Salud Mental 2016;39(1):47-58
ISSN: 0185-3325
DOI: 10.17711/SM.0185-3325.2015.067

Neurobiology of major depression and its pharmacologic treatment

Humberto Cruzblanca Hernández,[1] Patricia Lupercio Coronel,[1] Jorge Collas Aguilar,[1] Elena Castro Rodríguez[1]

Thematic update

ABSTRACT

Introduction
The major depressive disorder (MDD) arises from the interaction of environmental, genetic and epigenetic factors, producing a deficit in monoaminergic transmission within the brain. However, our understanding of its pathophysiology is quite limited.

Objective
To reach an integrative view of the MDD pathophysiology, as well as the mechanisms of action of antidepressant drugs.

Method
We used the PubMed database to search for the documents by using the appropriate key words. Most of them are experimental research and molecular genetics and brain imaging studies in humans.

Results
The pathophysiology of MDD is characterized by: i) shrinkage of the cingulate anterior cortex; ii) hyper-metabolism of the Cg25 area; iii) lower expression of the 5-HT_{1A} receptor; iv) enhanced expression of monoamine oxidase A. Besides, certain gene polymorphisms are strongly linked to the pathophysiology, and there is evidence that 5-HT_{1A} receptor expression is reduced by psychological stress. Antidepressants reverse the hyper-metabolic state of Cg25, stimulate neurogenesis and the cAMP pathway. We found that imipramine increases and reduces the expression of $G_{\alpha s}$ and $G_{\alpha z}$, respectively (data not published).

Discussion and conclusion
The disruption in monoaminergic transmission could be mediated by: i) the G1463A hTPH2 polymorphism that reduces the serotonin synthesis; ii) the C (-1019) G 5-HT_{1A} polymorphism that increases the receptor expression in the dorsal raphe, and reduces serotonin release; iii) an increase in monoamine degradation. The reduced 5-HT_{1A} expression is discussed considering its inhibitory properties in the prefrontal cortex. The effects of imipramine on $G_{\alpha s}$ and $G_{\alpha z}$ are in agreement with the antidepressant-induced stimulation of the cAMP pathway.

Key words: Major depression, antidepressant drugs, serotonin, stress, neurons.

RESUMEN

Introducción
La depresión mayor (DM) se debe a la interacción de factores ambientales, genéticos y epigenéticos, que atenúan la transmisión monoaminérgica en el cerebro. Sin embargo, poco se conoce sobre los mecanismos fisiopatológicos que subyacen a ella.

Objetivo
Proponer una visión integral sobre la fisiopatología de la DM y los mecanismos de acción de los fármacos antidepresivos.

Método
Se empleó la base PubMed para la búsqueda bibliográfica. La mayoría son investigaciones experimentales y estudios de genética molecular o de imágenes cerebrales en humanos.

Resultados
La DM se asocia con: i) menor volumen de la corteza cingulada anterior; ii) hiper-metabolismo del área Cg25; iii) menor expresión del receptor 5-HT_{1A}; iv) mayor expresión de la monoamino oxidasa A. Algunos polimorfismos están asociados a la fisiopatología. El estrés crónico reduce la expresión del 5-HT_{1A}. Los antidepresivos atenúan el hiper-metabolismo del área Cg25, estimulan la neurogénesis y activan la vía del AMPc. Encontramos que la imipramina aumenta y reduce la expresión de $G_{\alpha s}$ y $G_{\alpha z}$, respectivamente (datos sin publicar).

Discusión y conclusión
El déficit en la transmisión monoaminérgica puede deberse a: i) el polimorfismo G1463A en el gen de la enzima hTPH2 que reduce la síntesis de serotonina; ii) el polimorfismo C(-1019)G en el gen del receptor 5-HT_{1A}, aumentando su transcripción en el rafé e implicando menor liberación del neurotransmisor; iii) mayor degradación de las monoaminas. La menor expresión del receptor 5-HT_{1A} se discute considerando su acción inhibitoria en la corteza prefrontal. Los cambios en la expresión de $G_{\alpha s}$ y $G_{\alpha z}$ coinciden con la estimulación de la vía del AMPc.

Palabras clave: Depresión mayor, fármacos antidepresivos, serotonina, estrés, neuronas.

[1] University Center for Biomedical Research, Colima University, Colima, Col., México.
Correspondence: Dr. Humberto Cruzblanca. University Center for Biomedical Research, Colima University. Av. 25 de julio 965, Villas San Sebastián, 28045, Colima, Col., México. E-mail: cruzblan@ucol.mx
Received first version: December 9, 2014. Second version: October 8, 2015. Third version: November 26, 2015. Accepted: January 12, 2016.

INTRODUCTION

The main mood disorder is major depressive disorder (MDD) Specialized literature on this topic includes several studies regarding different aspects such as epidemiology, genetics, etiology, and pathophysiology.[1,2] Notwithstanding, a possible connection has not been proposed between the most recent findings on the cellular and molecular level and the anatomic-functional changes taking place in the brains of MDD patients. The objectives of this review are: 1. Offer a comprehensive perspective on pathophysiology of MDD and on the mechanism of action of antidepressant drugs, and 2. Discuss recent evidence which supports the two neurobiological hypothesis for MDD: monoaminergic, which underscores the serotoninergic component, and the neurotrophic.

METHODS

Bibliographic search was conducted using PubMed, with the following keywords: major depression, antidepressant drugs, serotonin, stress and neurons. Inclusion criteria were the following: i) publications focused on molecular, cellular and systemic pathophysiology of MDD; ii) experimental studies on isolated neurons and/or *in situ*, about action mechanisms of antidepressant drugs; iii) clinical and pre-clinical pharmacologic studies; iv) works published mostly during the last 10 years.

As mentioned, pathophysiology of MDD includes a neurotrophic mechanism. Within this context, there is evidence that heterotrimeric G proteins (G proteins) regulate the intracellular signaling ways activated by receptors to neurotrophic factors, making G proteins a possible molecular target of antidepressant drugs. Thence, an additional objective of this work is reporting the effect of antidepressant drug imipramine on the expression of subunits α (Gα) of G proteins. Therefore, the results shown in figure 1 were obtained using the following methodology: Six male rats (Wistar; 3 weeks) were injected intraperitoneally with a saline solution(n = 3) or imipramine (n = 3) (10 mg/Kg) during 21 days. Then, they were anesthetized and decapitated to dissect the superior cervical ganglia. The protocol was approved by the Ethics and Biosafety Committee of Colima University. The connective tissue capsule was removed and each pair of ganglia was deposited in PCR tubes with 1 ml trizol. Inverse transcription was performed with SuperScript TM III kit (Invitrogen) For real time PCR, a LightCycler Fat Start DNA Master^{PLUS} SYBR Green I (Roche) kit and a LightCycler 1.5 (Roche) thermocycler were used; *primers* were designed with intron spanning. CT parameters was obtained from the amplification curves to normalize the expression of every Gα (α) to that of the constitutive gene (actin). The relative expression (α/actin) was used to quantify the change in the expression, dividing the value obtained for the rats injected with saline solution $(\alpha/\text{actin})_c$ by the value with imipramine $(\alpha/\text{actin})_{imi}$; if the quotient is greater than one it means increase in the expression and vice versa.

