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The Neurobiology of Bipolar Disorder and Medication Used to Treat It

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ABSTRACT

Mental health has been a growing area of interest in recent years, correlating with increased awareness about conditions such as generalized anxiety, clinical depression, and bipolar disorder. This is thanks to the improvement in the quality of treatment for psychiatric conditions, social media contributing to a widespread awareness, and recent governmental campaigns. However, because the topic of mental health is relatively new, much is unknown about the etiology and science behind these conditions, in part due to many of these conditions mostly being the result of environmental pressures, and rarely have a genetic basis. As a result of this, recent research, including this paper, primarily aims to examine a number of receptors, polypeptides, and erroneous steps that stem from intracellular communication dysfunction. This paper primarily focuses on the signaling cascades that are most frequent in bipolar disorder, as well as the medication that controls them and potential adverse side effects. Through examination of primary sources and various experiments conducted in tandem with their respective drugs, this paper primarily aims to highlight the shifting landscape in bipolar disorder treatment, while also de-mystifying the etiology behind it. It also aims to highlight previously unknown roles of various genes and receptors important to the etiology of bipolar disorder.

Introduction

Bipolar disorder is a mood disorder characterized by violent mood swings. Diagnosis usually requires repeated episodes of manic (lasting about 2-3 days) and depressive (usually 2 weeks to a month), though the duration of these episodes can vary from person to person. Bipolar disorder is then separated into various classifications based on the experienced severity of the condition (Mayo Clinic). Bipolar 1's manic episodes, for example, last for a week and can lead to severe hospitalization, compared to hypomania's shorter and less severe manic episodes. However, the underlying factor that remains the same in all the classifications is the prolonged period of depression, which is often treated with antidepressants. Besides its symptoms, however, not much is actually known about the neurobiology and etiology behind the disorder. Recently, research has been beginning to suggest that various forms of neurological communication systems, such as signaling pathways, may be the root cause of the issue at hand. Said pathways include the Wnt, PKA, PKC, and cholinergic receptor pathways.

According to the CDC's 2019 report, 2.8% of the world's global population suffers from bipolar disorder, and often have trouble finding effective widespread treatment, in part due to the exacerbation of stigma surrounding various mental health disorders, and an all-around lack of understanding of bipolar disorder's underlying mechanisms. Medications currently on the market used to treat the condition are often in the form of antidepressants, a medication that targets the PKA receptor pathway, but the usage of such has been subject to controversy in psychiatric spaces, because of its side effects that can exacerbate the extent of the disorder. This indicates that at the very least, certain receptors may contribute to the severity of bipolar disorder. Additionally, various outdated treatment methods are still being used in psychiatric and therapeutic settings, such as CBT

(cognitive behavioral therapy), which has received scathing criticism from the autism community, due to its dehumanization of the patient and Pavlovian-esque conditioning (NAMI).

In the United States, reflecting the CDC's global statistics, bipolar disorder also has had a 2.8% prevalence in 2023, and a 4.4% prevalence within one's lifetime, according to the National Institute of Mental Health. Lithium has been the main medication administered for bipolar disorder in the United States, and is frequently used to treat extreme or mild cases of mania. Lithium has been shown to promote downregulation of insulin in its regulatory pathway, of which the Wnt canonical pathway receptor, GSK-3, is a part of, when the drug is administered (Campbell et al, 2022). Lithium induces regulatory effects on mood and has been recently used in Alzheimer's disease treatment, which has been tied to the Wnt pathway because of its neurodegenerative tendencies, suggesting that the usage of lithium targets various receptors and proteins in the Wnt pathway, and can potentially be expropriated for other uses.

Understanding how these specific signaling pathways contribute to bipolar disorder, and how they can be manipulated, is the key to understanding this disorder, and could possibly lead to breakthroughs in pharmacological contexts. As seen through the uses of medications such as lithium, which has been shown to impact the Wnt signaling pathway, and the aversion to antidepressants, which target the PKC pathway negatively, if signaling pathway abnormalities are detected more thoroughly, medicines to target specific receptors can be engineered.

