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Review Article

THE ROLE OF GENES AND MOLECULES ASSOCIATED WITH PATHOPHYSIOLOGICAL BEHAVIORAL DISORDERS IN THE BRAIN AND THEIR APPLICATIONS IN NEUROLOGICAL DISEASES

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ABSTRACT

An understanding of how we can impact on brain wiring and functioning is the key to treat neurological disorders and a core to mind-fullness training that aims to the rewiring of the brain. The emergence of the research that clarifies the neurological mechanisms of integrated modulators that regulate changes in genes, cells, the brain, and new treatments for depression leads towards research methods such as fMRI, Genetic study, LDAEP, HRV, and treatment responsiveness to determine the disorders caused by genetic deregulation and environmental stimuli. A pathophysiological disorder results from biochemical, metabolic, neurophysiologic and genetic dynamic processes set in motion that leads to deranged function in an organ. The molecular neurobiological mechanisms such as genetic biomarkers, neural circuitry, and neuroplasticity associated with neurological diseases have been discussed in this review. This study involves a discussion of genes such as MiR-218, ARC, TH, SLC6A4, PCLO, rapid-acting antidepressants such as N-methyl-D-aspartate, Ketamine with the promise of dramatically improving treatment options for depressed patients. The objective of this study is to understand how these genes and compounds affect the brain and to find ways that can be used in treating behavioral disorders. Here, we review the current understanding of up and down regulation effects of the genes mentioned above, how rapid-acting antidepressants to function, including their merits and demerits with their application in biotechnology-based strategies for treatment and the research techniques being used to address these approaches.

INTRODUCTION

A psycho physiological disorder is characterized by physical symptoms that are induced by emotional factors that commonly include the very common emotional states responsible for forming illness like anxiety, stress, and fear. The mechanism of anxiety disorder is explained in Figure-1. Psychiatric , psychological and pathological behavioral disorders includes behavioral emergencies (includes behavior that interferes with core life functions a kind of antisocial behavior) , pathophysiology of psychiatric disorders (includes mental health problems), assessment of behavioral emergency patients (includes ensuring of personal safety by mental examinations), specific psychiatric disorders (includes cognitive disorders such as dementia, delirium, schizophrenia, panic attack, phobias, post-traumatic stress syndrome, depression, bipolar disorder, suicide etc), management of behavioral emergencies includes medical and psychological management), violent patients (includes the patients that are threat to self and others) and restraint (includes restraining of patient). Disorder of the nervous system i.e. neurological disorder which is a structural, biochemical and electrical abnormality in the Brain, spinal cord or other nerves can result in a range of symptoms. Depression is a chronic, debilitating and common illness with available pharmacotherapies for treatment that are helpful but can have several major drawbacks.[1]. Depression is currently one of the most important causes of mortality and morbidity, which occurs in all genders, ages, and social backgrounds. Serious problems such as suicidal behavior are frequently occurring in patients with depression. Currently, many psychopharmacological means are available for the treatment of depression, a relevant percentage of patients (20%-30%) treated with commonly used antidepressants do not achieve complete recovery and develop a treatment-impervious depression.[2]. The most important reason associated with this disabling disorder is that depression is a multifaced disorder with diverse causes and that our knowledge about its pathogenetic mechanisms is limited [3].

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The pathogenesis and treatment mechanisms of depression are now understood thanks to multilateral neurobiological studies and the introduction and development of antidepressants. The significance of the neurotransmission system in patients with depression has been recognized alongside the introduction of antidepressants. The structural and functional anomalies of patients with depression have been reported through brain imaging studies. In inclusion, genetic mutations have been reported through genetic studies. Molecular biological studies and gene manipulation tests lead towards contribution to mounting evidence regarding the preclinical grounds associated with depression [4].