Symptoms of major depression and diagnosis criteria

MDD is characterized by episodes in which negative emotions and thoughts coexist with cognitive deficit and alterations in appetite, libido and sleep. The preferred diagnosis instrument in the United States and Mexico is the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) The manual includes the following symptoms: Feelings of sadness, despair, uselessness and guilt; low self-esteem; negative thoughts centered in suicide; cognitive deficit affecting motivation, selective attention, episodic and working memory and a lower capacity for reflexive thoughts; irritability, dysphoria and anhedonia. Neurovegetative symptoms include greater or lesser appetite, fatigue and alterations in the awake-sleep cycle. Diagnosis is established when at least five of these symptoms coexist and persist during at least two weeks. In 2013 DSM-5 appeared: it preserves the core of the symptoms but co-morbidity with anxiety is acknowledged; also new is the fact that it eliminates the grief exclusion criterion. In any case, diagnosis is still subjective, which makes it difficult to study the etiology, pathophysiology and treatment of MDD. However, advances in neuroscience will eventually allow for reformulation from a more scientific basis (v. gr. Proposing molecular or biological markers) the nosology and etiology of depressive disorders. MDD causes severe disability in the working, school and social environments; it is estimated that by the year 2020 it shall be the second cause of disability in the world and will continue to be the first in industrial countries.[3,4]

Epidemiology and risk factors

In Mexico, the psychiatric epidemiology survey of 2002-2003 estimated a prevalence of 4.5% in adult population and 1.7% in people younger than 18 years of age.[5,6] Globally, the prevalence in women is greater than in men, in a 2:1 proportion. For example, in Mexico, the prevalence in adult population is 5.8% in women and 2.5% in men; this proportion is maintained for early onset MDD (2.4% in women and 1.0 % in men).[5,6]

Consensus at present is that MDD is originated by interaction of genetic, epigenetic and environmental factors which eventually alter biochemistry, cytoarchitecture and the function of specific areas of the brain.[7-10] Here, two polymorphisms are analyzed due to their possible pathophysiologic relevance. ii) G1463A polymorphism of the gene

for human tryptophan hydroxylase type 2 enzyme and ii) polymorphism C(-1019)G in serotonin (5-HT) receptor gene 5-HT_{1A}. Within environmental factors one can consider chronic stress (physical or psychological) as a risk factor for MDD. This association comes from observing that nearly 50% of patients with MDD show hypercortisolemia.[11-13] These findings suggest that dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is a neuroendocrine factor contributing to the etiology of MDD.[14]

Anatomic and metabolic changes in the brain of patients with MDD

The heterogeneous symptomatology of MDD suggests the participation of different brain areas. To only mention a couple of them, dysfunction of dorsolateral prefrontal cortex (PFC) would affect cognitive functions such as reasoning, planning and decision making (figure 2). On the other hand, orbitofrontal and medial areas of pFC, at participating on the regulation of emotional experience, they would contribute to the affective component of the syndrome. Here, the findings made with brain imaging studies using magnetic resonance imaging(MRI) and/or positron emission tomography (PET), revealing the most frequent anatomic-functional abnormalities are discussed.

Changes in cortical and subcortical volume: studies with MRI

One of the structural changes is the reduction of hippocampus.[15-19] The average decrease is 8-10%; the change is bilateral as well as appearing in only one of the hemispheres. There is also a significant decrease only in patients who had recurrent depressive episodes,[18] or the decrease is inversely correlated with the duration of the depressive episode.[19] Other studies do not report changes in the hippocampus volume and either do they confirm the inverse relation between the duration of the depressive episode and on the degree of reduction in volume.[16,20] This evidence limits the pathophysiologic importance of the reduction of the hippocampus: i) patients in remission still show lower hippocampal volume;[21] ii) the reduction is also observed in schizophrenia and bipolar disorder,[16,22] i.e., such neuroanatomical change is not exclusive of MDD. To reconcile these observations, it is proposed that the reduction of the hippocampus does not cause the first depressive episode but becomes a factor of recurrence and eventual chronicity of depressive syndrome.[23]

Another area where gray matter is also reduced is the anterior cingulate cortex (ACC), specifically at the area ventral to the *genu* of the corpus callosum (subgenual cortex). The reduction is prominent (20-40%) in those patients with a family history of MDD.[24] MRI also reveals a lesser gray matter volume at the orbital PFC.[25] Such observations *in vivo* are concurrent with *post-mortem* studies. For example, Öngür[26] found a lesser number of glial cells in the subgenual cortex Cg24; its reduction is more acute in subjects with MDD (24%) or bipolar disorder (41%) with an evident family profile. In this study, patients with schizophrenia did not show variation in the cell density, suggesting that a lower glial density is an abnormality that is related to MDD and other affective syndromes. It is worth mentioning that subgenual cortex and orbital PFC, at processing information from sensory association areas, such as insular cortex, integrate it to generate emotional and affective behavior.[27,28]

Functional changes in MDD: studies with PET

Coincidently with the lesser volume of the subgenual cortex, PET reveals lesser metabolic activity in this cortical area.[29] However, when the image is corrected by the lesser volume, Cg25 area reveals hyper-metabolism regarding control individuals.[16] It is highly probable that such hyperactivity contributes to depressive behavior since: 1. When healthy individuals are caused a deep sadness feeling, the activity of Cg25 also increases,[30] 2. Antidepressant drugs reduce hyper-metabolism of Cg25 and other areas of PFC, both in patients with MDD and in depressive patients with Parkinson's disease,[16,31-34] 3. Electrical stimulation of Cg25 reverts depressive sympthomatology.[35,36]

Metabolic activity in the amygdala also increases.[37] Such functional alteration does not occur in schizophrenia or anxiety syndromes such as obsessive-compulsive, phobias and panic disorder.[7] There is evidence that the increase of amygdala activity precedes the relapse of depressive symptomatology in patients under the tryptophan depletion protocole.[38]

Neurobiology of major depression

Monoaminergic hypothesis. This hypothesis is the predominant concept framework that deals with pathophysiology of MDD and proposes that the syndrome originates due to the lesser availability of monoamines in the brain, especially 5-HT and noradrenaline (NA). This hypothesis is primarily based on the notion that most antidepressant drugs increase the brain level of 5-HT and NA by means of the inhibition of their recapture or of their enzymatic degradation. Recent studies offer greater support to this hypothesis. For example, PET images reveal that MDD patients show greater expression of monoamine oxidase A (MAO-A) in the PFC, temporal cortex, hippocampus, thalamus, *accumbens* nucleus (NAc) and mesencephalon.[39] These discoveries imply that the greater degradation rate of 5-HT and NA is one of the pathophysiologic mechanisms that attenuate monoaminergic transmission. On the other hand, G1463A polymorphism in the hTPH2 gene

Translation of the original version published in spanish in: Salud Mental 2016, Vol. 39 Issue No. 1.

