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Review Article

Exploring the Potential of Preventing Human Disease by Genetically Altering the Excitability of the Neurological System

Michael Raymond Binder

Adult and Adolescent Psychiatry, 5 Revere Drive, Suite 200, Northbrook, USA

Email address:

mbinder@drmichaelbinder.com

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Abstract: Although most human diseases are believed to be the consequence of chronic stress superimposed upon various risk genes, efforts to reduce stress are increasingly being thwarted by the ever-increasing pace of human society. However, there is mounting evidence that biopsychosocial stress is primarily dictated endogenously rather than environmentally. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis of psychiatric disorders, pathological hyperactivity in specific brain circuits can cause the related thoughts, emotions, and physiological processes to become abnormally amplified. This, in turn, can cause the brain to become even more hyperactive because cognitive-emotional stress and the byproducts of the affected physiological processes have a stimulating effect on the brain. Consistent with this hypothesis, calming the brain, whether by natural or medical means, can be highly effective in reducing both psychiatric symptoms and the risk of developing any of a wide range of chronic medical conditions. However, calming the brain naturally requires consistent effort, and medical interventions can be costly, burdensome, and side-effect prone. That raises the question of whether there might be a more effective and efficient way to reduce the excitability of the neurological system. Although neuronal excitability has clearly been linked to specific risk genes, previous efforts to modify genes in plants and animals have met with limited success. However, the recent discovery of CRISPR/Cas9 technology has changed all that. Now, for the first time, there may be a way to readily replace abnormal DNA sequences with wild-type sequences. This has far-reaching implications for disease reduction and prevention both because neuronal hyperexcitability appears to be the underlying driver of most mental and physical illnesses and because the neuronal hyperexcitability trait has been linked primarily to a relatively small number of gene loci. This article will discuss the pervasive effects of the neuronal hyperexcitability trait and the extraordinary implications of using CRISPR/Cas9 to eliminate its genetic fingerprint from the human genome.

Keywords: Neuronal Hyperexcitability, MCNH Hypothesis, CRISPR/Cas9 Technology, Genetic Engineering, Gene Editing, Genetic Scissors, Biomarkers of Disease, Preventive Medicine

1. Introduction

Mental and physical illnesses have traditionally been addressed through natural interventions, medical interventions, or a combination of the two. Yet even after centuries of study, the root cause of most illnesses remains unclear. However, what has become increasingly apparent is that chronic emotional stress, unhealthy dietary habits, and environmental toxins increase the risk of virtually all forms of mental and physical illness. Consequently, there has been an increasing emphasis on healthy living as a means of optimizing mental and physical health [1]. Yet there are many persons who enjoy good health despite having an unhealthy lifestyle, and, conversely, many persons who suffer poor health despite maintaining a healthy lifestyle. What this implies is that there are factors other than external stressors and dietary habits that influence sickness and disease. Clearly, one of those risk factors is genetic loading. Large-scale genomic studies have identified numerous risk genes for various illnesses ranging

from depression to schizophrenia [2-4] and diabetes to cancer [5]. However, for most disease processes, the determination of which of those genes is most important has yet to be made. A better understanding of disease formation and progression would help streamline efforts to prevent illness, particularly in light of the recently discovered ability to replace risk genes with healthy genes. This article will explore the underpinnings of disease development and discuss how a commonly occurring gene variant may be at the root of virtually all disease processes. It will also discuss how that abnormality might be corrected and possibly even eliminated from the human gene pool.

2. How Disease Processes Develop

A proper understanding of pathological biological processes begins with a proper understanding of healthy biological processes. The building and maintenance of a person's body can be compared to the building and maintenance of a person's house. A strong house—one that is resilient to high winds and inclement weather—requires an ample supply of good building materials. It also requires an accurate blueprint and workers who assemble the building materials according to plan. Insufficient building materials, defective building materials, hazardous building materials, an inaccurate blueprint, and worker distractions are all potential sources of structural and functional weakness. The same is true with the human body. A poor diet is the biological equivalent of defective building materials; an unbalanced diet is the biological equivalent of insufficient building materials; environmental toxins are the biological equivalent of hazardous building materials; and risk genes are the biological equivalent of errors in the blueprint. Last, but most important, is emotional stress. Stress is the biological equivalent of worker distractions and is the most influential vulnerability factor because inattentive workers cannot be relied upon to build a structurally and functionally sound house even if all the proper building materials and instructions are supplied. Anyone who has ever experienced the disruptive effects of severe emotional stress on concentration, digestion, and other bodily functions can attest to this. Psychophysiologically, mental and emotional stress cause the brain to become hyperactive, and this hyperactivity causes the associated organs and systems to be overstimulated, thereby disrupting their normal function. If this interference occurs occasionally and for brief periods of time, the associated errors are typically minor and readily correctable; but if they occur frequently or for prolonged periods of time, the errors can become compounded to the point of causing progressive and potentially irreversible mental and physical illness.