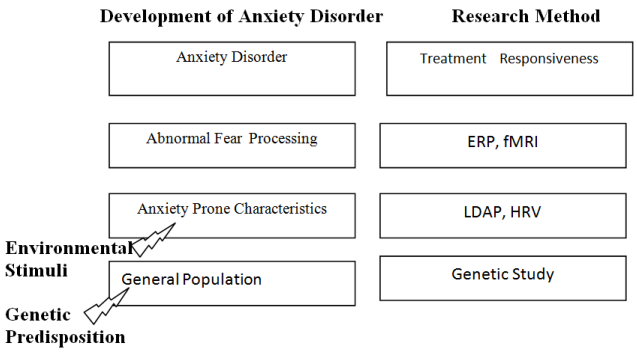
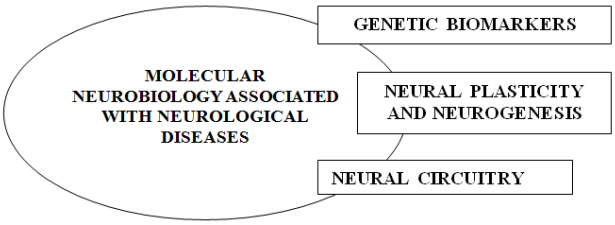


Figure 1 Mechanism of anxiety disorder

Figure-1 explains the anxiety disorder that occurs due to 2 reasons; one is a genetic predisposition in the general population that changes the genetic makeup which leads to characteristic changes in phenotypic traits under the influence of environmental conditions. The genetic study is the research method through which the identification of chromosomes, genes or proteins can follow and rule out a suspected genetic condition that may lead to a genetic disorder. Environmental stimuli that are responsible to elicit a response or reaction from a person leads to anxiety prone characteristics i.e. development of anxiety in response to sudden adverse stimuli from environment received for short or long duration of time. LDAEP is the loudness dependence of auditory evoked potentials which is been used to indicate serotonergic dysfunction (irregularities in serotonin function leads to affective disorders) in patients with predominant schizophrenic negative symptoms [5] and HRV the heart rate variability is the physiological phenomenon of variation in the time interval between heartbeats i.e. it detects the spontaneous fluctuations above and below the mean heartbeat serves as a detector of cardiac health in patient. After development of anxiety-prone characteristics it leads to abnormal fear processing which is detected by research methods such as fMRI functional magnetic resonance imaging which measures the activity of the brain by detecting blood flow associated changes, this method relies on the fact of coupling of cerebral blood flow and neuronal activation and ERP is the event-related potential which deals with the measurement of brain response. When an area of the brain is in use accordingly the blood flow in that particular region also gets elevated. Anxiety disorder followed by processes as mentioned above peaks which can be detected by responsiveness to the mentioned research methods such as LDAEP, HRV, fMRI and ERP.

The mechanisms arising in the nervous system, which are thought to play a key role in antidepressant action, can explain only part of the current treatment mechanisms for depression. But the emergence of necessity arises to clarify the neurobiological mechanisms of the integrated major modulators that regulate changes in the genes, the brain, and in behaviors associated with neurological diseases. Below follows the neurobiological theories and treatments specifically for the most common neurological disease i.e. depression [4].



Neural Circuitry

The limbic-cortical-striatal-pallidal-thalamic tract, which is connected to the hippocampus, amygdala, caudate nucleus, putamen, and the frontal cortex, is thought to be the key neuroanatomical circuit in depression [6].

The hippocampus is the most infinitely studied brain structure associated with stress, depression, and antidepressant mechanisms. Since the hippocampus is associated with learning and memory, it is also associated with cognitive impairment in depression. The hippocampus is involved in the feedback loop of the hypothalamic-pituitary-adrenal (HPA) axis, and this can result in the neuroendocrine disorders [7]. Chronic stress induces atrophic changes in hippocampal subregions, and the hippocampal volume decreases in depression [8]. Deterioration of prefrontal cortex functions can cause various symptoms such psychomotor retardation, because the prefrontal cortex is neurally connected to the hippocampus, basal ganglia, thalamus, ventral tegmental area, dorsal raphe nucleus, and locus ceruleus, which is closely associated with the pathophysiology of depression [9]. The amygdala allocates or assigns emotional importance upon receiving psychological stimuli. Also, the amygdala is associated with the pharmacological actions of antidepressant treatments [10]. A decrease in the amygdala volume [11] and a loss in glial cells [12] have been reported in patients suffering from depression.

Figure-1 explains the anxiety disorder that occurs due to 2 reasons; one

Neural Plasticity

Neural plasticity or structural plasticity is explained as a neuronal adaptation that is an individual response to the environment, which includes new cell formation and genetically healthy cell death in the adult brain [13]. The former is called neurogenesis, and the latter, apoptosis [13]. Each specific neural circuit is activated by learning, memory, stress, or the environment, which induce an intracellular signal transduction cascade that is a core of neural plasticity. The known circuit includes a cyclic adenosine monophosphate signal transduction cascade and neurotrophic factor signal transduction cascade [14].

