition to considerations on the hypothesized neurobiological mechanisms involved in the interface between RAS and suicidal behavior.

MOOD DISORDERS AND THE RENIN-ANGIOTENSIN SYSTEM

Alterations in systemic markers of RAS activity among mood disorder patients have been reported, and studies have shown lower rates of depressive symptomatology among patients receiving angiotensin receptor antagonists and ACE inhibitors for the treatment of hypertension or diabetic nephropathy[13,17]. Further, improvements in depressive symptoms and interpersonal sensitivity among patients with diabetes type II using angiotensin receptor blockers have been observed[21].

Nevertheless, the relationship between RAS activity and mood disorders seems to be more complex, involving interactions among the RAS, inflammation, the hypothalamic-pituitary-adrenal (HPA) axis, and mood regulation. A large amount of evidence supports the notion that increases in RAS activity result in the activation of the HPA axis. For example, stimulation of the angiotensin II receptor type 1 (AT1) in the hypothalamic paraventricular nucleus brings about increases in the release of corticotrophin releasing hormone, ultimately contributing to HPA axis hyperactivation in animal models[22]. Furthermore, certain variants of the ACE gene, such as rs4291 and the D allele, related with higher ACE serum activity and increased HPA axis activity, have been found to be associated with depressive disorders[23,24].

In addition, there are multiple interactions among RAS, inflammation, and psychiatric disorders[13,15,25,26], with strong evidence from *in vitro* and *in vivo* studies supporting the effects of angiotensin II as a potent pro-inflammatory agent[27]. Recently, it was hypothesized that the RAS is composed by two arms with opposite actions in terms of inflammatory activity and effects on the pathophysiology of mental illnesses. The first arm, composed by ACE, angiotensin II, and AT1, shows pro-inflammatory effects, while the second arm, comprised of ACE2, Ang (1-7), and angiotensin receptor type II (AT2) seems to have anti-inflammatory effects and a putatively protective effect against the development of neuropsychiatric conditions[15]. Moreover, decreases in angiotensin II activity induced by ACE inhibitors or angiotensin II receptor blockers have been found to significantly reduce the concentrations of inflammatory mediators such as IL-6, TNF- α , and CRP, and have been found to be of benefit for patients with inflammatory diseases[27-29].

Furthermore, it is not yet clear whether different patterns of associations with the RAS are found across distinct subtypes of mood disorders. Studies specifically examining the role of the RAS in bipolar disorder are scant and the cyclic nature of that condition adds an extra layer of complexity to the investigation of RAS-related abnormalities and their involvement in the pathophysiology of BD different mood states. Our group recently described decreased ACE levels among individuals with BD in acute mood states (irrespective of type of mood episode) when compared to controls, but no significant correlations were specifically found between ACE levels and depressive or manic symptoms[14]. Based on findings from animal models, it has been proposed that candesartan, an angiotensin receptor antagonist, may have antimanic-like properties[16] but, given the proposed antidepressive properties of RAS modulators, as described above, a possible the association between increased RAS activity and mania seems to be of difficult interpretation. Of notice, one anecdotal report described associations between ACE use and the onset of acute mania[30].

In summary, even though the exact neurobiological mechanisms underlying the relationship between RAS and mood are not yet completely clarified, there is strong evidence suggesting that the relationship in question is mediated by possible effects of the RAS on the HPA and on inflammatory processes. That is of particular importance when analyzing possible interactions between RAS and suicide, as discussed in the next section.