3. The Elusive Instigator of Stress and Its Consequences

Traditionally, cognitive-emotional stress has been linked to environmental factors, such as dysfunctional family dynamics, peer pressure, job stress, grief, and financial crises. However, a glaringly overlooked source of cognitive-emotional stress is the brain itself. Everything that the mind sees, hears, and thinks is processed by the brain. Normally, the brain simply works in parallel with the mind just as a computer works in parallel with the computer operator. However, in some persons the brain is inherently hyperexcitable. As such, it abnormally amplifies and perpetuates every sensory input, thought, and emotion. This is not so much of a problem in the absence of mental and emotional stressors. However, as stress levels begin to rise, the perceived level of stress can begin to increase exponentially, and various thoughts and emotions can keep replaying like a broken record. In addition to the cognitive-emotional distress that this can cause, it can interfere with the ability to manage the stress. Misunderstandings, impulsive decisions, and emotional outbursts are just some of the ways that the hyperexcitable brain can interfere with the ability to resolve the stressors that caused it to become hyperactive in the first place. In extreme cases, the neurons can become so hyperactive that the associated magnetic fields stimulate the mind as strongly as input from the body's sensory organs. As a result, the mind begins to have difficulty distinguishing internal from external reality—a state known as "psychosis" [6, 7]. At the same time, the pathological hyperactivity in specific neural circuits can dysregulate the corresponding functions of the body. The consequent biological dysfunction, in turn, can feed back on the brain both directly (via afferent nerves) and indirectly (via chemical mediators), both of which can further amplify the already elevated neurological activity. According to the multi-circuit neuronal hyperexcitability (MCNH) hypothesis of psychiatric disorders [6], this endogenously-mediated stress is the fundamental driver of both mental and physical illness [8]. The validity of this is supported by the high comorbidity between mental illness and physical illness [9], and by the observation that persons with severe mental illness die of the same kinds of diseases as the general population but at a much earlier age [8]. It is as if the pathologically-elevated neurological activity is accelerating the aging process and the risk of the biological errors that lead to sickness and disease.

The degree to which an inherent hyperexcitability of the neurological system can disrupt the lives of those affected is demonstrated by the intense emotions and radical changes in behavior that tend to occur when such persons are under stress. Regardless of their age, they tend to become anxious, depressed, irritable, or withdrawn in the face of severe or persistent cognitive-emotional stress. They may also experience cyclic changes in mood, energy, and concentration as pathologically hyperactive neural circuits aberrantly fuel hyperactivity in relatively *hypo*active circuits while themselves quieting down due to synaptic fatigue [6, 10]. In most cases, affected persons attempt to rationalize their uncomfortable thoughts and emotions by blaming themselves, blaming others, or blaming their circumstances. This, in turn, tends to create secondary psychosocial problems due to the adverse effects that it has on their self-esteem, work performance, and personal relationships. Although symptoms

can develop at any age, they most commonly develop during the adolescent years because the transition from childhood to adulthood is usually the first prolonged period of high stress in a person's life. For those affected, cognitive-emotional stress is like throwing stones at a hive of irritable bees. Yet because hyperexcitable neurons, like irritable bees, behave just like normal bees until they are perturbed, the effects of the neuronal hyperexcitability trait tend to be misattributed to the effects of environmental stressors. Parents, teachers, and friends tend to rationalize the affected person's behavior as being a variant of normal. However, the discomfort of the abnormally-amplified thoughts and emotions can lead affected persons to become desperate in their efforts to relieve their mental and emotional distress. It might lead them to lie, steal, take risks, eat unhealthfully, and argue with their parents and other authority figures because these behaviors require less self-discipline than healthier behaviors. It might also lead them to navigate away from their healthy friends and begin to connect with peers who are more like-minded; that is, ones who themselves are experiencing abnormally high levels of emotional distress due to the hyperexcitability of their brains.