Genetic Biomarkers

The candidate genes related to major depression were discovered through collective studies on family history and twins that targeted patients with depression and patients treated

by antidepressants. The recombinant prevalence of inheritability is represented as the LOD (logarithm (base 10) of odds) score. The alternative forms of genes i.e. alleles inheritability is calculated mainly through linkage analyses. If the LOD score is greater than 3, it is relatively and comparatively inheritable[4]. The genes related to depression, those had been discovered through these analyses, are as follows:

Tyrosine hydroxylase (TH) genes: Chromosome 11 has TH genes that express the TH enzyme, which is most condemnatorily associated with dopamine synthesis. Healthy individuals suffered from depressive symptoms when TH inhibition was succeeded [15].

Serotonin transporter (SLC6A4) genes: SLC6A4 genes are positioned on chromosome 17. The utterance of serotonin transporter is regulated in part by an insertion/deletion polymorphism in the serotonin-transporter-linked polymorphic regions. The SLC6A4 genes have two types of polymorphisms: the 528 (L) allele with a lengthy promoter region, and the 484 (S) with a shorter one. In the case of the 484 (S) allele, reduced expression of the serotonin transporter was noticed on the nerve cell membrane [16], and severe depression symptoms such as suicide and melancholic depression were reported [17]. when individuals with 484 (S) allele experienced from physical and emotional abuse during childhood, they showed a higher incidence of crucial depression than those without this allele [18].

Piccolo presynaptic cytomatrix protein (PCLO) genes: PCLO genes convey the protein piccolo, and are associated with chromosome 7. Piccolo protein is concerned with monoamine transmissions, such as serotonin, epinephrine, and dopamine transmission in the brain. Amongst the PCLO genes, rs2522833 has a single nucleotide polymorphism and is knows to be associated with depression by regulation of the HPA axis [19].

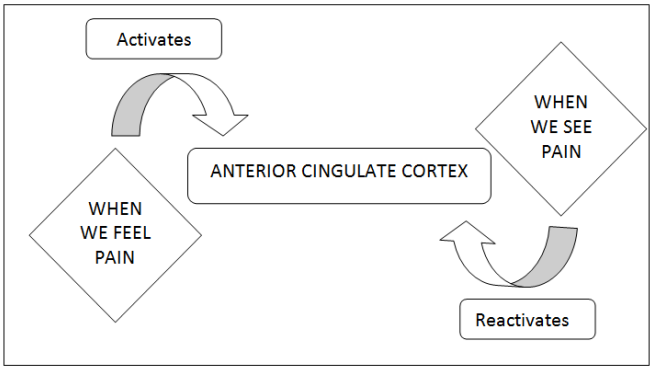
Genes Associated with Brain Functioning and Their Role in Treatment of Neurological Diseases

ARC genes

Activity Regulated Cytoskeleton Associated Protein is a protein encrypting gene. Diseases associated with ARC incorporate amphetamine abuse and hepatocellular carcinoma. Among its connected pathways are neuroscience and cytoskeletal signaling. The master controller of synaptic plasticity that self-assembles into virion-like capsids that encapsulate RNAs and mediate intercellular RNA transfer in the nervous system. When released in extracellular matrix ARC mRNA can undergo activity-dependent translation. ARC capsids are endocytosed and can relocate ARC mRNA into the cytoplasm of neurons. Behave as a key regulator of synaptic plasticity: required for protein synthesis-dependent forms of long term potentiation (LTP) and depression (LTD), and the formation of long term memory. Controls synaptic plasticity by promoting endocytosis of AMPA receptors (AMPARs) in response to synaptic activity: this endocytic pathway maintains levels of surface AMPARs in response to chronic changes in neuronal activity through synaptic scaling, thereby contributing to neuronal homeostasis. Behaves as a postsynaptic mediator of activity-dependent synapse elimination in the developing cerebellum by mediating the elimination of surplus climbing fiber synapsis. Gathered at weaker synapses, probably to prevent their undesired enhancement. This suggests that ARC-containing virion-like capsids may be necessary to eliminate synaptic material. Needed to transduce experience into long-lasting changes in visual cortex plasticity and long term memory. Concerned with postsynaptic trafficking and processing of amyloid-beta A4 via interaction with PSEN1. In addition to its role in synapses, it is also involved in the modulation of the immune system: specifically expressed in skin migratory dendritic cells and regulates fast dendritic cell relocation, thereby regulating T-cell activation (GeneCards-Human gene database).