THE RENIN-ANGIOTENSIN SYSTEM AND SUICIDE

Epidemiological data

The first studies looking at possible relationships between the RAS and suicide were published in the later 1990s and early 2000s. For example, in a cross-sectional ecological study carried out in 152 municipalities in Sweden[31], the use of ACE inhibitors by patients with hypertension, in contrast with calcium channel blockers, was not associated with increased suicide rates. In another study, which utilized data from a 5-year Danish cohort comprised by 58529 subjects receiving beta blockers, calcium channel blockers, or ACE inhibitors[32], there was a slight, non-significant elevation in the standardized mortality ratio (SMR) for suicide among patients on ACE inhibitors [SMR: 1.2; 95% confidence interval (CI): 0.7-1.8]. Similarly, in a subsequent nested case-control study analyzing 743 cases of completed suicide and 14860 matched controls [33], ACE inhibitors were not significantly associated with suicide (OR: 1.11; 95%CI: 0.68-1.83). In the same study, based on five of the cases exposed, current use of ARBs was associated with elevations in suicide risk (OR: 3.52; 95%CI: 1.33-9.30). Nonetheless, when a subsequent restricted analysis (which excluded subjects with a history of psychotropic drug use) was performed, the associations between current ARB use and risk of suicide became non-significant (OR: 3.32; 95%CI: 0.93-11.8).

While in the studies mentioned above the possibility of increased suicide risk among individuals receiving RAS medications was analyzed in a broader context, *i.e.*, studies of the possible associations between suicide and use of cardiovascular drugs, more recent studies have specifically focused on the hypothesis that ACEs and ARBs could be related to elevation in the risk of suicide. Mamdani *et al*[18] carried out a population-based nested case-control study involving 964 individuals aged 66 years and older who died by suicide and 3856 matched controls. Data were obtained from administrative claims databases in Canada, over a period of 20 years (1995 to 2015). The authors reported significant associations between the use of ARBs (but not ACE inhibitors) and higher suicide risk (adjusted OR: 1.63; 95%CI: 1.33-2.00). Of notice, the findings remained significant even after individuals with a previous history of self-

harm were excluded from the analysis (OR: 1.60; 95%CI: 1.29-1.98). However, data on past history of substance abuse and personality disorders among cases and controls was not available.

On the other hand, in a similarly designed study using data from the Veterans Health administration in the United States[34], no significant associations between the use of ARBs or ACE inhibitors and elevations in suicide risk were found. Data of 1309 cases of completed suicide and matched 5217 controls, collected between 2015 and 2017, were included in the analysis. The adjusted suicide OR for ARBs was 0.98 (95%CI: 0.83-1.16), whereas the crude suicide OR for ARBs *vs* ACE inhibitors was 0.966 (95%CI: 0.828-1.127).

Moreover, a study using information from the National Health Insurance Research Database in Taiwan looked at associations between ARB use and suicidal behavior [35]. The authors conducted a retrospective population-based cohort study and estimated the rates of suicide attempts among ARB users, propensity-score matched with non-users. The suicide attempt rates were significantly lower among ARB users than among non-users (adjusted hazard ratio: 0.48; 95%CI: 0.26-0.87), and a Kaplan Meyer survivor analysis showed a lower cumulative incidence of suicide attempts among ARB users compared to non-users.

Last, Köhler-Forsberg *et al*[36] recently performed a register-based nationwide cohort study comparing individuals started on a selective serotonin reuptake inhibitor (SSRI) with and without concomitant use of a RAS medication. Both groups were propensity-score matched and were followed over a period of up to three years. Individuals in the group receiving SSRIs plus RAS medications showed reduced risks for psychiatric hospital contacts and lower mortality rates when compared to those receiving only SSRIs. Differences between groups in terms of suicidal behavior were not statistically significant (hazard rate ratio: 1.06; 95%CI: 0.79-1.42).

In summary, available data from epidemiological studies suggesting relationships between use of RAS medications and suicide are inconsistent, with important variations in terms of the direction of such interactions (increased *vs* decreased risk of suicide in association with RAS medications) and of possible differences between different classes of RAS medications (ACE inhibitors and ARBs). Additionally, it is not totally clear, in light of current available evidence, whether these relationships, if present, are modulated by other factors, such as previous psychiatric history, age, and other demographic data. Methodological issues might explain at least part of the discrepant findings across different studies, as explained in the discussion section.