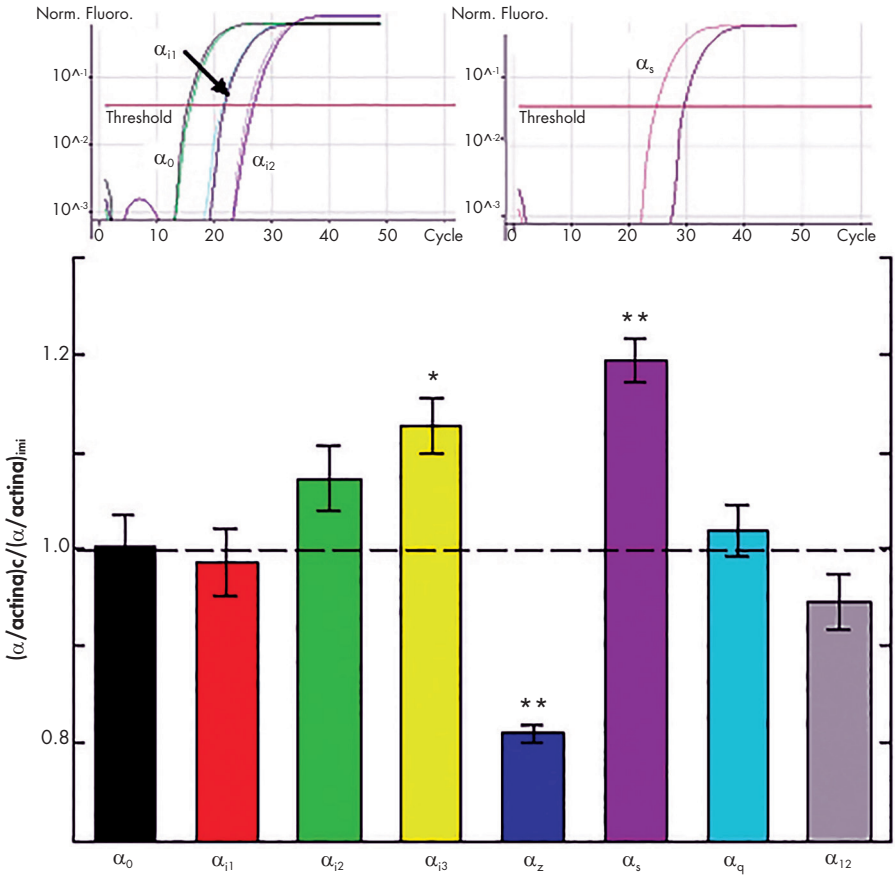

Figure 1. Effect of Imipramine on the expression of G_α subunits of neurons of the superior cervical ganglion. On the top are shown the amplification curves for the transcripts of $G_{\alpha o}$, $G_{\alpha i1}$ y $G_{\alpha i2}$ (left panel) and $G_{\alpha s}$ (right panel). Notice that imipramine only produces a shift to the left (pink stroke) of the amplification curve of $G_{\alpha s}$ compared to saline solution treatment (fuchsia stroke) The graph shows (average ± standard error) the change in the level of expression of G_α subunits. Notice that chronic treatment with imipramine strongly increases the expression of $G_{\alpha s}$ and reduces the expression of $G_{\alpha z}$. Statistically significant changes to 95% (*) or 99% (**) reliability are shown (paired student t).

suggests that serotoninergic deficit resides in the 5-HT synthesis since the corresponding change of aminoacid results in the loss of 80% of the enzymatic function.[40] The association with MDD is confirmed when in a group of 87 patients, 10% was carrying G1463A polymorphism, a significantly higher percentage than the value found (1%) in the sample (n = 219) of healthy individuals.[40] Clinical evidence that supports the monoaminergic hypothesis comes from studies in patients subject to brain tryptophan depletion protocol (Trp). Prediction of the paradigm is that depletion facilitates depressive relapse only in those patients who responded to treatment with selective 5-HT recapture inhibitors (SSRIs). A meta-analysis of 45 studies published until 2006 reveals results which are consistent with the hypothesis.[41]

The number of studies is limited when the brain level of NA and dopamine is reduced; however, data points in the same direction as Trp depletion.[41,42] Evidence in favor or noradrenergic component comes from *post-mortem* studies, where the union of a NA transporter ligand was measured in the *locus coeruleus* (LC). In a sample of patients with MDD, a lower density of the transporter was found when compared to control subjects.[43] It is proposed that such change comes from the lower bioavailability of NA at the synapsis, which may be deemed possible, considering that the greater expression of MAO-A at the mesencephalon[39] would increase enzymatic degradation of NA. Another study for the LC reports an increment in the density of α_2-adrenergic receptors (its functional impact is further discussed ahead in the study).[44]

Neurotrophic hypothesis. This hypothesis proposes that MDD is also caused by neuronal atrophy as a consequence of the lesser expression of the brain derived growth factor BDNF.[45] It also proposes that chronic stress dysregulates

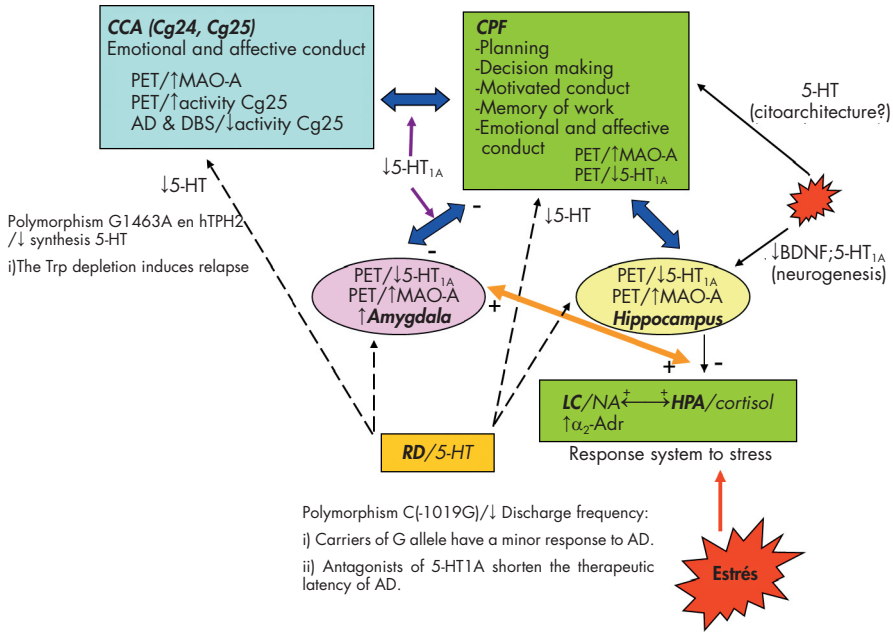

Figure 2. Integrating basic and clinical evidence of MDD. It is proposed that the deficit in monoaminergic transmission may be due to: i) lower synthesis (G1463A polymorphism) or liberation (C-1019G) polymorphism of 5-HT; ii) increase in the expression of MAO-A; iii) lesser liberation of NA, due to the greater (↑) density of $_{\alpha 2}$-adrenergic receptors ($_{\alpha 2}$-Adr). Stress reduces (purple arrows) the post-synaptic density of 5-HT$_{1A}$ receptor, a molecular change consistent with hyper-metabolism of Cg25 area and the amygdala; probably revealing dysfunction (blue arrows) of intra-cortical circuits (v. Gr., between CCA and PFC and other areas of association), and limbic-cortical. Antidepressant drugs (AD) or deep brain stimulation (DBS) revert the hyper-metabolism of Cg25. Greater amygdala activity may potentiate (orange arrow) the dysregulation of HPA axis induced by chronic stress. At the hippocampus, stress reduces the expression of BDNF and produces neuronal atrophy, but also reduces neurogenesis, due to the lower expression of BDNF and 5-TH$_{1A}$. In the cortex, stress also affects cellular and synaptic plasticity processes. The mechanisms proposed here evidently require a direct experimental assessment.

HPA axis promoting a sustained exposure of nervous tissue to cortisol and, thence, the inhibition of BDNF expression.[7] *Post mortem* studies offer evidence of neurotrophic mechanism, since a lesser expression of BDNF has been observed, as well as of TrkB receptor in the hippocampus and PFC of patients with MDD, when compared with individuals who are not suffering from psychiatric disorders at the time of their death.[46] Another study reports that patients with MDD under pharmacologic treatment show a greater expression of BDNF in the hippocampus when compared with patients who are not receiving treatment.[47]

The rest of the evidence comes from studies in rodents subject to chronic stress. A common effect of stress paradigms is a lesser expression of BDNF and of its TrkB receptor in the hippocampus, while chronic administration of antidepressant drugs reverts the effect of stress on both proteins.[48-50] On the other hand, antidepressant drugs reduce stress-induced damage on the dendritic arborization of pyramidal neurons of the hippocampus[51,52] and stimulate neurogenesis.[53,54]

Behavioral evidence comes from murine models of depressive behavior. For instance, the forced swim test (FST) mimics the despair behavior of the human and, in spite of its methodological simplicity, it has a great predictive value of the therapeutic efficacy of antidepressant drugs.[55] With FST, it is reported that a BDNF injection (one day before the test) to the hippocampus of the rat has an antidepressant effect with a similar efficacy of that of the pharmacologic treatment.[56] However, this acute behavioral effect of BDNF is in contrast with the fact that only the chronic treatment (21 days) with antidepressant drugs increases the expression of BDNF and its receptor in the same species.[49] I.e. The gap between the behavioral effect of FST and gene effect of BDNF must be considered with some reservations as a support of the neurotrophic hypothesis.