Researchers have established that the rat brain activated similar cells when they observe the pain of others as when they experience pain themselves. That means that same cells that are accountable for causing pain sensation of our experienced pain gets activated when we someone else in pain and such cells are known as ‘Mirror Image Neurons’ allows us the commotion of I feel your pain. Besides without the activity of these ‘mirror neurons,' the animals no longer share the pain of others. There has consistently existed an unasked question about why is that we can get emotional when we see some other person crying? Why is that we wince, when a friend slash his finger? [20]

Many psychiatric disorders are indicated by a lack of empathy, finding the neural basis for allocating emotions of others and being able to modify how much an animal shares emotions of others, is an exciting step towards understanding empathy and these disorders. Human neuroimaging studies have manifested that when we experience pain ourselves, we activate a region of the brain called "the cingulate cortex" when we see someone else in pain we reactivate the same region [20].



On the premises of this researchers formulated two speculations: (a) the cingulate cortex contains mirror image neurons, i.e. neurons that trigger our feeling of pain and are resuscitated when we see the pain of others, and (b) that this is the reason why we grimace and feel pain while seeing the pain of others [20].

Neuroimaging shows that humans replenish their anterior cingulate cortex (ACC) both while experiencing pain and, vicariously, while witnessing pain in others [21]. The vicarious activity is powerful in more empathic individuals [22] and reduced in psychopathy. Lowering ACC activity using a placebo or pharmacological analgesia alters empathy to pain [23,24]. This discovery makes the ACC region of particular interest in the search of a neural mechanism of affect sharing. Some propose these neuroimaging findings reflect the existence of mirror neurons, i.e. neurons responding during the

experience of pain and the perception of the other people's pain [25]. One report of neurons in the mouse ACC revealed that immediate-early gene arc is more expressed following the experience of footshocks i.e. the genes were expressed in high amounts both while experiencing and witnessing the footshock [26]. The review article further explains the experiment conducted and the applications of arc genes in treating over empathic behavior which leads to stress.

MIR-218, MIR-214-3P AND MIR-124 GENES

microRNAs (miRNAs) are short (20-24nt) non-coding RNAs that are associated with post-transcriptional regulation of gene expression in multicellular organisms by influencing both the stability and translation of mRNAs. They are transcribed by RNA polymerase II as a piece of capped and polyadenylated primary transcripts (prior-miRNAs) that can be either protein-coding or non-coding. The initially formed segments after transcription are disassociated by the Drosha gene containing ribonuclease III enzymes to forge an approximately 70-nucleotides-stem-loop precursor miRNA (pre-miRNA), which is further cleaved by the cytoplasmic Dicer ribonuclease to produce the mature miRNA and antisense miRNA star (miRNA*) products. The mature miRNA is included into an RNA-induced silencing complex (RISC), which identifies target mRNAs through imperfect base pairing with the miRNA and most frequently results in translational inhibition or destabilization of the target miRNA (GeneCards-Human Gene Database).

Gathering evidence reveals that microRNAs (miRNAs) are influential molecular links between environmental risk factors and psychopathy. Changed brain expressions of miRNAs have been related to major depressive disorder (MDD) in humans [27,28]. These changes, which localize to brain structures that have a role in mood regulation, containing the prefrontal cortex (PFC), have been noticed in humans and rodents exposed to chronic stress [29,30]. and can contain single miRNAs or clusters of miRNAs [31]. Genome-wide miRNA expression approaches have recognized reduced levels of miRNAs involved in neurotransmission, synaptic plasticity and gene regulation in the PFC of antidepressant-free MDD subjects who died by suicide in contrast to non-psychiatric control subjects [32,33,34,35,36]. In inclusion, rodents unveiled to chronic stress or chronic injection of stress-related hormone corticosterone display depression-like behaviors and exhibit differential expression of several miRNAs, including miR-214-3p, miR-124-3p and miR-218, in the medical PFC (mPFC) [30,37,38].