Because the stress of adolescence is generally prolonged, the related cognitive-emotional chaos can completely derail the lives of persons with neuronal hyperexcitability; and because the symptoms tend to be recurrent, they can prevent them from ever getting back on track. Also, because the brain regulates virtually every organ and system of the body, its hyperactivity can, as previous mentioned, affect these organs and systems just as much as it does the cognitive-emotional system. This is what increases the risk that affected persons will develop various functional symptoms, such as migraine headaches, irritable bowel, and fibromyalgia, as well as various chronic diseases, such as diabetes, high blood pressure, cardiovascular disease, endocrinopathies, and autoimmune diseases. Which of these diseases they develop would depend upon a variety of constitutional factors as well as which other risk genes they carry. However, because the kindling effect of stress on neuronal hyperexcitability is what places most of the strain on physiological function, the genes for neuronal hyperexcitability are likely the most important determinants of sickness and disease.

Although anticonvulsants and other brain-calming drugs do have the ability to reduce neuronal excitability, they typically have to be dosed multiple times per day. They might also have to be combined with one another; but even then they sometimes fail to reduce neuronal excitability enough to normalize brain function. Also, for affected persons, recognizing when the brain (rather than the mind) is causing psychiatric and physical symptoms can be extremely difficult. Consequently, such persons often wait far too long to seek medical attention or restart medications that had previously been effective in controlling their symptoms. In addition to the emotional suffering that these delays in treatment can cause, untreated neuronal hyperexcitability can increase the risk of developing the aforementioned physical illnesses in a time-dependent fashion. Hence, correcting the gene abnormality that underlies neuronal hyperexcitability could be a way to substantially prevent most mental and physical illnesses.

4. A Windfall for Genetic Engineering

The results of large-scale genomic studies suggest that various psychiatric disorders, such as generalized anxiety disorder, major depressive disorder, bipolar disorder, and schizophrenia, are rooted in various combinations of risk genes that contribute collectively to their development [2-4]. This idea is supported by the lack of a consistent pattern of inheritance for any of the common psychiatric disorders. However, the multiple-gene, multiple-disorder theory of mental illness is inconsistent with the observation that different psychiatric disorders can manifest at different times in the same individual and that various different psychiatric disorders tend to co-occur with one another [4]. It is also inconsistent with the observation that many different psychiatric disorders respond to the same classes of medications, such as antidepressants, mood stabilizers, benzodiazepines, antipsychotics, and psychostimulants. Importantly, however, the treatment response to all but one of these drug classes tends to be unpredictable, inconsistent, and short-lived. The only exceptions are drugs that have purely brain-calming effects, such as anticonvulsants, lithium, and non-stimulating antipsychotics [11]. Thus, a more plausible explanation than the multiple-gene, multiple-disorder theory of mental illness is that all of the common psychiatric disorders are rooted in a shared physiological abnormality; namely, neuronal hyperexcitability [6].

Another finding that suggests that neuronal hyperexcitability is at the root of most psychiatric disorders is the recently-discovered link between upper-end-of-normal resting vital signs and the later development of a variety of different psychiatric disorders. For example, in a longitudinal study involving more than one million men in Sweden, Latvala et al. [12] found that subtle elevations in resting heart rate (RHR) were predictive of the later development of generalized anxiety disorder, obsessive-compulsive disorder, and schizophrenia. Similarly, Blom et al. [13] found that adolescent girls with emotional disorders had increased resting respiratory rates (RRR) in comparison to healthy controls. Persons with higher resting heart and respiratory rates have also been found to be at increased risk of developing a wide range of physical illnesses, including diabetes, high blood pressure, cardiovascular disease, autoimmune disease, and all-cause mortality [8]. The subtle vital-sign elevations with which these illnesses are associated are thought to be the consequence of a tonic elevation in basal neurological activity in those persons who inherit the genes for neuronal hyperexcitability [8]. This is the MCNH explanation for why the lifespan of persons with severe mental illness tends to be so much shorter than the general population [8]. Hypothetically, the reason that psychiatric and "functional" physical symptoms tend to precede the development of diagnosable physical abnormalities is that the cognitive-emotional system is more expressive of neuronal

excitation than other organs and systems of the body. The physical consequences tend to be delayed because they express the gradual erosive effects of neuronal hyperexcitability [8].

