

The Renin Angiotensin System and Bipolar Disorder: A Systematic Review



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comorbidities, particularly cardiovascular diseases. The neurobiology of BD is complex and multifactorial and several systems have been implicated. Considering that the Renin Angiotensin System (RAS) plays an important role in cardiovascular diseases and that recently evidence has suggested its role in psychiatric disorders, the aim of the present study is to summarize and to discuss recent findings related to the modulation of RAS components in BD. A systematic search of the literature using the electronic databases MEDLINE and LILACS was conducted through March 2019. The search terms were: "Bipolar Disorder"; "Renin Angiotensin System"; "Angiotensin 2"; "Angiotensin receptors"; "Angiotensin 1-7"; "ACE"; "ACE2"; "Mas Receptor". We included original studies assessing RAS in BD patients. Two hundred twenty-two citations were initially retrieved. Eleven studies were included in our systematic review. In the majority of studies (6 of 8), the ACE insertion/deletion (I/D) polymorphism did not differ between BD patients and controls. BD patients presented higher plasma renin activity in comparison with controls. The studies evaluating the RAS molecules in BD are very scarce and heterogeneous. The literature suggests a potential role of RAS in BD. Further studies are necessary to investigate this relationship.

Abstract: Bipolar Disorder (BD) is a chronic a multifactorial psychiatric illness that affects mood, cognition, and functioning. BD is associated with several psychiatric conditions as well clinical

Keywords: Renin angiotensin system, angiotensin peptides, bipolar disorder, mania, depression, plasma renin activity.

1. INTRODUCTION

Bipolar disorder (BD) is a chronic, progressive and multifactorial illness, involving episodes of severe mood disorder. cognitive and functioning impairment. neurobiological disruption, and immunological imbalance [1]. The largest and most recent cross-sectional survey reported that the overall lifetime prevalence of BD was 2.4% [2]. BD is one of the most disabling diseases worldwide [3]. The mean age of onset for the first mood episode in patients with BD is at late adolescence and young adulthood, with an overall average age of onset of 25 years [4]. The recurrence of mood episodes is frequent. Patients with BD present subsyndromal symptoms, for approximately half of their lives [5].

There is an increased prevalence of comorbid medical conditions in BD. Patients with BD had a 2.3-fold increased

rate of mortality secondary to cardiovascular disease [6]. Patients with BD also exhibited higher prevalence of metabolic conditions, including 3 times increased risk for type II diabetes [7]. Moreover, overweight and obesity were two of the most prevalent general medical conditions in patients with BD [8, 9]. Several studies strongly suggest an association between BD and autoimmune disorders, including inflammatory bowel disease, systemic lupus erythematosus, autoimmune thyroiditis, psoriasis, Guillain-Barré syndrome, autoimmune hepatitis, multiple sclerosis and rheumatoid arthritis [9, 10]. The presence of immune dysfunctions can also be one of the factors responsible for the association between BD and other comorbidities [9]. Studies also support a role for immune-mediated mechanisms in BD. Interleukin-4 (IL-4), Tumor Necrosis Factor (TNF), soluble interleukin-2 receptor (sIL-2R), soluble type 1 receptor of TNF (sTNFR1) and soluble receptor of interleukin 6 (sIL-6R) were found in higher plasma levels in BD patients if compared with healthy controls [10-13].

Another regulatory system potentially responsible for the link between BD and cardiovascular diseases is the Renin