The determination of MDD relies primarily on the existence of symptoms such as constant feelings of sadness, lack of interest or pleasure, social isolation/avoidance or suicidal ideation. However given its heterogeneousness and the lack of objective biological indicators, the treatment of MDD is still suboptimal for a large percentage of patients [39]. One principal feature of miRNAs is that they can be measured in peripheral fluids, including blood, saliva or urine, and their expression could potentially represent a signature of alterations occurring in the central nervous system [40,41]. Actually, miRNAs are being acknowledged as potential diagnostic biomarkers of disease and mediators of antidepressant reaction to pharmacological and behavioral interventions [28,40].

Neurofeedback Mechanisms

It is recognized as a safe intervention for ameliorating electro neurological flexibility also known as direct brain training and EEG Biofeedback because it is based on electrical brain activity, the electroencephalogram. It is fairly a Brain exercise. Neurofeedback training stated to the brain for less than one hour leads to enhancing of neural connections and communications among brain areas. This paves the way for the optimization and development of therapeutic approaches in anticipation of stroke and Parkinson's. A perception of brain wiring and functioning is playing a key in mindfulness training. Neurofeedback is the most considerable and promising way to regulate dysfunctional brain areas that leads to brain disorders such as chronic pain and depression [42].

Antidepressant Molecules

Depression relating monoamine hypothesis estimates that the elementary pathophysiological basis of depression is a reduction in the levels of serotonin, norepinephrine and/or dopamine in the central nervous system. The monoamine neurotransmission system, which comprises serotonin and norepinephrine systems is the primary target of most major antidepressant drugs that are presently used. Drugs that enhance serotonin and norepinephrine levels at synaptic junctions through reuptake inhibition were developed first, followed by drugs that influence dopamine and acetylcholine systems [43].

Ketamine

Ketamine is a medication mostly used for starting and maintaining anesthesia. It prompts the trance-like (half-conscious) state while providing pain relief, sedation and memory loss. Other uses incorporate chronic pain, sedation in intensive care and depression. Earlier research revealed that Ketamine blocks the NMDA subtype glutamate receptors (blocks an excitatory neurotransmitter) the net consequencing effects seems to be an increase in excitatory neurotransmission [44]. This image from Nature's journal explains this effect follows in Figure 2.

Mechanism of Action of Ketamine

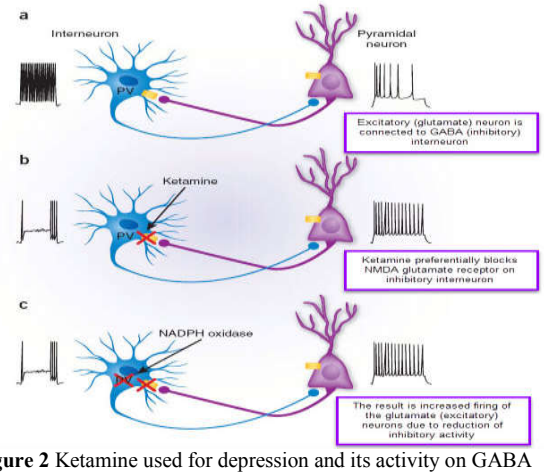


Figure 2 Ketamine used for depression and its activity on GABA interneuron[45].

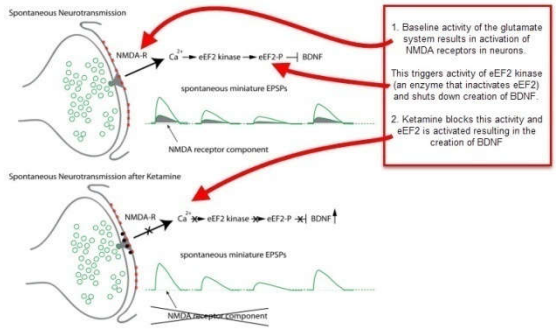


Figure 3 Ketamine used for depression and its activity on BNDF and Elongation factor-2 [45].