Receptors and altered signaling pathways in MDD

We discuss here the possible pathophysiologic relevance of 5-HT$_{1A}$ receptor, a receptor that signals with the pathway of G$_1$ of G proteins, since depending on their density and their pre- or post-synaptic localization, they have a differential impact on the deficit of serotoninergic transmission.

A) 5-ht$_{1A}$ auto receptor

C(-1019)G polymorphism in the promotor of 5-HT$_{1A}$ receptor gene reveals another pathophysiologic mechanism of

MDD. This change of nucleotide provokes its differential transcription in the NCS, since the carriers of G allele have greater density of the receptor in the dorsal raphe (DR) and greater association with MDD.[57] The degree of expression of auto-receptor depends on the allele composition, according with genotype CC<CG<GG.[58] Besides, carriers of G allele show lesser therapeutic response to antidepressant drugs.[59] To ponder the impact of the greater density of 5-HT1A auto-receptor, suffice to say it has an inhibitory effect on DR neurons, limiting its discharge frequency in 2-4 Hz.[60] The rigid control over the discharge rate determines that receptor 5-HT_{1A} controls the liberation of 5-HT in the brain cortex and the limbic system from the neuronal soma. Consequently, C(-1019)G polymorphism would be provoking a lower liberation of 5-HT.

Even when there is no direct proof of the aforementioned pathophysiologic mechanism, there is some clinical evidence in support. For instance, it is known that antagonists of 5-HT_{1A} reduce the therapeutic latency of antidepressant drugs.[61,62] Such clinical synergy is due to the SSRIs desensitizing 5-HT_{1A} auto receptor by a mechanism which implies its disengage with G protein and not by the diminishing density of the receptor.[63-65] Lastly, attenuation of the signaling of 5-HT_{1A} auto receptor may be achieved by means of desensitization or through their antagonists. In both cases, the result is that DR neurons are liberated from auto-inhibition.

B) 5-HT_{1A} post-synaptic receptor

Studies with PET with patients who are not receiving antidepressant drug treatment, consistently reveal a lower density of 5-HT_{1A} receptor in the PFC, the hippocampus and the amygdala.[66-69] This molecular change also occurs in the ACC both of patients diagnosed with some anxiety syndrome and in those who suffer from anxiety and depression.[70,71] This was to be expected due to the co-morbidity between anxiety and depression.[30]

5-HT receptors which are mainly expressed in PFC are 5-HT_{1A} and 5-HT_{2A}; the former is located in the soma and the basal dendrites of pyramidal neurons, while the latter is found in the apical dendrite.[72-74] In these neurons, 5-HT_{1A} stimulates a K^+ efflux through GIRK channels.[72,73,75] Inhibitory action includes those neurons in PFC layers II and III.[75] Thence, the lower post-synaptic density of 5-HT_{1A} may imply that in MDD there is an alteration in the processing of intracortical and interhemispheric information, as well as in the feedback between the cortex and the limbic system (figure 2). This dysfunction would account for certain findings made by fMRI which reveal a decrease in communication between the amygdala and the ACC.[23] The lower density of 5-HT_{1A} receptor in the amygdala is also consistent with the greater amygdala activity in patients with Trp depletion.[38] Concurrent with this, it is known that antidepressant drugs or electroconvulsive treatment increase, directly or indirectly, 5-HT_{1A} receptor signaling.[74]

Gene manipulation in rodents of proteins participating in 5-HT_{1A} receptor signaling also supports its relevant role in anti- (greater function) or pro-depressive (lesser function) behavior. For example, on prolonging signaling of this receptor, either by mutation in sub-unit $G_{\alpha i2}$ which prevents its interaction with RGS proteins,[76] or eliminating the expression of RGS6,[77] the phenotype obtained are mice with antidepressive and anxiolytic behavior. Greater knowledge is obviously required as to how 5-HT_{1A} receptor regulates the communication between cortical areas and with the limbic system (figure 2) in order to present more precise hypothesis about its role in affective and cognitive behavior.

Lower post-synaptic density of 5-HT_{1A} is not derived from a "down-regulation" mechanism secondary to deficit in the liberation of 5-HT, since the injury of DR does not alter its density in the cortex and the hippocampus.[68] Conversely, HPA axis does regulate its expression since extirpation of adrenal glands in the rat increases the transcript of the receptor in the hippocampus, where 5-HT_{1A} is co-located with the receptors to glucocorticoid.[78,79] Concurrent with this, it is reported that in a model of social stress, rats subordinated to a dominant male show a greater level of corticosteroids and a lower density of 5-HT_{1A} receptors in the hippocampus.[80] Another study found that stress in the adult rat diminishes signaling of 5-HT_{1A} receptor in the brain cortex, as long as the rodent be subject to stress at an early age.[75] In the hippocampus, 5-HT1A receptor stimulates proliferation,[81] thence its lower density would affect neurogenesis.

C) 5-HT2 receptors

5-HT_2 receptor subtypes that are more abundantly expressed in the brain are 5-HT_{2A} and 5-HT_{2C}. 5-HT_{2A} is expressed in the limbic system and PFC; however, evidence on the sense in which it modifies its density in MDD is controversial, since increase as well as decrease has been reported, as well as no change.[82-84] 5-HT_{2A} receptor is more closely related to schizophrenia (atypical antipsychotic clozapine is an antagonist of this receptor) or with altered states of consciousness such as hallucinations (LSD is an agonist of this receptor).

D) NA receptors

As we have mentioned, patients with MDD with no prescription or without a trace of antidepressant drugs at the time of their death, reveal a strong increase in the density of the α_2-adrenergic receptor at the LC.[44] In the DR, density of this receptor does not change, which rules out that its increase at the LC be a compensatory response to noradrenergic deficit. The greater expression of α_2-adrenergic receptor at the LC would be reducing the liberation of NA in the cor-

tex and the limbic system, because, at being located pre-synaptically, it inhibits the calcium channels which mediate the liberation of neurotransmitters.[85,86]

Treatment of MDD and action mechanism of antidepressant drugs

Antidepressant drugs are the first therapeutic choice,[87,88] however, their efficiency is limited since an average of one third of the patients do not respond to its effects.[7] Other clinical strategies include electroconvulsive therapy, vagus nerve stimulation, deep brain stimulation or transcranial magnetic stimulation. A discussion of non-pharmacologic treatment can be seen in other revisions.[30,35]

Gap between pharmacologic and therapeutic action of antidepressant drugs

Antidepressant drugs are classified as: i) selective recapture inhibitors of 5-HT (SSRIs: Fluoxetine, citalopram, etc.) or of NA (NSRIs: Desipramine, reboxetine); ii) of both monoamines (tricyclic: Imipramine, nortriptyline); iii) MAO-A inhibitors (tranylcypromine, selegiline, etc.) Notwithstanding, one of the enigmas of pharmacologic treatment is its time gap with therapeutic action (4 to 6 weeks) In this regard, it is propound that antidepressant drugs induce molecular adaptations of greater latency and duration which are more closely related to their therapeutic action. Advances have been achieved in this sense by chronically injecting the rodent (during 2 to 3 weeks) with therapeutic doses of the drug.