Methodology

The primary goal in the research presented is to analyze neurological causes of bipolar disorder, and detail its etiology aside from its common hypothesis. This hypothesis of onset bipolar disorder is generally a model of external factors that activate certain underlying genes that have been passed down. This paper essentially functions as a literature review that focuses on interactions between various receptors and transmitters. First, a quantitative data analysis was conducted on many of the experiments shown in this paper, to ensure statistical significance by using an alpha value of 0.05. Next, a qualitative review of the PKA pathway's main function and role in bipolar disorder was done. However, after observing that there was controversy for the particular medication and its derivatives used for treatment, investigation into its controversy, side effects, and other uses was conducted. The Wnt pathway was studied next, upon finding two receptors that played a heavy role in popular bipolar medication such as Lithium and valproate. Connections were also made to various other neurological conditions that originate from the Wnt pathway such as Alzheimer's Disease and Parkinson's Disease. The PKC signaling pathway was researched next, and was found to have much in common with the cholinergic pathway, so discussions of acetylcholine were moved to the cholinergic pathway section, while the PKC pathway section mainly focuses on dopamine and serotonin receptors.

Bipolar Disorder Pathology

Bipolar disorder, formerly known as manic depression, is a mental health condition characterized by episodes of mania and depression, followed by occasional periods of euthymia (feeling of well-being), depending on the severity of the condition experienced. Depressive mood swings cause symptoms frequently seen in clinical depression/major depressive disorder. Mania, on the other hand, is characterized by symptoms similar to anxiety, and can lead to impaired judgment and decision-making skills. Specifically, periods of mania can induce side effects similar to those of schizophrenia, such as auditory and visual hallucinations, racing thoughts, decreased lack of attentiveness, and a tendency for the patient to be unhindered by their body's limits. Recuperating from each mood swing is an arduous task for many, requiring psychiatric services and medicine in order to ensure a good quality of life (Mayo Clinic). Currently, medicine on the market for bipolar disorder only

targets one mood swing at a time, such as antidepressants. Agents like lithium carbonate on the other hand, are able to cause "numbing" effects on emotion and cognitive dysfunction, thereby affecting both states of mind. However, this comes with the adverse result of the patient's emotional response being hindered, which can cause some patients to forgo medication entirely.

Based on the frequency of these episodes, and how long they last, the diagnosis can be further broken down into 4 main categories: bipolar type 1, bipolar type 2, cyclothymia, and rapid cycling. Bipolar type 1 is primarily characterized by extreme mania that can lead to hospitalization without proper intervention or supervision, and less pronounced/less cycling to depressive mood swings. Bipolar type 2 is primarily characterized by prominent depressive mood swings, and hypomania. Cyclothymia occurs when the patient experiences multiple shifts in mood within a certain timeframe (i.e; month, year), and does not display any frequency towards one state of mood. Rapid cycling's mood swings, while similar to cyclothymia, happen at a much more frequent pace than that of cyclothymia, and can often be brought about as an adverse side effect to trauma, medication, and other external factors. There are additional features used to describe these mood swings, in the case when at least three symptoms from the opposing moodswing are present in another moodswing. For example, a patient experiencing a depressive episode with the presence of racing thoughts, auditory hallucinations, and irritability would have a classification of depression with mixed features.

In the clinical setting, diagnosis of bipolar disorder requires the patient to have experienced at least one episode of mania, even if a subsequent episode of depression hasn't yet been experienced. This diagnosis criterion has led many to speculate about the nature of a "unipolar mania," however, no clinical evidence has been found to prove this condition a legitimate one. Additionally, despite treatment, life expectancy for patients with bipolar disorder is lower than the average, due to individuals with bipolar disorder exhibiting a proclivity to harmful behavior and often coming from backgrounds marked by unrest in the domestic setting, which is also another contributing factor to the tendency of bipolar disorder.