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Angiotensin System (RAS). The RAS was firstly described in the 70's as a system involved in the maintenance of blood pressure and fluid homeostasis [14]. The so-called classical axis of the RAS consists of circulating renin, acting on Angiotensinogen (AGT), to produce angiotensin I (Ang I), which in turn is converted in the vasculature into angiotensin II (Ang II) by Angiotensin-Converting Enzyme (ACE) [14, 15]. Despite the importance of a "circulating RAS", the physiological role of this system has expanded, and earning new significance by the finding of local or "tissue RAS", also found in the brain, and of novel active components for the system [15-21]. Among these new RAS components, some molecules should be highlighted such as the enzyme homologue to Angiotensin-Converting Enzyme (ACE), the ACE2 [22, 23], the heptapeptide angiotensin-(1-7) [Ang-(1-7)] [24, 25], and its G-protein coupled receptor, the Mas receptor [26]. Ang II is still regarded as the most important product of RAS, acting in angiotensin type 1 and type 2 receptors (AT1R and AT2R). AT1R activation increases blood pressure, stimulates aldosterone release, and produces renal salt retention and sympathetic nervous system activation [21]. The exacerbated effect of Ang II-AT1R pathway has been related to reduced life span, increased inflammation and accelerated autoimmune response [19]. On the other hand, the effects of the named alternative RAS axis, formed by ACE2, Ang-(1-7) and Mas receptor, have generally opposed the classical RAS axis [20, 21]. By binding to receptor Mas, Ang-(1-7) produces vasodilation, anti-inflammatory, anti-proliferative and anti-fibrotic actions in several tissues, including the brain [20, 21].

Several studies have investigated RAS activity in cerebral tissue [17, 18]. The physiological effects of central Ang II are mainly mediated by AT1R and include vasoconstriction, vasopressin release, retention of salt and water, cell growth, tissue remodeling, vascular inflammation and oxidative stress. Altogether, these effects may result in deleterious changes of Cerebral Blood Flow (CBF) [17, 18]. Therefore, this system can exert a role in several neurodegenerative and neuropsychiatric disorders like Alzheimer's Disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS), major depression and BD [15-20]. The aim of our systematic review was to evaluate the literature evidence about RAS components in patients with BD.

2. METHODS

2.1. Search Strategy and Study Selection Criteria

A systematic search of the literature, including the electronic databases PUBMED and LILACS was conducted through March 2019. The search terms were: "Bipolar Disorder"; "Renin Angiotensin System"; "Angiotensin 2"; "Angiotensin receptors"; "Angiotensin 1-7"; "ACE"; "ACE2"; "Mas Receptor". There was no restriction regarding the date of publication. Studies written in English, Portuguese or Spanish were selected for review. Two reviewers independently evaluated the titles and abstracts, and then the full text for inclusion eligibility (C.R.J. and G.C.F.). Disagreements were evaluated by arbitration with a third reviewer (I.G.B.). Studies with animals and without control group were excluded from the review. Review

studies were searched for the manual extraction of additional possible references. Only original studies assessing RAS components in patients with BD were eligible for inclusion.

2.2. Data Extraction Process and Literature Quality Assessment

We developed a data extraction table based on the Cochrane template [27]. One investigator (G.C.F.) extracted the data and a second reviewer (C.R.J.) verified the extracted data. In addition, two reviewers (C.R.J. and G.C.F.) independently crosschecked the risk of bias using the Newcastle-Ottawa Scale for observational studies [28]. The Newcastle-Ottawa form assigns a maximum of four stars for selection, two stars for comparability and three stars for exposure or outcome. In the current study, we considered a study awarded seven or more stars as a high-quality study [28]. Studies awarded four or lesser stars were considered of low quality and were excluded from this review. Any disagreement between authors was resolved by consensus, if necessary, a third author (I.G.B.) was consulted.

The data extracted included publication data (the first author's last name, and year of publication), type of study, and characteristics of the study population (sample size, mean age and gender, and specific characteristics of the bipolar disorder population), characteristics of the study protocol (which RAS components were measured and which laboratory methodology was adopted) and main outcomes.

This systematic review was registered on Prospero under the protocol CRD42018105961.

3. RESULTS

3.1. Description of the Studies

A total of 222 studies were identified through database search (PUBMED: 174, LILACS: 48). Twelve additional articles were identified through reference lists. Duplicate articles were excluded (N=43) and 144 studies were further excluded after title and abstract screening. Of the 47 articles selected for full text review, thirty-six were excluded (8 studies were review of literature, 10 articles did not evaluate RAS components, 9 articles did not include patients with BD, one study was a case report, 5 studies did not include control subjects, and 3 studies awarded four or less stars at New Castle-Otawa Scale. A total of 11 studies were selected for this review (Figure 1).

3.2. Characteristics of Included Studies

The all selected studies comprised case-control studies. Eight studies evaluated genetic components of the RAS in patients with BD [29-36] and three studies evaluated circulating concentrations of RAS molecules [37-39]. In seven studies, the authors described the criteria for the diagnosis of BD [29, 30, 32-35, 39].