A) Effect over the $_{c}$AMP pathway

There is enough evidence showing that in MDD, the $_{c}$AMP/protein kinase A (PKA)pathway[89,90] is dysfunctional, just as cellular and synaptic plasticity processes dependent of $_{c}$AMP, such as long term post-tetanic potentiation, neurite growth, synaptogenesis or neurogenesis.[90] One of the molecular effects of antidepressant drugs is the stimulation of the $_{c}$AMP/PKA pathway in the brain cortex, hippocampus and amygdala.[91,92] Considering that among the proteins phosphorylated by PKA are the CREB transcription factor,[93,94] which stimulates BDNF expression and of its TrkB[49] receptor and MAP2 protein which stimulates the depolymerization of microtubules,[89,92] it is proposed that part of the therapeutic effect is due to the stimulation of the aforementioned cellular and synaptic plasticity processes.[90]

B) Effect on the expression of G proteins

Heterotrimeric G proteins ($G_{\alpha\beta\gamma}$)are the molecules that first were considered as possible molecular targets of antidepressant drugs. This is so because 5-HT and NA stimulate the receptors coupled to these information transducers, with the exception of 5-HT_3. Most of the studies published were made with western blot or ELISA techniques. Thus, in the hypothalamus, fluoxetine reduces immunoreactivity to $G_{\alpha i1}$ (38%) y $G_{\alpha z}$ (27%), while $G_{\alpha i3}$, $G_{\alpha i2}$ and $G_{\alpha o}$ remain unchanged.[95] In the neoestriate and LC, imipramine, clomipramine or desipramine reduce (20-40%) $G_{\alpha s}$ immunoreactivity.[96] Contrastingly, there is no effect on the expression of $G_{\alpha s}$, $G_{\alpha i1,2}$, $G_{\alpha q/11}$ in the cortex and/or the hippocampus, by desipramine,[97-98] amitriptyline[97,99] or fluoxetine.[100] There are practically no studies which assess the G_{α} transcripts. One of them uses northern blot technique and reports that amitriptyline and desipramine do not affect the expression of $G_{\alpha s}$ y $G_{\alpha i1/2}$ in the brain cortex.[99] Another study with conventional PCR shows that imipramine and fluoxetine do not have an effect on the expression of $G_{\alpha s}$ $G_{\alpha i1/2}$, $G_{\alpha o}$ and $G_{\alpha q}$ in the frontal cortex and the hippocampus, but there is a significant effect only in $G_{\alpha 12}$.[101]

For three decades it is known that antidepressant drugs provoke downregulation of β-adrenergic receptors[102] or of other receptors coupled to G_s (v. Gr. 5-HT_4, 5-HT_6).[91] Considering that G_s stimulates adenylyl cyclase (AC) for the synthesis of cAMP, adaptive response of receptors coupled to G_s opposes "downstream" stimulation of cAMP/PKA pathway induced by antidepressant drugs.[91,92] The answer to this paradox may be found in $G_{\alpha s}$, however, immunological evidence does not report changes in the expression of $G_{\alpha s}$.[97-100] Thence, using noradrenergic neurons of the superior cervical ganglion of the rat and PCR technique in real time, it was found that chronic treatment with imipramine increases and reduces significantly the expression of $G_{\alpha s}$ and $G_{\alpha z}$ transcripts respectively (figure 2; data still unpublished). The strong change in the expression of $G_{\alpha s}$ y $G_{\alpha z}$, if it occurred in CNS, might contribute the stimulant effect of antidepressant drugs over the cAMP pathway.

C) Effect over glycogen synthase kinase 3β(GSK-3)

Interest on pro-apoptosic protein GSK-3 as a target of antidepressant drugs arises from several findings: a) it is known that lithium, an ion with antimanic properties, is an inhibitor of this enzyme,[103] at preventing its interaction with β-arrestin phosphatase2A-Akt complex;[104] b) greater activity of GSK-3 is associated to alterations in neuron plasticity, structure and cell survival; c) *post-mortem* studies reveal an increase in the activity of GSK-3 on the PFC on patients with MDD[105] and d) activation of 5-HT_{1A} receptor results in phosphorylation and inhibition of GSK-3, in the hippocampus and the cortex of the mouse.[76] Although serotoninergic agonist d-fenfluramine or fluoxetine and imipramine inhibit GSK-3 in the PFC, hippocampus and estriate,[106] it is too early to arrive to the conclusion that inhibition of GSK-3 contributes to the therapeutic effect of antidepressant drugs because its phosphorylation reaches maximum 30 to 60 min. after the d-fenfluramine or fluoxetine injection, declining to base level in the following hours.[106]

Translation of the original version published in spanish in: Salud Mental 2016, Vol. 39 Issue No. 1.

D) Epigenetic effects

Recently, epigenetics has contributed with additional knowledge on pathogenesis of MDD and the action mechanism of antidepressant drugs.[107] In this perspective, chronic stress is granted a relevant role in the interaction of the environment with the gene load of an individual, as acetylation (activator of expression) and/or methylation (inhibitor of expression) of histones are the molecular mechanism by which stress modifies the pattern of gene expression.

Tsankova et al.[108] found that stress due to social rejection inhibits expression of BDNF in the rodent's hippocampus and increases methylation of histone H3-K27; whereas imipramine reverts the effect on BDNF at inhibiting the expression of deacetylase-5 (Hdac5) histone subsequently generating increase in the acetylation of H3 histone. Concurrent with the aforementioned findings, overexpression in the hippocampus of Hdac5 reverts the behavioral effect of imipramine, which fosters socialization behavior.[108] Another study shows that the infusion in the NAc of the Hdac5 inhibitor, MS-275, has antidepressive effects in the social rejection tests and FST.[109]

Epigenetic mechanism also contributes to stress vulnerability. For example, social stress produces in the NAc an increase in methylation of 1285 genes; it is noteworthy that imipramine reverts the degree of methylation with a gene profile similar to that found in mice that tolerate the presence of an aggressive male.[110] Uchida et al.[111] using two strains of mice, one vulnerable (BALB/c) and another one resistant (C57BL/6) to chronic physical stress, suggest that one of the genes whose level of expression correlates with vulnerability or tolerance to stress is that of glial cell line–derived neurotrophic factor (GDNF). For example, BALB/c strain responds to stress reducing both H3 acetylation and GDNF expression (these effects are reverted with imipramine); contrastingly, C57BL/6 responds in the opposite way to stress.[111] Behavioral tests show that the level of expression of GDNF is positively correlated with the test that assesses hedonic and social interaction behavior, but not with FST. Such findings suggest that some depressive behaviors in the human have their molecular basis on changes in the level of expression of specific genes and in defined areas of CNS.

E) Other molecular targets

Another protein whose expression is inhibited by imipramine is p21 protein.[112] This protein is an inhibitor of cycline dependent kinases and thence, it regulates cellular proliferation It is proposed that inhibition of expression of p21 is a part of the mechanism by which antidepressant drugs stimulate neurogenesis in the hippocampus.[112] However, it is not clear whether neurogenesis in the hippocampus is essential for the antidepressive effect seen in FST test. This is proposed because at inhibiting neurogenesis by X-ray irradiation of hippocampus, fluoxetine keeps exerting its antidepressive action in FST test.[113]

Another molecular target of antidepressant drugs is protein p11. This signaling molecule interacts with 5-HT1B and 5-HT4 receptors, and their expression is reduced in CCA and NAc of patients with MDD.[114] In the rodent, fluoxetine, imipramine and tranylcypromine, but not NSRI desipramine, stimulate the expression of p11 in the frontal cortex and hippocampus.[114,115] Besides, cytokines such as interferon-γ and TNF-α increase the expression of p11.[115] The crossover degree of signaling pathways stimulated by cytokines (effect in four hrs.) and antidepressant drugs (effect in 14 days) is unknown. Another revealing point is that non-steroidal anti-inflammatory drugs reduce efficacy of SSRIs to increase the expression of p11, and this antagonism extends to its antidepressive effect in FST test and MDD.[115] Contrastingly, NSAIDs increase the therapeutic efficacy of NSRI reboxetine.[116] As a whole, all these findings suggest a divergence in the molecular mechanism which underlies the therapeutic action of SSRIs and NSRIs.