Basically, ketamine preferentially blocks the NMDA receptors on obstructing inhibitory interneurons (neurons that regulate the activity of the glutamate system). By blocking the inhibitory interneuron pursuit the net outcoming effect is an expansion in glutamate activity. But this expansion in excitatory or stimulating neurotransmission doesn't describe the effects on depression since the agents that increase glutamate activity generally increase anxiety, and triggers or activates seizures, but haven't usually been showed shown to diminish depression. However, one of the findings states that ketamine promptly increased BDNF. They discovered that ketamine's blockade of NMDA receptors conducts towards the activation of a protein named elongation factor 2 (eEF2), which helps to generate more BDNF protein. Elongation factor 2 is a necessary regulator of protein synthesis in general and plays an essentially important part in deciding and determining levels of BDNF in the brain. The process by which NMDA activity affects BDNF levels is illustrated in the above Figure-3 which is obtained from the article Lisa Monteggia in Biological Psychiatry(2013). When they used enzyme inhibitors to manipulate and influence this pathway directly and improve BNDF protein levels, they saw antidepressant-like effects to those seen with ketamine. Recently researchers have recognized ketamine-induced brain-related changes that are responsible for maintaining the restitution of behaviors related to depression in mice. This study shows that ketamine restored dendritic spines and recovered coordinated neural activity in the prefrontal cortex (PFC) in mice. Ketamine is a blistering antidepressant which relieves depressive symptoms in hours instead of weeks or longer [45]

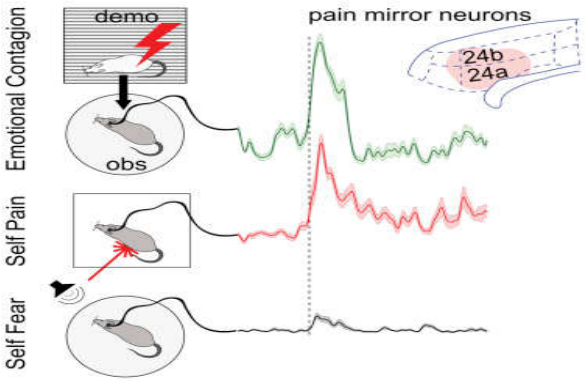
MATERIALS AND METHODS

For ARC genes association with empathy in ACC

Overview of the Experiment

This experiment involved testing of empathy in rats using chronically implanted silicon probes in 17 rats. They had rats look at other rats receiving an unpleasant stimulus (mild shock), and measured what happened with the brain of the observing rat.

Usually, rats freeze as a natural reaction when they get scared to avoid being detected by predators. The researchers found that the rat also froze when it observed another rat exposed to an unpleasant situation. This finding suggests that the observing rat shared the emotion of the other rat [20].



(Current Biology 2019 29, 1301-1312)

METHOD

In this study, the emotional contagion model was utilized in which an animal observes a conspecific experience painful electroshocks [46,47,48,49,50,51,52], which was recorded as multi and single unit pursuit using chronically implanted silicon probes in 17 rats. Researchers analyzed whether some ACC locations and neurons are recruited during our social condition of shock witnessing. Then the activity was recorded in 2 sittings while the spectator himself experiences conditions thought to trigger pain (laser) or fear (listening to shock conditioned sound). Following the culture in the action-observation literature to classify mirror neurons based on their preferences [53,54]., here the neurons were explained broadly responding to the expectation and experience of an emotion as emotional mirror neurons, and those that respond more scarcely to pain but not fear or fear but not pain as emotion-specific pain or fear mirror neurons. Three questions were formulated about the ACC: does the ACC contain 1. Emotional mirror neurons, 2. Emotion-specific mirror neurons, and 3.common coding (that is the genes responsible for observing and experiencing pain follows similar codes for activation). Rigorously establishing attentiveness for an emotion would require testing neurons with a comprehensive battery of all emotions in the self and other, perfectly similar for salience and arousal, alternative of this the experiment was contrasted by the experience of two high salience aversive states (pain and fear) in the self, and tentatively operationalize the terms pain and fear mirror neurons as those that differ between the given pain (laser) and fear (CS) states in the self [20].