PKA Pathway and Antidepressants

The PKA signaling pathway is perhaps the signaling pathway most heavily involved in mood dysregulation in bipolar disorder. PKA, or protein kinase A, is part of the larger cyclic AMP pathway that controls apoptosis and cell growth. PKA activates once cAMP binds to its active site, and promotes phosphorylation throughout the pathway. The role this process plays in the CNS (Central Nervous System) is integral, contributing to neurogenesis and memory (Gao et al., 2022).

This mentioned phosphorylation has been targeted by various forms of antidepressants, eliciting therapeutic effects in most depression patients. Phosphorylation of the GluR1 receptor protein at PKA site P845, facilitates the protein being transported to the cell membrane and forming a ligand-gated ion channel. Since it is observed that the efficiency of this process only increases when antidepressants are administered to the patient, it is reasonable to assume that the dysfunction of this process contributes to less therapeutic effects in those who have this dysfunction (Du et al., 2014).

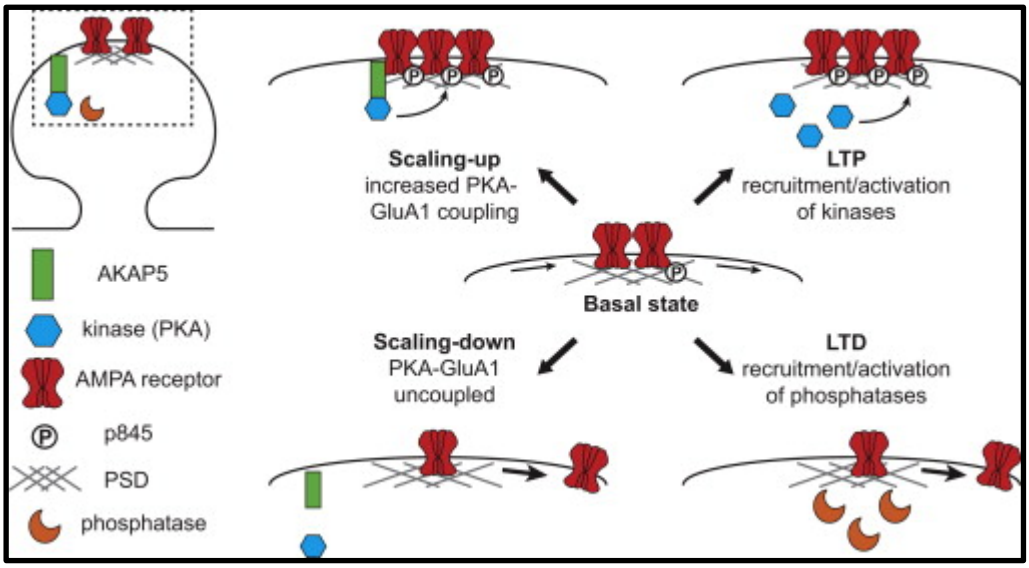

Figure 1. Diagram of phosphorylation of GluR1 at P485. The results of increasing and decreasing activity are shown (Semantic Scholar, 2014).

Antidepressants, as mentioned in the introduction, have recently been contested as a valid treatment for bipolar disorder. Many psychopharmacologists had previously prescribed antidepressants for depressive mood swings in the past, given the similarity in symptoms of clinical depression and depressive mood swings. However, this has been shown to do more harm than good, due to antidepressants' tendency to induce harmful side effects, such as the "triggering" of manic episodes and rapid cycling (Cascade et al., 2007).