CONCLUSION

Diverse mechanisms may cause deficit in serotoninergic transmission. In some cases, they have a genetic basis, as in polymorphism G1463A in the gene of enzyme hTPH2 or C(-1019)G in the gene of receptor 5-HT_{1A}; the former reduces the synthesis of 5-HT while the latter attenuates its liberation. From this perspective, it is suggested that MDD diagnosis includes a molecular genetics study to identify such polymorphisms. Besides, it can be inferred that carriers of polymorphism C(-1019)G shall respond better to the combination of SSRI with some antagonist of 5-HT_{1A}. The lower post-synaptic density of 5-HT_{1A} receptor is also a relevant pathophysiologic mechanism since its inhibitory action on neuronal excitability is consistent with hyper metabolism of Cg25 area and amygdala. Such metabolic changes may reveal the dysfunction of intra-cortical and limbic-cortical circuits (figure 2). In this context, it is suggested that the diagnosis be accompanied by a study with PET to confirm the lower cortical density of 5-HT_{1A}.

Pre-clinical studies show that stress reduces the expression of BDNF and GDNF of 5-HT_{1A} receptor, and provokes dendritic atrophy on the hippocampus. The effect on the expression of growth factors works through epigenetic mechanisms, either by increasing methylation or by reducing acetylation of H3 histone. Imipramine reverts such effects at inhibiting the expression of Hdac5 in the hippocampus and, consequently, increasing acetylation of H3 and the expression of BDNF. In the NAc, tricyclic reduces the expression of Hdac5, increasing the expression of GDNF. Latency of epigenetic effect of imipramine coincides with the latency of its therapeutic action. It is likely that the inhibitory effect of

stress on the expression of 5-HT_{1A} might be due to an epigenetic mechanism. In the hippocampus, 5-HT_{1A} receptor also has proliferative and neurogenic effects, although it is unknown whether BDNF intervenes in the action of receptor.

A common cellular effect of antidepressant drugs is the stimulation of AMPc/PKA pathway and the consequent stimulation of genes regulated by CREB transcription factor, including BDNF. We have proved here that imipramine increases the expression of $G_{\alpha s}$ (stimulator of AC) and reduces the expression of $G_{\alpha z}$ (inhibitor of AC) Such changes in the expression are in agreement with the stimulation of the cAMP pathway.

The antagonist clinical effect of NSAIDs over SSRIs, but not over NSRIs, suggests it is relevant to identify in a more precise way the etiology of MDD to define (SSRIs *vs*. NSRIs) the proper pharmacologic strategy.

Funding

This work was partially subsidized by the National Council of Science and Technology (donation 168734).

Conflict of interest

Authors hereby declare to have no conflict of interest whatsoever.

REFERENCES

1. Albert PR, Benkelfat C, Descarries L. The neurobiology of depression: revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms. Phil Trans R Soc B 2012;367:2378-2381.
2. Lee S, Jeong J, Kwak Y, Park SK. Depression research: where are we now? Molecular Brain 2010;3:1-10.
3. Hyman SE. A glimmer of light for neuropsychiatric disorders. Nature 2008;455:890-893.
4. Murray CJ, Lopez AD. Evidence-based health policy-lessons from the global burden of disease. Science 1996;274:740-743.
5. Belló M, Puentes-Rosas E, Medina-Mora ME, Lozano R. Prevalencia y diagnóstico de depresión en población adulta en México. Salud Pública Méx 2005; 47(supl1):s4-s11.
6. Benjet C, Borges G, Medina-Mora ME, Fleiz-Bautista C et al. La depresión con inicio temprano: prevalencia, curso natural y latencia para buscar tratamiento. Salud Pública Méx 2004;46:417-424.
7. Belmaker RH, Agam G. Major depressive disorder. N Engl J Med 2008;358:55-68.
8. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes of major depression. Neuropsychopharmacology 2004;29:1765-1781.
9. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature 2008;455:894-902.
10. Mill J, Petronis A. Molecular studies of major depressive disorder: the epigenetic perspective. Mol Psychiatry 2007;12:799-814.
11. Bissette G, Klimek V, Pan J, Stockmeier C et al. Elevated concentration of CRF in the locus coeruleus of depressed subjects. Neuropsychopharmacology 2003;28:1328-1335.
12. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: Does cortisol play a role? Biol Psychiatry 2004;55:1-9.
13. Wong M-L, Kling MA, Munson PJ, Listwak S et al. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: Relation to hypercortisolism and corticotropin-releasing hormone. Proc Natl Acad Sci USA 2000;97:325-330.
14. Holsboer F. The corticosteroid receptor hypothesis of depression. Neuropsychopharmacology 2000;23:477-501.
15. Campbell S, MacQueen G. The role of the hippocampus in the pathophysiology of major depression. J Psychiatry Neurosci 2004;29:417-426.
16. Drevest WC, Gadde KM, Krishnan RR. Neuroimaging studies of mood disorders. En: Charney DS, Nestler EJ (eds). Neurobiology of mental illness. Nueva York: Oxford University Press; 2004; pp.461-490.
17. MacMaster FP, Kusumakar V. Hippocampal volume in early onset depression. BMC Med 2004;2:1-6.
18. MacQueen GM, Campbell S, McEwen BS, Macdonald K et al. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci USA 2003;100:1387-1392.
19. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but no age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034-5043.
20. Campbell S, Marriott M, Nahmias C, MacQueen GM. Lower hippocampal volume in patients suffering from depression: A meta-analysis. Am J Psychiatry 2004;161:598-607.
21. Neumeister A, Wood S, Bonne O, Nugent AC et al. Reduced hippocampal volume in unmedicated, remitted patients with major depression versus control subjects. Biol Psychiatry 2005;57:935-937.
22. Shenton ME, Kikinis R, Jolesz FA, Pollak SD et al. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N Engl J Med 1992;327:604-612.
23. Maletic V, Robinson M, Oakes T, Iyengar S et a. Neurobiology of depression: an integrated view of key findings. Int J Clin Pract 2007;61:2030-2040.
24. Hajek T, Kozeny J, Kopecek M, Alda M et al. Reduced subgenual cingulate volumes in mood disorders: a meta-analysis. J Psychiatry Neurosci 2008;33:91-99.
25. Bremner JD, Vythilingam M, Vermetten E, Nazeer A et al. Reduced volume of orbitofrontal cortex in major depression. Biol Psychiatry 2002;51:273-279.
26. Öngür D, Drevest WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci USA 1998;95:13290-13295.
27. Carretié L, López-Martin S, Albert J. Papel de la corteza prefrontal ventromedial en la respuesta a eventos emocionalmente negativos. Rev Neurol 2010;50:245-252.
28. Fuster JM. The prefrontal cortex-an update: Time is of the essence. Neuron 2001;30:319-333.
29. Drevets WC, Price JL, Simpson JR Jr, Todd RD et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386:824-827.
30. Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nature Neurosci 2007;10:1116-1124.
31. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. Eur J Neuropharmacol 2002;12:527-544.
32. Goldapple K, Segal Z, Garson C, Lau M et al. Modulation of specific cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. Arch Gen Psychiatry 2004;61:34-41.
33. Kennedy SH, Konarski JZ, Segal ZV, Lau MA et al. Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. Am J Psychiatry 2007;164:778-788.

Translation of the original version published in spanish in: Salud Mental 2016, Vol. 39 Issue No. 1.