Biological findings

To date, the neurobiological evidence analyzing the relationship between RAS activity and suicidality is scant. One early study described increases in ACE activity in the substantia nigra of individuals who completed suicide[37]. More recently, Hallberg *et al*[38] looked at the levels of renin and aldosterone among depressive disorder patients [major depressive disorder (MDD), dysthymic disorder, and adjustment disorder] with and without a history of suicide attempt, as well as healthy controls. Serum levels of aldosterone were significantly lower among MDD patients with a history of suicidal behavior when compared to the other groups. Interestingly, no association between history of suicide attempt and aldosterone levels was found among individuals with other depressive disorders, and MDD patients without a history of suicidal attempt were similar to healthy controls in terms of their aldosterone levels. Together, these findings suggest that decreased aldosterone could represent a marker of suicidality among patients with MDD.

Given the evidence suggesting that increased RAS activity may be associated with depressive symptomatology, Hong *et al*[39] investigated the distribution of the ACE gene insertion/deletion (ACE I/D) polymorphism among major depressive disorder patients with and without a history of suicide attempts. The authors hypothesized that D allele (which has been associated with increases in RAS activity compared to I allele) would be found at a higher frequency among suicide attempters. No statistically significant differences between groups regarding the polymorphisms in question were found. Nevertheless, other studies have reported positive findings regarding the association between the ACE D allele and suicidal behavior. In one of them[40], significant differences in the distribution of ACE I/D polymorphisms between suicide attempters and non-attempters were reported, with higher frequencies of the DD genotype among attempters. Furthermore, the results of two other unrelated case-control studies were jointly reported by Sparks *et al*[41]. In the first study, 64 subjects who completed suicide were compared to 90 controls, with higher rates of the ACE DD allele in the completed suicide group. Among individuals carrying the DD allele, the OR for completed suicide was 2.4 (95%CI: 1.2-4.8) when compared to II and ID

bearers. In the second study, 588 patients hospitalized following a suicide attempt were compared to 639 healthy controls. While statistically significant higher frequencies of the D allele were reported among cases, differences between groups with respect to genotype frequencies were not statistically significant.

On the other hand, a 2006 study carried out in Japan[42] looked at possible associations between suicide and functional polymorphisms in ACE gene and three other RAS-related genes: angiotensin, angiotensin type-1 receptor, and GNB3. A total of 166 completed suicides and an equal number of unrelated controls were included in the analysis. While there were no statistically significant differences between groups with regards to genotype distributions, the I allele frequency of the ACE insertion/deletion (ACE I/D) polymorphism was significantly higher in the complete suicide group, specifically in males. The risk of suicide among male individuals with the I allele was found to be more than 50% higher (OR: 1.55, 95%CI: 1.07-2.26). Furthermore, among male I/I homozygotes, the risk of suicide was estimated as more than 80% higher (OR: 1.84, 95%CI: 1.08-3.12). Even though the results in question did not remain positive after correction for multiple comparisons, since the I allele is associated with low ACE levels, these results suggest that decreased RAS activity could contribute to elevations in suicide risk. These findings were partially replicated by Fudalej *et al*[43], who described an increased frequency of the ACE I allele among male victims of suicide compared to male controls (OR: 1.69, $P < 0.006$).

DISCUSSION

The evidence outlined above points to associations between RAS activity and suicide risk. Despite the great variability of the results, the most replicated findings suggest a higher risk of suicidal behavior among carriers of the ACE gene DD allele. Results from epidemiological studies are less consistent, with different patterns of association between suicidal behavior and use of RAS medications.

Several theories aiming at explaining the putative pathophysiological mechanisms responsible for the relationship between RAS activity and suicidal behavior have been formulated. One of the most frequently discussed hypothesis is based on the described interactions between RAS, stress regulation, and the HPA axis. This is of particular importance given the recent attention given to the role of HPA axis hyperactivation as a possible diagnostic-independent suicide biomarker[44]. Elevated HPA activity contributes to the development of depression, which, on its turn, is associated with higher risks of suicide. Therefore, this mechanism provides a simple and straightforward explanation for the hypothesized relationship between increased RAS function and suicide risk, as suggested by the genetic studies describing higher rates of suicide among ACE D allele carriers (who show increased ACE activity) and the epidemiological data pointing to lower risk of suicidal behavior in individuals receiving RAS medications.