Because of the uptick of these side effects in bipolar patients, many physicians have turned to other medications that impact the PKA signaling pathway to induce the same effects, such as AC agonists, cAMP analogs and supplements, and PDEs inhibitors (Gao et al., 2022). These alternative treatments, however, completely disregard the role antidepressants (and medications derivative of it) play in the CNS. Because of excessive neurogenesis, signaling misfires are bound to happen, which can result in the worsening of the disorder and could even lead to neuronal death in the worst circumstances. As such, these drugs that target the PKA pathway ultimately cause more harm in the patients they're prescribed to than good, which is why there should be a shift away from the prescription of these drugs to bipolar patients in the future.

Wnt Pathway/GSK-3 and Lithium

The Wnt pathway is well documented in the realm of neurodegenerative diseases such as Parkinson's Disease and Alzheimer's Disease, but has been seldom discussed in psychiatric contexts. This pathway promotes neurogenesis and cell survival, and dysfunction of such has been shown to harm the cell cycle and cellular communication. The Wnt pathway has been shown to play a major role in manic episodes, which involve increased excitement, irritability, or agitation. GSK3β regularly functions as a serine/threonine kinase and plays an important part in regulating the cell cycle. Within the Wnt pathway, glycogen synthase kinase 3β (an isozyme of GSK-3) is a frequent target of common mood stabilizers such as lithium (lithium carbonate) and valproate, whose inhibition has been shown to induce mood-stabilizing effects, indicating that GSK3β has some degree of control over mood regulation and expression the CNS (Iwahashi et al., 2014).

In recent studies, the tendency for manic episodes has been statistically proven to be linked to genetics, such as the GSK3B gene (codes for GSK3β), and the PPARD gene (Zandi et al., 2008). The PPARD gene was

investigated in a study by Peter P. Zandi and others, in which researchers genotyped 34 preliminary genes in over 1,000 participants who have a family history of bipolar disorder. Among the 34 genes, PPARD–a gene that represses transcription and aids nuclear receptor signaling (GeneCards)– had the most statistically significant result, with an alpha value of 0.05. The GSK3B gene has similarly been tested among a Japanese population, with a similar experimental set up to identify specific haplotypes that respond well to lithium carbonate (Iwahashi et al., 2014).

These linkages are well established with lithium, but are tentative with valproate, despite inducing similar effects.

Additionally, recent studies have also pinpointed another gene that interacts with GSK3B, and contributes to the expression of bipolar disorder, known as AKAP11, which codes for the AKAP-11 protein. While AKAP11 doesn't contribute much to the etiology of bipolar disorder and doesn't belong to the Wnt pathway (it belongs to the PKA/cAMP pathway), what's important about the gene is its interactions with GSK3B, and its frequency for mutation. According to the Broad Institute, in 2022, the Stanley Institute Of Research compared 14,000 of the exon sequences in people who had bipolar disorder to 14,000 exomes of those who didn't, and found that those with bipolar disorder are more likely to have variants of AKAP11 that are dysfunctional and faulty than those who didn't have bipolar. This study was then extended to comparing the exomes of 24,000 people who had schizophrenia (during SCHEMA's study) vs. bipolar disorder, and found that there were several rare mutations in the AKAP11 gene that increased the risk for the disease by 10-20%.

Lithium is currently the most commonly prescribed drug for bipolar disorder in recent times, as well as valproate, because of the precision of the drug to the gene and its surrounding environment, and their lack/very minimal adverse side effects. To put the above into perspective, genetics plays an important role in the rarity of this disorder, and by highlighting specific genes, there can be talks of gene therapy and CRISPR in order to modify the sensitivity of PPARD and AKAP11, so that bipolar disorder is less phenotypically expressed.