34. Wagner G, Koch K, Schachtzabel C, Sobanski T et al. Differential effects of serotoninergic and noradrenergic antidepressants on brain activity during a cognitive control task and neurofunctional prediction of treatment outcome in patients with depression. J Psychiatry Neurosci 2010;35:247-257.
35. Kuhn J, Gründler TOJ, Lenartz D, Stum V et al. Deep brain stimulation for psychiatric disorders. Dtsch Arztebl Int 2010;107:105-113.
36. Mayberg HS, Lozano AM, Voon V, McNeely HE et al. Deep brain stimulation for treatment-resistant depression. Neuron 2005;45:651-660.
37. Drevets CW, Videen TO, Price JL, Preskorn SH et al. A functional anatomical study of unipolar depression. J Neurosci 1992;12:3628-3641.
38. Bremner JD, Innis RB, Solomon RM, Staib LH et al. Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. Arch Gen Psychiatry 1997;54:364-374.
39. Meyer JH, Ginovart N, Boovariwala A, Sagrati S et al. Elevated monoamine oxidase A levels in the brain. An explanation for the monoamine imbalance of major depression. Arch Gen Psychiatry 2006;63:1209-1216.
40. Zhang X, Gainetdinov RR, Beaulieu J-M, Sotnikova TD et al. Loss-of-function mutation in tryptophan hydroxilase-2 identified in unipolar depression. Neuron 2005;45:11-16.
41. Ruhé HG, Mason NS, Schene AH. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Mol Psychiatry 2007;12:331-359.
42. Hasler G, Fromm S, Carlson PJ, Luckenbaugh DA et al. Neural response to cathecolamine depletion in unmedicated subjects with major depressive disorder in remission and healthy subjects. Arch Gen Psychiatry 2008;65:521-531.
43. Klimek V, Stockmeier C, Overholser J, Meltzer HY et al. Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. J Neurosci 1997;17:8451-8458.
44. Ordway GA, Schenk J, Stockmeier CA, May W et al. Elevated agonist binding to α_2-adrenoreceptors in the locus coeruleus in major depression. Biol Psychiatry 2003;53:315-323.
45. Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. Nature Neurosci 2007;10:1089-1093.
46. Dwivedi Y, Rizavi HS, Conley RR, Roberts RC et al. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 2003;60:804-815.
47. Chen B, Dowlatshahi D, MacQueen GM, Wang J-F et al. Increased hippocampal BDNF inmunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 2001;50:260-265.
48. Groves JO. Is it time to reassess the BDNF hypothesis of depression? Mol Psychiatry 2007;12:1079-1088.
49. Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 1995;15:7539-7547.
50. Saarelainen T, Hendolin P, Lucas G, Koponen E et al. Activation of the trkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressant-induced behavioral effects. J Neurosci 2003;23:349-357.
51. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ et al. Neurobiology of depression. Neuron 2002;34:13-25.
52. Norrholm SD, Quimet CC. Altered dendritic spine density in animal models of depression and in response to antidepressant treatment. Synapse 2001;42:151-163.
53. Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 2000;20:9104-9110.
54. Santarelli L, Saxe M, Gross C, Surget A et al. Requirement of hippocampal neurogenesis for the behavioral effect of antidepressants. Science 2003;301:805-809.
55. Reed AL, Happe HK, Petty F, Bylund DB. Juvenile rats in the force-swim test model the human response to antidepressants treatment for pediatric depression. Psychopharmacology 2008;197:433-441.
56. Shirayama Y, Chen AC-H, Nakagawa S, Russell DS et al. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 2002;22:3251-3261.
57. Lemonde S, Turecki G, Bakish D, Du L et al. Impaired repression at a 5-hidroxytriptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci 2003;23:8788-8799.
58. Hesselgrave N, Parsey RV. Imaging the serotonin 1A receptor using [^{11}C] WAY100635 in healthy controls and major depression. Phil Trans R Soc B 2013;368:20120004. http//dx.doi.org/10.1098/rstb.2012.0004.
59. Parsey RV, Olvet DM, Oquendo MA, Huang Y-Y et al. Higher 5-HT$_{1A}$ receptor binding potential during a major depressive episode predicts poor treatment response: preliminary data from a naturalistic study. Neuropsychopharmacology 2006;31:1745-1749.
60. Richardson-Jones JW, Craige CP, Guiard BP, Stephen A et al. 5-HT$_{1A}$ receptor levels determine vulnerability to stress and response to antidepressants. Neuron 2010;65:40-52.
61. Artigas F, Romero L, De Montigny C, Blier P. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT$_{1A}$ antagonists. Trends Neurosci 1996;19:378-383.
62. Celada P, Puig V, Amargós-Bosch M, Adell A et al. The therapeutic role of 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors in depression. J Psychiatry Neurosci 2004;29:252-265.
63. Castro ME, Diaz A, Del Olmo E, Pazos A. Chronic fluoxetine induces opposite changes in G protein coupling at pre and postsynaptic 5-HT$_{1A}$ receptors in rat brain. Neuropharmacology 2003;44:93-101.
64. Hensler JG. Differential regulation of 5-HT$_{1A}$ receptor-G protein interactions in brain following chronic antidepressant administration. Neuropsychopharmacology 2002;26:565-573.
65. Pejchal T, Foley MA, Kosofsky BE, Waeber C. Chronic fluoxetine treatment selectively uncouples raphe 5-HT$_{1A}$ receptors as measured by [^{35}S]-GTPγS autoradiography. Br J Pharmacol 2002;135:1115-1122.
66. Sargent PA, Kjaer KH, Bench CJ, Rabiner EA et al. Brain serotonin1A receptor binding measured by positron emission tomography with [^{11}C] WAY-100635. Arch Gen Psychiatry 2000;57:174-180.
67. Bhagwagar Z, Rabiner EA, Sargent PA, Grasby PM et al. Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [^{11}C] WAY-100635. Mol Psychiatry 2004;9:386-392.
68. Drevets WC, Frank E, Price JC, Kupfer DJ et al. PET imaging of serotonin 1A receptor binding in depression. Biol Psychiatry 1999;46:1375-1387.
69. Savitz J, Lucki I, Drevets WC. 5-HT$_{1A}$ receptor function in major depressive disorder. Prog Neurobiol 2009;88:17-31.
70. Lanzenberger RR, Mitterhauser M, Spindelegger C, Wadsak W et al. Reduced serotonin-1A receptor binding in social anxiety disorder. Biol Psychiatry 2007;61:1081-1089.
71. Neumeister A, Bain E, Nugent AC, Carson RE et al. Reduced serotonin type 1A receptor binding in panic disorder. J Neurosci 2004;24:589-591.
72. Azmitia EC, Gannon PJ, Kheck NM, Whitaker-Azmitia PM. Cellular localization of the 5-HT$_{1A}$ receptor in primate brain neurons and glial cells. Neuropsychopharmacology 1996;14:35-46.
73. Puig MV, Celada P, Artigas F. Control serotoninérgico de la corteza prefrontal. Rev Neurol 2004;39:539-547.
74. Riad M, Garcia S, Watkins KC, Jodoin N et al. Somatodendritic localization of 5-HT$_{1A}$ and preterminal axonal localization of 5-HT$_{1B}$ serotonin receptors in adult rat brain. J Comp Neurol 2000;417:181-194.