On the other hand, there are also findings indicating that suicidal patients with depression, in comparison to non-suicidal ones, might show decreased HPA response and lower cerebrospinal fluid levels of CRH[45,46]. In consonance with the results of the studies pointing to correlations between suicide and the ACE I allele, associated with decreased ACE activity, and the description of reduced aldosterone levels among suicidal MDD patients, those findings suggest that, in fact, decreased RAS activity could contribute to elevation in the risk of suicide.

How to explain these apparently conflicting findings? It has been proposed that the relationship between RAS activity and HPA axis might actually be bidirectional, with the RAS system not only having direct effects in the regulation of the HPA axis but also suffering downstream effects of increased HPA activity[14]. In rats, the expression of angiotensin 1 receptors seems to increase as a result of stress exposure[22], and this effect might be mediated by HPA axis-modulated increases in cortisol levels. As demonstrated in another animal study, the number of angiotensin 1 receptors in the brain was significantly decreased by adrenalectomy, and this effect was reversed by the administration of corticosteroids[47]. Therefore, one can hypothesize that, in some suicidal individuals, elevations in the HPA axis could bring about reductions in angiotensin 1 receptor expression which could lead to increases in the circulating brain levels of angiotensin II and, in its turn, produce compensatory reductions in ACE levels and downstream RAS activity through negative feedback. The exact mechanisms involved in this putative self-regulatory interaction between HPA axis and RAS are still poorly understood, and it is not clear either, in light of available evidence, whether the different ACE gene polymorphisms described above could have

distinct impacts on the modulation of this interaction.

Moreover, the different case-control studies reported show different patterns of association between use of RAS medications and suicide risk. While the study by Mamdani *et al*[18] pointed to increased risk of suicide associated with the use of ARBs but not ACE inhibitors, other studies failed to identify increases in suicide risk among ARB users. The study in question has received some criticism with respect to certain methodological limitations, some of which related to the age range of the subjects included in the study (which included only individuals 65 years and older), the lack of better characterization of the groups in terms of their psychiatric history and comorbidity, and other limitations inherent to case-control studies[19]. Still, one possible explanation to the reported elevation in suicide risk associated with ARBs but not ACE inhibitors involves interactions between RAS and substance P. Evidence indicates that the RAS plays a role in the regulation of substance P, with increases in ACE activity resulting in correspondent angiotensin II-mediated elevations in substance P levels in the brain[24,34,48]. The D allele of the ACE gene, which is associated with a higher risk of affective disorders, is correlated with elevated levels of substance P in the basal ganglia and substantia nigra[24]. Further, increases in substance P activity seem to be associated with anxiety and mood symptomatology, and substance P receptor antagonists have been investigated as for their possible antidepressant properties[49,50]. It has been proposed that ARBs use could result in compensatory elevations in the circulating levels of angiotensin II, leading to increases in the levels of substance P and, consequently, with elevations in the risk of suicide.

CONCLUSION

While available evidence does support the existence of an association between RAS dysfunctions and suicide, there are inconsistent findings with respect to the direction of this association. In other words, in contrast to the findings strongly suggesting that a hyperactive RAS seems to play a role in the pathophysiology of mood disorders, in the case of suicidal behavior, it is not possible to pinpoint whether increased or decreased RAS contributes to elevations in the risk of suicide and even if a direct cause-and-effect relationship does exist. Moreover, it is not yet clear whether this relationship, if present, corresponds an indirect effect, modulated by a putative role of RAS dysfunctions in the development of mood disorders and other psychiatric conditions (which would, by default, bring about increases in the risk of suicide) or results from an independent effect of RAS dysfunctions on the neurobiological mechanisms associated with suicide. Given the importance of suicide and the urgent need for interventions aiming at improving its prevention, a better understanding of the involvement of the RAS in its pathophysiology would have profound implications for psychiatry, neuroscience, and public health.

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