The only arguable weakness of the MCNH hypothesis is that it appears to be inconsistent with the wide variety of ways that mental illness can manifest. However, if one considers that thoughts, emotions, and behaviors are influenced by the mind as well as by the brain and that every person is unique, different manifestations of the neuronal hyperexcitability trait should not be surprising; in fact, they should be expected. If, with this in mind, we go back and reconstruct family pedigrees based not on specific psychiatric diagnoses but on a wide range of symptoms independent of diagnosis, including soft signs of neuronal hyperexcitability, such as hyper-emotionality, mood instability, sleep difficulties, attentional problems, functional somatic complaints, and substance misuse, a consistent pattern of distribution emerges; that pattern is strikingly autosomal dominant! [6]. This improbable finding suggests that most of the common psychiatric and co-occurring functional disorders can be driven by polymorphisms of a single gene locus. The validity of this is supported by the observation that a predictable proportion of individuals in affected families will be completely free of symptoms irrespective of how dysfunctional their family dynamics might be. These so-called "survivors," who appear in a classic autosomal recessive distribution, are not necessarily more mentally tough than their affected siblings but rather more neurologically stable presumably because they did not inherit one of the gene variants that have been linked to neuronal hyperexcitability. Moreover, the fact that these individuals are so resistant to both mental and physical illness [14] suggests that among the variables that contribute to the development of chronic disease, the trait of neuronal hyperexcitability may be the most important [15]. Additionally, the autosomal dominant pattern of inheritance and sharp clinical distinction between those who inherent the susceptibility genes and those who do not combine to suggest that most of the candidate genes that have been linked to psychiatric disorders make small contributions in comparison to a few genes that make large contributions and may by themselves be enough to markedly increase one's vulnerability to mental illness [15]. This has important implications for emerging technologies that have the potential to correct abnormalities in the human genome.

5. Evidence of Which Specific Gene Loci Underlie Neuronal Hyperexcitability

In the largest study of its kind, a collaborative research group involving institutions from across the United States performed a genome-wide association analysis in search of susceptibility loci for bipolar disorder [16]. Bipolar disorder can be thought of as a kind of clinical umbrella that contains elements of most of the common psychiatric disorders. Symptoms of bipolar disorder commonly include periods of depression that characterize major depressive disorder; periods of euphoria that characterize mania; periods of irritability that characterize intermittent explosive disorder; rapid cycling of symptoms that characterizes cyclothymia; various degrees of anxiety that characterize anxiety disorders; panic attacks that characterize panic disorder; psychotic states that characterize schizophrenia; mood instability that characterizes borderline states; primitive defense mechanisms that characterize personality disorders; and the triad of inattention, hyperactivity, and impulsivity that characterizes ADHD. Bipolar patients commonly also suffer from one or more functional somatic disorders, such as migraine headaches, irritable bowel syndrome, fibromyalgia, chronic musculoskeletal pain, or some other disorder that has been linked to a hypersensitivity (or hyperexcitability) of the central nervous system (CNS) [17-20].

The collaborative research group tested 1.8 million gene variants in 4,397 cases of bipolar disorder and 6,209 controls, and found two regions of strong association [16]. The most significant was Ankyrin 3 (ANK3) on chromosome 10q21, which codes for a protein that is found at the axon initial segment and nodes of Ranvier of neurons in the central and peripheral nervous systems [21]. The protein, which has also been linked to schizophrenia [22], has been shown to regulate the assembly of voltage-gated sodium channels [16], thereby affecting neuronal excitability. ANK3 was also linked to epilepsy [23], a disorder that is known to be fueled by neuronal hyperexcitability. The second strongest region of association was located in the third intron of CACNA1C on chromosome 12p13 [16]. Like ANK3, CACNA1C, which has also been linked to schizophrenia and major depressive disorder [24, 25], codes for a protein that regulates the movement of ions—in this case calcium ions—across neuronal membranes [16, 26]. Strikingly, CACNA1C is the site of another medication that is used to treat mood disorders. That medication reduces the movement of the same ions across neuronal membranes, thereby helping to compensate for the defective gene product. The same researchers found that in the mouse brain, both ANK3 and subunits of the calcium channel were down regulated in response to lithium, a drug that is known to have anticonvulsant effects [27-29] and one of the oldest used to treat bipolar disorder, schizophrenia, and schizoaffective disorder.