75. Goodfellow NM, Benekareddy M, Vaidya VA, Lambe EK. Layer II/III of the prefrontal cortex: Inhibition by the serotonin 5-HT_{1A} receptor in development and stress. J Neurosci 2009;29:10094-10103.
76. Talbot JN, Jutkiewicz EM, Graves SM, Clemans CF et al. RGS inhibition at $G\acute{\alpha}_{i2}$ selectively potentiates 5-HT_{1A}-mediated antidepressant effects. Proc Natl Acad Sci USA 2010;107:11086-11091.
77. Stewart A, Maity B, Wunsch AM, Meng F et al. Regulator of G-protein signaling 6 (RGS6) promotes anxiety and depression by attenuating serotonin mediated activation of the 5-HT_{1A} receptor-adenylyl cyclase axis. FASEB J 2014;28:1735-1744.
78. Chalmers DT, Kwak SP, Mansour A, Akil H et al. Corticosteroids regulate brain hippocampal 5-HT_{1A} receptor mRNA expression. J Neurosci 1993;13:914-923.
79. Checkley S. The neuroendocrinology of depression and chronic stress. Br Med Bull 1996;52:597-617.
80. McKittrick CR, Blanchard DC, Blanchard RJ, McEwen BS et al. Serotonin receptor binding in a colony model of chronic social stress. Biol Psychiatry 1995;37:383-393.
81. Banasr M, Hery M, Printemps R, Daszuta A. Serotonin-induces increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology 2004;29:450-460.
82. Meyer JH, Kapur S, Houle S, DaSilva J et al. Prefrontal cortex 5-HT_2 receptors in depression: An [^{18}F] setoperone PET imaging study. Am J Psychiatry 1999;156:1029-1034.
83. Pandey GN, Dwivedy Y, Rizavi HS, Ren X et al. et al. Higher expression of serotonin 5-HT_{2A} receptors in the postmortem brains of teenage suicide victims. Am J Psychiatry 2002;159:419-429.
84. Yatham LN, Liddle PF, Shiah I-S, Scarrow G et al. Brain serotononin$_2$ receptors in major depression. Arch Gen Psychiatry 2000;57:850-858.
85. Stephens GJ, Mochida S. G protein βγ subunits mediate presynaptic inhibition of transmitter release from rat superior cervical ganglion neurones in culture. J Physiol 2005;563:765-776.
86. Jewell ML, Currie KPM. Control of Ca_V2 calcium channels and neurosecretion by heterotrimeric G protein coupled receptors. En: Stephens G, Mochida S (eds.). Modulation of presynaptic calcium channels. New York: Springer; 2013; p.101-130.
87. Mathew SJ, Manji HK, Charney DS. Novel drugs and therapeutic targets for severe mood disorders. Neuropsychopharmacology 2008;33:2080-2092.
88. Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. CMAJ 2009;180:305-313.
89. Dwivedi Y, Pandey GN. Adenylyl cyclase-cyclicAMP signaling in mood disorders: Role of the crucial phosphorylating enzyme protein kinase A. Neuropsychiatric Disease Treatment 2008;4:161-176.
90. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: A convergence of mechanisms. Neuropsychopharmacology 2008;33:88-109.
91. Nestler EJ, Hyman SE, Malenka RC. Molecular neuropharmacology: A Foundation for Clinical Neuroscience. Segunda ed. New York: McGraw-Hill; 2009.
92. Tardito D, Perez J, Tiraboschi E, Musazzi L et al. Signaling pathways regulating gene expression, neuroplasticity, and neurotrophic mechanisms in the action of antidepressants: A critical overview. Pharmacol Rev 2006;58:115-134.
93. Nair A, Vaidya VA. Cyclic AMP response element binding protein and brain-derived neurotrophic factor: molecules that modulate our mood? J Biosci 2006;31:423-434.
94. Thome J, Sakai N, Shin K-H, Steffen C et al. cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. J Neurosci 2000;20:4030-4036.
95. Raap DK, Evans S, Garcia F, Li Q et al. Daily injections of fluoxetine induce dose-dependent desensitization of hypothalamic 5-HT_{1A} receptors: Reductions in neuroendocrine responses to 8-OH-DPAT and in levels of Gz and Gi proteins. J Pharmacol Exp Ther 1999;288:98-106.
96. Lesch KP, Aulakh CS, Tolliver TJ, Hill JL et al. Regulation of G proteins by chronic antidepressant drug treatment in rat brain: tricyclics but not clorgyline increase $G_{o\alpha}$ subunits. Eur J Pharmacol 1991;207:361-364.
97. Chen J, Rasenick MM. Chronic antidepressant treatment facilitates G protein activation of adenylyl cyclase without altering G protein content. J Phamacol Exp Ther 1995;275:509-517.
98. Dwivedi Y, Pandey GN. Effect of subchronic administration of antidepressants and anxiolytics on levels of α subunits of G proteins in the rat brain. J Neural Transm 1997;104:747-760.
99. Emamghoreishi M, Warsh JJ, Sibony D, Li PP. Lack of effect of chronic antidepressant treatment on Gs and Gi α-subunit protein and mRNA levels in the rat cerebral cortex. Neuropsychopharmacology 1996;15:281-287.
100. Li Q, Muma NA, Battaglia G, Van de Kar LD. Fluoxetine gradually increases [^{125}I]DOI-labelled 5-$HT_{2A/2C}$ receptors in the hypothalamus without changing the levels of G_q - and G11-proteins. Brain Res 1997;775:225-228.
101. Lesch KP, Manji HK. Signal-transducing G proteins and antidepressant drugs: evidence for modulation of α subunit gene expression in rat brain. Biol Psychiatry 1992;32:549-579.
102. Vetulani J, Stawarz RJ, Dingell JV, Sulser F. A possible common mechanism of action of antidepressant treatments: reduction in the sensitivity of the noradrenergic cyclic AMP generating system in the rat limbic forebrain. Naunyn-Schmiedeberg's Arch Pharmacol 1976;293:109-114.
103. Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. Proc Natl Acad Sci USA 1996;93:8455-8459.
104. Beaulieu J-M, Marion S, Rodriguiz RM, Medevev IO et al. A β–arresting signaling complex mediates lithium action on behavior. Cell 2008;132:125-136.
105. Karege F, Perroud N, Burkhardt S, Schwald M et al. Alteration in kinase activity but not in protein levels of protein kinase B and glycogen synthase kinase-3β in ventral prefrontal cortex of depressed suicide victims. Biol Psychiatry 2007;61:240-245.
106. Li X, Zhu W, Roh M-S, Friedman AB et al. In vivo regulation of glycogen synthase kinase-3β (GSK3β) by serotoninergic activity in mouse brain. Neuropsychopharmacology 2004;29:1426-1431.
107. Vialou V, Feng J, Robison AJ, Nestler EJ. Epigenetic mechanisms of depression and antidepressant action. Annu Rev Pharmacol Toxicol 2013;53:59-87.
108. Tsankova NM, Berton O, Renthal W, Kumar A et al. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. Nature Neurosci 2006;9:519-525.
109. Covington HE III, Maze I, LaPlant QC, Vialou VF et al. Antidepressant actions of histone deacetylase inhibitors. J Neurosci 2009;29:11451-11460.
110. Wilkinson MB, Xiao G, Kumar A, LaPlant Q, Renthal W et al. Imipramine treatment and resiliency exhibit similar chromatin regulation in the mouse nucleus accumbens in depression models. J Neurosci 2009;29:7820-7832.
111. Uchida S, Hara K, Kobayashi A, Otsuki K et al. Epigenetic status of Gdnf in ventral striatum determines susceptibility and adaptation to daily stressful events. Neuron 2011;69:359-372.
112. Pechnick RN, Zonis S, Wawrowsky K, Pourmorady J et al. p21Cip1 restricts neuronal proliferation in the subgranular zone of the dentate gyrus of the hippocampus. Proc Natl Acad Sci USA 2008;105:1358-1363.

Translation of the original version published in spanish in: Salud Mental 2016, Vol. 39 Issue No. 1.

113. David DJ, Samuels BA, Rainer Q, Wang J-W et al. Neurogenesis-dependent and –independent effects of fluoxetine in an animal model of anxiety/depression. Neuron 2009;62:479-493.

114. Svenningsson P, Cherguri K, Rachleff I, Flajolet M et al. Alterations in 5-HT_{1B} receptor function by p11 in depression-like states. Science 2006;311:77-80.

115. Warner-Schmidt JL, Vanover KE, Chen EY, Marshall JJ et al. Antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) are attenuated by antiinflamatory drugs in mice and humans. Proc Natl Acad Sci USA 2011;108:9262-9267.

116. Müller N, Schwarz MJ, Dehning S, Douhe A et al. The cyclooxygenase-2 inhibitor celecoxib has therapeutic effects in major depression: results of a double-blind, randomized, placebo controlled, add-on pilot study to reboxetine. Mol Psychiatry 2006;11:680-684.

Translation of the original version published in spanish in:
Salud Mental 2016, Vol. 39 Issue No. 1.