The samples included in these 11 studies were very heterogeneous. These studies comprised a total of 999 patients with BD and 2363 controls. It was not possible to extract if the data were from BD type I or from BD type II patients, neither the mood currently episode.



Figure 1. Flow diagram for studies retrieved through the searching and selection process. RAS = Renin Angiotensin System

3.3. Genetic Studies of RAS Molecules in BD

Eight studies evaluated genetic polymorphisms of RAS components patients with BD (ACE and AGT genes polymorphisms) (Table 1). The quality of the case-control studies evaluated by Newcastle-Ottawa Score [28] was assessed and the majority of studies scored 8 (Table 2).

All studies about genetic polymorphisms of RAS molecules evaluated ACE insertion/deletion (I/D) polymorphism (rs4646994). In five studies, the frequency of DD genotype and D allele did not differ between patients with BD and controls [30-35]. In two studies, the frequency of DD genotype and D allele were significantly higher in

patients with BD when compared with healthy controls [29, 36].

One study evaluated AGT M235T polymorphism and showed that the frequency of M and MT genotype was higher in patients with BD than in controls [34]. Only one study that evaluated the NK and PAM polymorphisms did not report differences between patients with BD and controls [32].

3.4. Circulating Molecules of the RAS in BD

Three studies evaluated circulating levels of RAS molecules in patients with BD [37-39] (Table 3). The quality

References	Sample Size (Patient/Control)	Age (Years) (Patient/Control)	Male Frequency (%) (Patient/Control)	SNPs	Findings
Kucukali et al., 2010 [29]	184 / 210	42.81 / 42.51	38.04 / 34.28	ACE insertion/deletion (I/D)polymorphism - rs4646994	II P < C ID P = C DD P > C I P < C D P > C
Heck <i>et al.</i> , 2009 [30]	194 / 541	47.76 / 47.41	48.5 / 45.3	ACE SNPs: rs8076157 rs4459609 rs4291 rs4295 rs4305 rs4309 rs4311 rs4329 rs4646994 (I/D polymorphism) rs4343 rs4357 rs4461142 rs4267385 rs8066276 rs12451328 rs8066276 rs12451328 rs867640 rs9914151 Haplotypes formed by ACE SNPs	P = C (for all ACE SNPs and haplotypes)
Konuk <i>et al.</i> , 2006 [31]	44 / 90	37 / 35	45.5 / not describe	ACE I/D - rs4646994	P = C
Mendlewicz et al., 2005 [32]	132/92	49.3/47.4	47.72 / 72.82	ACE1 (dbSNP4295:C>G) ACE2 (dbSNP4298:C>T) ACE3 (dbSNP4309:C>T) ACE4 (dbSNP4333:C>T) ACE5 (dbSNP12709437:C>T)	P = C (for all ACE SNPs and haplotypes)
Pauls <i>et al.</i> , 2000 [33]	106 / 169	47.81 / not describe	48.11 / not describe	ACE I/D - rs4646994	P = C
Meira-Lima <i>et</i> <i>al.</i> , 2000 [34]	115 / 323	43 / 32	38 / 50	ACE I/D - rs4646994 AGT M235T - rs699	P = C $M P > C$ $MT P > C$
Furlong <i>et al.</i> , 2000 [35]	157 / 313	not describe / not describe	42.03% / 42.17%	ACE I/D - rs4646994	P = C
Arinami <i>et al.</i> , 1996 [36]	31 / 579	55.4/49.2	58.06 / not describe	ACE I/D - rs4646994	DD P > C $D P > C$

Table 1. Genetic studies evaluating RAS components in Bipolar Disorder patients in comparison with controls.