6. An Unprecedented Opportunity for Illness Treatment and Prevention

If it is indeed true that most psychiatric disorders are rooted in polymorphisms of a single gene locus, then correcting the nucleic acid sequence at that locus would have the potential to alleviate all of an individual's psychiatric symptoms and prevent them from ever recurring. If, in addition to treating somatic cells, the person's stem cells could be treated, it would create the potential to prevent the abnormal gene from being passed to the next generation. If such an intervention were found to be safe and effective, and if it were ultimately

implemented on a large scale, mental illness and all of its comorbidities could potentially be eradicated from society.

An emerging technology called“ CRISPR/Cas9” (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9), also known as “genetic scissors,” has the potential to do just that. It has the potential to edit genes using the molecular tools that bacteria use to defend themselves against invading viruses. Over the last few decades, researchers have discovered that bacteria “memorize” the nucleic acid sequences with which they have been infected by incorporating a small portion of those sequences into their own DNA. Next, they transcribe these so-called “spacer sequences” and pair them with a protein called Cas9, which allows the molecular complex to seek out and destroy the same sequences in re-invading viruses [30]. Currently, this technology is being harnessed to target human DNA, thus making it possible to cut out and replace abnormal gene sequences with healthy ones; hence the expression “genetic scissors.” In 2020, Jennifer Doudna and Emmanuelle Charpentier were awarded the Nobel Prize for their pivotal work in this area.

Until now, one of the main barriers to successfully implementing CRISPR technology has been the belief that most of the commonly occurring psychiatric disorders, such as generalized anxiety disorder, major depressive disorder, bipolar disorder, attention deficit disorder, and schizophrenia [2-4], and most of the commonly occurring chronic diseases, such as diabetes, high blood pressure, heart disease, autoimmune disease, cancer, and dementia, are multi-factorial and involve numerous risk genes [5]. However, as previously discussed, the MCNH hypothesis reconceptualizes this idea in identifying neuronal hyperexcitability as the orchestrator of the many factors that are thought to contribute to the development of the aforementioned mental and physical illnesses. The validity of this reconceptualization can now be tested through CRISPR/Cas9 technology. For instance, one could study the behavioral consequences of replacing polymorphisms at one of the identified single-gene loci with a wild-type sequence. Conducting such experiments in animals may actually be easier and more generalizable than one would think because the locations of the two primary genes related to neuronal hyperexcitability (i.e., ANK 3 and CACNA1C) are already known in humans, and those genes likely have the same functions in other animal species [31]. Such animal studies could also help work out methodological difficulties in applying CRISPR technology to CNS disorders, such as the challenge of delivering guide RNA/Cas9 complexes into solid tissue within the CNS and preventing collateral sequencing errors from occurring during the gene-editing process.

7. Experimental Models for Targeting Neuronal Hyperexcitability with CRISPR/Cas9

Some of the animal species that have already been studied for behaviors suggestive of neuronal hyperexcitability include rodents [32, 33], dogs [34, 35], cattle [36-38], and primates [39, 40]. For instance, some mice have been observed to exhibit motoric hyperactivity and attentional difficulties suggestive of ADHD in humans [32, 33]. Similarly, some dogs, sheep, cows, and monkeys demonstrate elevated fear responses, avoidance behaviors, and adaptive difficulties that are characteristic of human psychiatric disorders such as generalized anxiety disorder, major depressive disorder, and post-traumatic stress disorder. Such animal models have also been found to have endocrinologic and immunologic patterns similar to those found in humans with psychiatric disorders. In the meat-packing industry, a relationship was observed between the temperament of beef cattle and both their physical health and the quality of their meat [38]. According to research scientists, beef cattle that have a nervous temperament also have a heightened fight-or-flight response, increased metabolism, and, due to the chronic tension in their muscles, tougher meat upon slaughter. Another characteristic finding in these cattle, also in line with their heightened emotional reactivity, is greater pupillary dilation when excited. Taken together, these observations suggest that other animal species harbor a hyperexcitability of the neurological system parallel to that in humans. In animals, however, environmental factors are less of a confounder than in humans, especially in cattle, which are generally handled and fed according to regulatory standards. This suggests that the temperamental differences between animals can reflect differences in genetic loading alone. That is not to say that environmental factors are unimportant but only to say that under similar environmental conditions an inherent hyperexcitability of the neurological system can make sizable differences in behavior. This underscores the importance of the neuronal hyperexcitability trait as a determinant of an organism’s stress levels. It also re-emphasizes the utility of using animals to study the potential benefits of therapeutically modifying the genes for neuronal hyperexcitability.