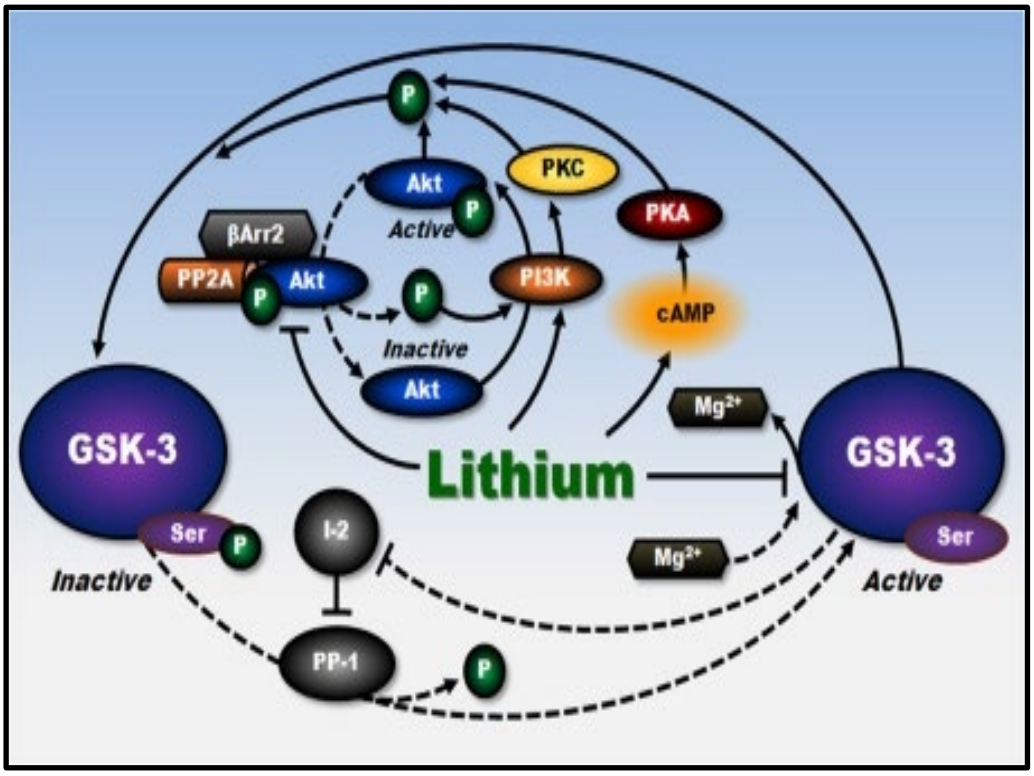

Figure 2. Diagram of the effects on Lithium on GSK3β, and what processes it controls/inhibits (Research Gate, 2011).

PKC Signaling Pathway, Serotonin and Dopamine

The role of the PKC signaling pathway has also been targeted in medications like valproate and Lithium. The PKC signaling pathway controls other proteins and enzymes via the phosphorylation of hydroxyl ground or serine and threonine. In doing so, this signaling cascade regulates synaptic plasticity, learning, and memory. The pathway normally forms as a result of communication between cells via neurotransmitters, which include acetylcholine's M1, M3 and M5 receptors and serotonin 5HT2A receptors (Du et al., 2004).

Serotonin is a neurotransmitter that primarily regulates mood, sleep, digestion, and sexual desire. Abnormal levels of such can result in various sleep or psychological disorders (Cleveland Clinic). These psychological disorders can have symptoms similar to that of bipolar disorder, such as depression, anxiety, and mania, all of which are present in various stages of the condition. Through manipulation of the 5-HT2A receptors with specialized probes, researchers were able to observe connections to pain sensitivity, locomotor activity, aggression, and sexual behavior, and these respective behaviors being exacerbated when 5-HT2A receptor levels are depleted. The patterns noted in these behaviors are strikingly similar to those observed in both manic and depressive stages of bipolar disorder (Mahmood et al., 2001). Typical bipolar symptoms similar to the aforementioned behaviors include propensity to risky behavior, aggression, anxiety, and dissociation.