References	Representativeness of the Case	Sample Size	Non Respondents	Ascertainment of the Exposure	Comparability	Assessment of the Outcome	Statistical Test	Overall Quality Score
Kucukali <i>et al.</i> , 2010 [29]	1	0	1	2	1	2	1	8
Heck <i>et al.</i> , 2009 [30]	1	0	1	1	2	2	1	8
Konuk <i>et al.</i> , 2006 [31]	0	0	1	0	2	2	1	6
Mendlewicz <i>et</i> <i>al.</i> , 2005 [32]	1	0	1	2	1	2	1	8
Pauls <i>et al.</i> , 2000 [33]	1	0	1	2	2	2	1	8
Meira-Lima <i>et</i> <i>al.</i> , 2000 [34]	1	0	1	2	0	2	1	7
Furlong <i>et al.</i> , 2000 [35]	1	0	1	2	0	2	1	7
Arinami <i>et al.</i> , 1996 [36]	1	0	1	1	0	2	1	6

 Table 2.
 Quality of included studies that evaluate genetic in Bipolar Disorder patients in comparison with controls according New Castle [23].

Table 3. Peripheral RAS components system in Bipolar Disorder patients in comparison with controls.

References	Sample Size (Patient/Control)	Age (Years) (Patient/Control)	Male Frequency (%) (Patient/Control)	Laboratory Methodology	Measured Biomarkers	Findings
Stewart <i>et al.</i> , 1988 [37]	16 / 16	46 (±17) / 45 (±14)	$6(\pm 17)/45(\pm 14)$ - Radioimmuno Ion-electivemetho photometry		PRA Plasma Aldosterone Electrolytes	P > C $P > C$ $P = C$
Altamura <i>et al.</i> , 1977 [38]	6 / 7	33-49 / 27-50	33-49 / 27-50 83% Radioimmunoassy		PRA	P > C
Altamura <i>et al.</i> , 1975 [39]	7 / 23	41.1 (±1.2) / 28.8 (±12.1)	71 / 30	ELISA	PRA	P < C

Abreviations: ELISA: Enzyme Linked Immuno Sorbent Assay; PRA: plasma renin activity

of these studies was evaluated by Newcastle-Ottawa Score [28], and the majority of them scored 7 (Table 4). In two studies, measurements were in plasma samples and, in the remaining study, whole blood was used. Two studies [37, 38] analyzed the specimens by radioimmunoassays and one study [39] used Enzyme Linked Immuno Sorbent Assay (ELISA).

Plasma Renin Activity (PRA) was evaluated in these three studies [37-39]. Two studies reported that patients with BD had higher PRA in comparison with controls [37, 38]. In the remaining study, PRA was higher in controls than in BD patients [39].

Plasma levels of aldosterone were investigated in one study comprising 16 patients with BD and 16 healthy

controls. Patients with BD had higher levels of aldosterone than controls [37].

4. DISCUSSION

The relationship RAS and BD is still unknown with a relative paucity of consistent findings. This systematic review showed that, in six among eight studies, genetic polymorphisms of ACE insertion/deletion (I/D) (rs4646994) did not differ in the comparison of patients with BD and controls. On the other hand, despite the very scarce number of studies, PRA and circulating levels of aldosterone seemed to be increased in BD. No study investigated angiotensin peptides, enzymes and receptors in BD.

References	Representativeness of the Case	Sample Size	Non Respondents	Ascertainment of the Exposure	Comparability	Assessment of the Outcome	Statistical Test	Overall Quality Score
Stewart <i>et al.</i> , 1988 [38]	0	0	1	0	1	2	1	5
Altamura <i>et al.</i> , 1977 [39]	1	0	1	0	2	2	1	7
Altamura <i>et al.</i> , 1975 [40]	1	0	1	1	1	2	1	7

 Table 4.
 Quality of included studies that evaluate Peripheral RAS components system in Bipolar Disorder patients in comparison with controls according New Castle [23].

The lack of association between the ACE gene I/D polymorphism and BD in six among eight studies is to some extent unexpected. Considering that cardiovascular diseases and hypertension are more frequently detected in patients with BD than in the general population [6], we might expect that the ACE D allele and DD genotype would predominate in BD. In fact, it was previously demonstrated that individuals who have the D allele would exhibit more chances to develop hypertension and cardiovascular diseases, once the presence of D allele is associated with higher ACE levels and activity [40, 41]. The I/D polymorphism accounted for 47% of the total phenotypic variance ACE. The ACE gene locus is the major locus that determines ACE concentration [40]. Additionally, Ishimitsu et al. [42] detected that D allele of the ACE gene polymorphism is an independent risk factor for cardiovascular diseases in longterm hemodialysis patients. Guney and co-workers [43] reported that the ACE D allele and DD genotype were the major risk factors for coronary heart disease.