8. Discussion

The goal of this review was to highlight the importance of a hidden source of stress—one that may actually be the biggest determinant of a person’s overall health—and to introduce a revolutionary new way to reduce that stress. Historically, the assumption has been that cognitive-emotional stress is driven by psychological factors and that biological stress is driven by physical factors. Although this is largely true, there is clinical and genetic evidence that neither of these sources of stress is the primary driver of stress-related sickness and disease. Rather, the primary driver appears to be a constitutional hyperexcitability of the neurological system that abnormally amplifies every sensory input, every cognitive-emotional response, and every physiological process in the body. Though the phenomenon of neuronal hyperexcitability has been described previously [41], its true significance has historically been obscured by the assumption that mental function is purely a manifestation of brain function. However, a rapidly growing body of clinical and veridical evidence suggests that

the mind is not merely a product of complex brain activity but rather an independent entity that has the ability to think and emote either in conjunction with the brain or independent of it [7, 42]. Along with this has come the recognition that the mind and the brain are in a continuous dialogue and that they can bat cognitive-emotional stress back and forth like two people caught in an argument. Over time, this argument can escalate, particularly if the neurological system is inherently hyperexcitable [43]. Moreover, the greater the excitability of the neurological system, the greater the risk that stress will dysregulate the body as a whole due to the pathologically-elevated output from the hyperexcitable brain.

Historically, neuronal hyperexcitability had unwittingly been managed through natural interventions, such as stress reduction, regular exercise, and avoidance of stimulant-type drugs. In recent years, however, brain-calming drugs and various somatic therapies, such as electroconvulsive therapy, vagus nerve stimulation, and repetitive transcranial magnetic stimulation, have been used with increasing frequency [44]. Although some of these interventions can be highly effective, their benefits are more often limited, they require persistent effort, and their cost can be prohibitive. That raises the question of whether there might be a more consistently effective, efficient, and affordable way to reduce the excitability of the neurological system.

For more than a decade, geneticists have known that neuronal hyperexcitability is rooted in gene polymorphisms at specific loci [16, 22-26]. What was not known, however, was the extent to which those polymorphisms could cause other risk genes to be expressed as sickness and disease. However, with the growing recognition that chronic stress may be the single greatest instigator of disease, and with the concomitant recognition that neuronal hyperexcitability acts as an accelerant that can cause cognitive-emotional stress and, by extension, physiological stress to escalate like a wildfire, it becomes apparent that the genes for neuronal hyperexcitability may be the most important determinants of whether other risk genes will be expressed as disease states. The strong link between mental illness, which is hypothetically rooted in neuronal hyperexcitability, and a wide range of physical illnesses bears witness to this.

That underscores the importance of identifying and treating neuronal hyperexcitability as early in life as possible. Unfortunately, however, neuronal hyperexcitability is not currently recognized as a psychiatric, neurological, or medical disorder. Also, the trait does not always manifest as any known psychiatric condition…and even when it does, it may not be identified as the underlying cause of a patient's symptoms. Hence, most affected persons are never properly diagnosed and treated. Instead, they typically wind up being treated for the long-term consequences of neuronal hyperexcitability, which include major illnesses such as diabetes, high blood pressure, cardiovascular disease, autoimmune disease, cancer, and dementia [8, 14]. Other consequences of neuronal hyperexcitability that typically go untreated include dysfunctional relationships, unemployment, homelessness, criminality, suicidality, homicidality, and other serious psychosocial problems.