Thus, bipolar disorder suggests a deficiency in the 5-HT2A receptor, and other receptors in the 5-HT family. Serotonin levels are normally manipulated with common mood stabilizers, and currently don't have a medical application for the transmitter itself. That being said, because manipulation of 5-HT2A has provided similar results and behavior to that of bipolar disorder, there is a possibility of 5-HT2A being administered as a drug similar to common uses of dopamine-based medication. Direct agonist agents may be preferable to increase frequency of signaling between synapses.

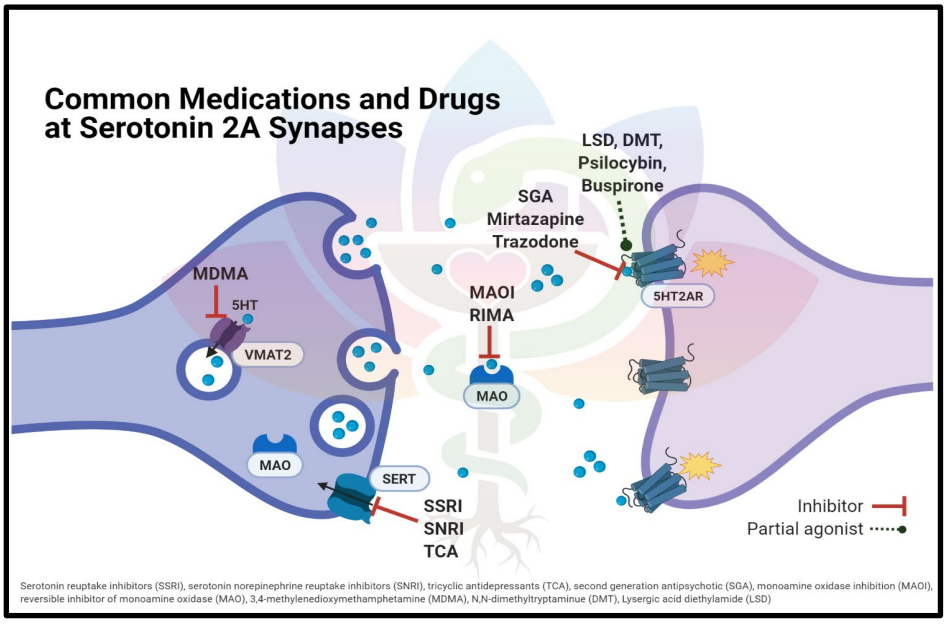

Figure 3. Diagram of 5HT-2A communication and inhibit/agonist interactions (Spirit Pharmacist, 2021)

Additionally, the PKCβ (isozyme of PKC) has also been found to be able to regulate the D2-Like dopamine autoreceptor (regulates dopamine) through various methods, such as blocking potassium channels, activating the pathway with phorbol esters (class of compounds known for their tumor promoting properties), and electrical stimulation of brain slices (Goel et al., 2007). The D2-Like dopamine receptor mainly controls extracellular dopamine levels and signaling pertaining to dopamine, and reduction of such levels are the primary function of antipsychotics (Luderman et al., 2015).

Currently, treatment for bipolar disorder utilizing dopamine itself is becoming a topic of interest for psychopharmacologists. It has previously been used as treatment for various aforementioned neurodegenerative diseases, and given that bipolar disorder has been linked to similar receptors in the Wnt pathway, many have thought to extrapolate the treatment. These treatments help to stimulate dopamine transmission and alleviate symptoms of depressive mood swings (these agents are currently being tested on manic mood swings as well). Potential treatments include stimulants, stimulant-like agents, dopamine agonists, and partial dopamine agonists (NeuRA).