On the other hand, in contrast from the six studies mentioned above, the remaining two studies found significantly higher frequency of D allele and DD genotype in patients with BD compared to controls [29, 36]. The heterogeneity of these studies makes difficult any comparison. In addition, none of the eight studies about ACE gene polymorphism in BD evaluated cardiovascular comorbidities, hypertension and other associated clinical conditions in the samples. Therefore, the exclusion of confounding factors was not even mentioned in these studies, precluding any conclusion regarding the role of ACE gene polymorphism in BD.

The American Heart Association Scientific Statement positioned BD as tier II-moderate risk condition that predisposes youth to accelerated atherosclerosis and early cardiovascular disease [44]. Moreover, patients with BD had almost doubled the risk of deaths from cardiovascular disease than the general population [45, 46]. Despite of this well-established association between BD and cardiovascular disease, the pathophysiology remains to be explained. Hypothetically, homeostatic changes related to BD including increased inflammatory response, high oxidative stress and alterations of neurothrophic factors might link both conditions [47]. In this regard, changes of RAS molecules might also play a role in this scenario. Unfortunately, very few studies (only three) measured components of RAS in patients with BD and the only molecules evaluated are renin, expressed as PRA, and aldosterone [37-39]. Two studies showed higher PRA in patients with BD in comparison with controls [37, 38], probably indicating an activation of circulating RAS. Moreover, high levels of PRA have been associated to worse outcome in cardiovascular diseases [48]. Taken together, these findings may suggest that enhanced PRA results in high levels of Ang II, which, in turn, contribute to mortality related to cardiovascular diseases in BD. It is known that increased levels and/or activity of Ang II may elicit inflammatory responses, oxidative stress, proliferative and fibrogenic pathways, thus contributing to cardiovascular and brain system damage [21, 49]. Unfortunately, circulating levels of Ang II was not measured in BD. An indirect evidence of increased activity of Ang II was provided by the one study that reported increased aldosterone concentrations in patients with BD patients in comparison to controls [38].

In fact, recent studies have supported a role for RAS molecules in central nervous system and in neuropsychiatric disorders [18, 49, 50]. It is well know that angiotensin receptors are present in the brain, although the origin of active angiotensin peptides in the brain remains a matter of debate [18, 49, 50]. In brain tissue, Ang II can interact with Angiotensin receptor (AT) 1R and AT2R. The activation of AT1R leads to detrimental actions to neurons and to central nervous system. On the other hand when Ang II binds to AT2R neuroprotective effects were mediated. In addition, the activation of the alternative RAS axis, formed by ACE2, Ang-(1-7) and Mas receptor, also results in neuroprotection. Figure 2 shows a schematic view of RAS pathways related to protection. central nervous system damage and Unfortunately, the role of AT2R and components of the alternative RAS axis was not evaluated in BD. However, as suggested by Altamura and Morganti 1975 [40], there is an indirect evidence of increased activity of Ang II in BD patients and this might be associated with the neurodegenerative process related to the neurobiology of this condition [11].

This systematic review has some limitations. First, the paucity and heterogeneity of the studies preclude any conclusion on the role of RAS in BD. Second, the lack of evaluation of confounding factors related to cardiovascular disorders may probably compromise the conclusions of these



Figure 2. Diagram of Renin Angiotensin System pathways related to central nervous system damage and protection. ACE = Angiotensin–Converting Enzyme ; AT1R = Angiotensin Type 1 Receptor; AT2R = Angiotensin Type 2 Receptor

studies. On the other hand, our analysis clearly showed the need of evaluation of RAS molecules in BD patients.

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Declared None.

CONCLUSION

In conclusion, cohort studies including information on clinical characteristics of BD patients, the presence of comorbidities, medications used and with serial measurements of several RAS molecules will certainly help elucidating this issue.

STANDARD OF REPORTING

The study was registered according to PRISMA guidelines suggest on Prospero under the protocol CRD42018105961.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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