Fortuitously, there is now a way to detect neuronal hyperexcitability objectively. In the absence of confounding factors, such as drug intoxication, cardiorespiratory disease, and cardiorespiratory medications, any person who has a resting pulse above 75 beats/min or a resting respiratory rate above 15 breaths/min is likely a carrier of the neuronal hyperexcitability trait [8, 47]. Also, there tends to be some correlation between the degree of the vital-sign elevations and the degree of neuronal hyperexcitability. Hypothetically, what makes resting vital signs reliable markers of the neuronal hyperexcitability trait is that the heart and respiratory-rate elevations are driven by pathological hyperactivity in the associated neurons and circuits. More than being helpful diagnostically, these markers indicate that the individual is a carrier of one or more of the gene polymorphisms that have been linked to neuronal hyperexcitability. Until now, the benefits of this information have been limited to patient education and family planning. However, with the recent discovery that abnormal genes can be replaced by normal ones, the recognition of these biomarkers has become even more important. Also, because clinically significant levels of neuronal hyperexcitability appear to be linked to a relatively small number of gene loci, and because these loci have been well-characterized, the stage is set to begin studying the clinical effects of modifying the genes for neuronal hyperexcitability.

In performing the initial experiments, there would be no need to place humans at risk because, as previously stated, many different species show evidence of neuronal hyperexcitability. Also, performing experiments on these mammals would greatly diminish the potential for environmental differences to act as confounding factors. If such genetic engineering studies were to prove successful in reducing the excitability of the neurological system, similar experiments could potentially be performed on the stem cells of these species to determine the feasibility of preventing the abnormal genes from being passed from one generation to the next. Ultimately, the ability to use this technology successfully in humans would be the largest advance ever realized in the field of preventive medicine.

9. Conclusion

From the perspective of the first comprehensive neurophysiological hypothesis of psychiatric disorders, an inherent hyperexcitability of the neurological system is at the root of most psychiatric and chronic medical conditions. However, reducing the excitability of the neurological system without modifying the genes that drive it requires either continuous attention to diet and lifestyle or various forms of medical therapy or both. Unfortunately, most affected persons fail to make the necessary lifestyle changes, and even if they do, the degree of improvement is usually only modest. Those who choose to seek formal treatment tend not to fair much better due to the high rate at which neuronal hyperexcitability is misdiagnosed and mismanaged. Fortuitously, all of that may

be about to change with the development of CRISPR/Cas9 technology. CRISPR/Cas9 has the potential to therapeutically modify or completely replace the genes for neuronal hyperexcitability. In so-doing, it has the potential to change the treatment of the related psychiatric and medical conditions from management to cure, and symptom relief to prevention. Moreover, because neuronal hyperexcitability appears to have such a decisive influence on mental and physical health, and because it appears to exert the bulk of its influence through a very small number of previously identified gene loci, the likelihood of markedly reducing the risk of both mental and physical illness through targeted allele modification is high. Never in the history of medicine has there been so great an opportunity to prevent sickness and disease.

10. Directions for Future Research

Urgently needed are animal studies aimed at determining the feasibility of using CRISPR/Cas9 technology to target and therapeutically modify gene variants for neuronal hyperexcitability. In addition to allowing methodological difficulties and risks to be better assessed in this burgeoning area of research, animal studies ease the challenge of distinguishing genetic factors from psychological and environmental factors. One way that the benefits of altering the genes for neuronal hyperexcitability could be tested would be to select, via resting vital-sign measurements and clinical observations, animal models exhibiting evidence of neuronal hyperexcitability. Next, the DNA of symptomatic animals, particularly at loci known to be related to neuronal hyperexcitability in humans (i.e., ANK 3 on chromosome 10q21 and CACNA1C on chromosome 12p13) could be sequenced and compared to that of controls. Of note, SNPiR [45], a relatively new technique for identifying gene variants, could potentially aid in this process. Next, CRISPR/Cas9 technology could be used to modify the identified risk genes. After studying the consequences of this targeted gene editing, a discussion should be had about attempting to do the same with the stem cells of affected animals. Though technically more difficult and unpredictable [46], stem cell editing could potentially prevent both the development of disease in the offspring of affected animals and the transfer of disease-risk to future generations.

Conflicts of Interest

The author declares that he has no competing interests.

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