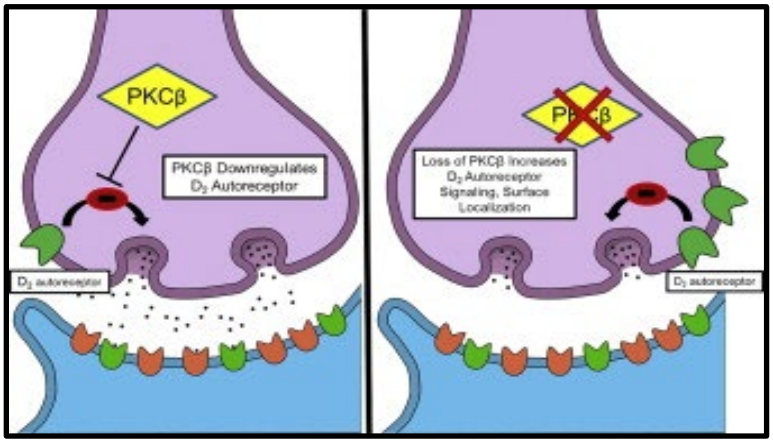

Figure 4. A comparison of the presence and absence of PKCβ on downregulation of the D2-Like dopamine autoreceptor (Science Direct, 2015).

The Cholinergic Pathway and Acetylcholine

Erroneous steps in the cholinergic pathway are especially crucial in terms of the visibility of these symptoms, especially since this pathway in particular can be vital to how an individual processes various emotions. The cholinergic pathway is an important branch of the autonomic nervous system (ANS) that plays an important role in memory, digestion, heartbeat control, mood, and movement. Specifically, acetylcholine is a neurotransmitter that plays similar roles to that of the overall cholinergic pathway, and deficiencies or surpluses in the amount of the receptor have been linked to Alzheimer's disease. Acetylcholine is common to the PNS (parasympathetic nervous system) mainly binds to both nicotinic and muscarinic receptors upon being fired off, whose interactions are subject to manipulation by pharmaceutical drugs. It is also the primary signaling molecule that has been implicated in a multitude of mental health disorders, such as depression, ADHD, and of course, bipolar disorder (Mental Health America).

The correlation between acetylcholine concentration and depressive states of mood have long been a subject of study with several researchers hypothesizing that higher levels of acetylcholine tend to induce depressive symptoms. Notably, Stephanie C. Dulawa and others have reported a correlation between depressive patients having high amounts of acetylcholine derivative molecules, as well as a negative correlation between acetylcholine activity in red blood cells, and the number of past suicide attempts. Additionally, SPECT imaging

studies have also revealed that acetylcholine levels are statistically higher in patients who have bipolar disorder (Saricicek et al., 2012).

Cholinergic agonists are primarily used to treat imbalances and irregularities of acetylcholine and various other neurotransmitters. Of these drugs, there exist two categories, direct and indirect acting varieties. Direct agonists directly bind to the muscarinic receptor. Drugs in this category include acetylcholine and muscarine itself, along with several other neurotransmitters, such as methacholine and pilocarpine. Indirect agents often increase the availability and the concentration of acetylcholine near cholinergic receptors. These drugs also have two categories, which include reversible (physostigmine, neostigmine) and irreversible agents (sarin, soman). These agents have the effect of regulating amounts of extracellular acetylcholine so as to give users a sense of euthymia, or at the very least, a hypodepressive state.

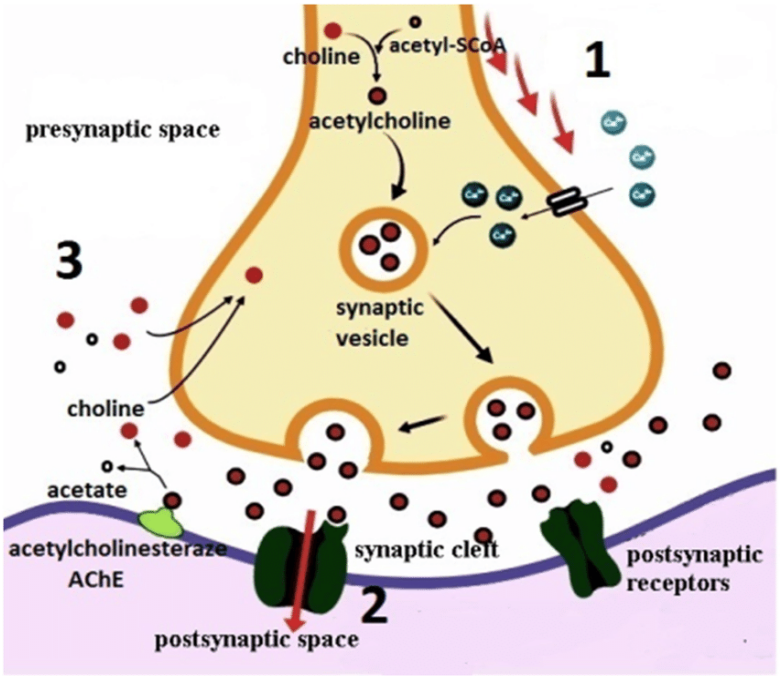

Figure 5. Diagram of acetylcholine pathway, and the normal flow of acetylcholine signaling (ResearchGate, 2019).

Conclusion

On the global scale, many countries lack proper research or high regard for mental health. Many people, even in the U.S., often silently suffer from similar conditions like these because of the social stigma that has come from the symptoms of these mental health disorders, and because of increasing amounts of misinformation and colloquial expressions that obfuscate its actual meaning. In conducting this research, the primary goal was to combat this tide of misinformation and increase awareness of the importance of signaling pathways and neurotransmission to bipolar disorder. Exploring the various particle-level interactions in cell signaling and neurotransmission are what will eventually help us to understand the neurobiology and etiology of bipolar disorder. While trauma does play a role in the phenotypic expression of bipolar disorder, it is ultimately the genetic and transmissive factors that enable this disorder to have the impact that it does, given its rarity. Detailing these cascades is ultimately helpful in discussion or testing of new treatments for bipolar disorder, and what families

of agonists and antagonists one should stay away from in diagnosis. This also helps to clarify the impact of medications on certain receptors, proteins, and genes.

While this study has delved into both common and relatively underexplored cellular processes and signaling cascades, there are plenty more that exist. Many parts of these signaling cascades often have parts that overlap with other conditions, or even regulate the same core processes, such as the acetylcholine pathway, which exists within that of the PKC. As a result, many smaller pathways that exist alongside these bigger ones are easily overlooked. However, care was put into this paper to highlight smaller pathways, and strengthen connections between their often overlooked aspects, in order to find novel solutions and up and coming research/treatment for these processes. More research should be done on these overlooked aspects in the future, in order to fully de-mystify the neurobiology of bipolar disorder.

Limitations

As this paper was a secondary literature review, quantitative and qualitative data was analyzed in order to report on the figures and findings shown throughout the body of this paper. The author of this paper had made sure to consult sources and experiments conducted in various parts of the world, in order to remain impartial on the matter, given that bipolar disorder and other conditions have disparaging diagnosis rates and qualities of life. While exact methodology (sample size, blocking) and results of the experiments were researched, exact procedure and time-frame were unavailable for some, which may affect the validity of the data presented. Additionally, some of the treatments shown in this paper are relatively new for its application to bipolar disorder, and some are currently undergoing testing. As a result, side effects have not been explored yet for these treatments, and as such, are not listed here. For these treatments, it is also unclear whether dosage would be similar to its other applications, such as the widespread use of cholinergic drugs for circulation and heart problems, rather than its use for bipolar disorder. While the author did have pre-existing knowledge of the condition (specifically pertaining to bipolar 1), their knowledge of the etiology behind the disorder was mostly unknown. Lastly, the author of this paper did not suffer from the condition themselves, so there was a lack of first-hand experience when writing this paper, which may reflect in the description of the pathology of the condition. Some evidence also may be affected by second-hand accounts that the author has been subject to. In summation, despite these limitations on the output of the study, great care was taken to circumvent some of these circumstances.

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