Several particular methodological options were made in this pattern. The researchers chose rats, because area 24 of the rat ACC (formally referred to as Cg1 and Cg2) is similar in cytoarchitecture and association to the ACC involved in pain empathy in humans [21,55.56] and is activated by the suffering of others, and rats are large enough to ease chronic recordings in awake behaving animals. In this experiment, the spectators were pre-exposed to footshocks 2-3 weeks before the main experiment, because having experienced electroshocks is adverse in rats for showing strong signs of vicarious distress while witnessing another animal receive electroshocks [46]. This proposes that emotional contagion in the model is mediated in part by sensory signs that the animal learns to decode through self-experience, with the sound and sight of the shock reactions playing remarkable roles [46,48,57]. They utilized footshocks to the demonstrator because this is the best

distinguishable trigger of emotional contagion in rats. During pre-exposure, they coupled the shocks with a tone to later compare responses to self-pain (laser) and other's pain (shock obs) against the fear triggered by hearing this fear conditioned tone played again. Since shocks to the implanted animal would include artifacts in the recordings, to test responses to self-pain without compromising signal quality, an alternative of shocks they used $C0_2$ heat laser adjusted to trigger a noncomparable reaction, a well-characterized pain-induction method [58,59].

Firstly, the multiunit activity (MUA) was given from the silicon probes. MUA pools spiking activity of thousands of neurons within about 0.2mm of each electrode contact [60], and is specifically stable across days [61], which is advantageous given that ShockObs, laser, and CS conditions were recorded in sessions spread across 2 days, with this signal researchers explored that the rat ACC has locations in a way that approximates the mesoscopic spatial scale of human fMRI. ACC activity is necessary for getting contacted by the suffering of another which was proved by transiently deactivating ACC using muscimol microinjections in a new group of animals while exposing them to high shock Obs and CS [20].

For miR-218 genes as a biomarker of susceptibility to stress

Overview of the experiment

The experimental series was managed to assess whether miR-218 in the mPFC grants resilience or susceptibility to depression-like behavior in adult mice, using the Chronic Social Defeat Stress (CSDS) model of depression. Also, the study detected stress-induced variations of miR-218 expression in the medical prefrontal cortex can be recognized in blood. Down-regulation of miiR-218 in the medical prefrontal cortex (PFC) enhances vulnerability to a single session of social defeat. Overexpression of miR-218 particularly in PFC pyramidal neurons promotes resilience to CSDS and prevents stress produced morphological alterations to those neurons. After CSDS, vulnerable mice have low levels of miR-218 in blood, compared with control and resilient groups. Up-regulation and downregulation of miR-218 levels peculiarly in the PFC correlate with miR-218 expression in blood [62].

Animals

Experimental methods were executed incommensurate with the guidelines of the Canadian Council of Animal Care and approved by the McGill University and Douglas Hospital Animal Committee. All mice used in these studies were procured from Charles River Canada and maintained on a 12^{th} light-dark cycle with ad libitum availability to food and water throughout the experimental conditions [62].

Male C57BL/6 wildtype mice were provided as experimental subjects in CSDS and the single sitting of defeat paradigms. Male CD-1 retired breeder mice previously screened for hostile behavior were used as social aggressors. CD-1 mice were single-house throughout the study. Animals were randomly distributed by cage before exposure to the stressor before stereotaxic surgeries [62].

Social defeat stress Paradigms

CSDS was executed as in [63,64], each adult male mouse C57BL/6 experimental mouse was exposed to 5 min of physical aggression by male CD-1 mice. At the execution of the sitting, C57BL/6 experimental and CD-1 mice were accommodated overnight in a 2 sectioned rat cage and separated by a transparent divider to provide sensory but not physical contact the method was repeated for 10 consecutive days in which the experimental mice faced new attacker mice each day. Control C57BL/6 mice were housed in similar 2 sectioned rat cages with a different littermate every day [62].

Single social defeat

The SSD pattern consisted of a distinctive sitting of social defeat, as described above with minor changes [65]. In detail, adult C57BDL/6 experimental mice were exposed to 5 min of physical hostility by a novel CD-1 mouse and then housed with the same aggressor CD-1 mouse in a 2-compartment rat cage during 15 min to provide psychological stress. After the SSD session, C57BL/6 experimental mice were single-housed 24h preceding to the SIT [62].

Social Interaction test

24h after the last session of CSDS or SSD, C57BL/6 experimental mice were evaluated in the SIT as before [63]. This test composed of 2 sittings in which defeated mice and control mice explored a square-arena in the absence or presence of a novel aggressor CD-1 mouse for a period of 2.5 min each session [62].

Forced swim test

Immobility was evaluated in the forced swim test where each mouse was placed in a Plexiglas beaker for a 5 min sitting. The beaker was permeated with the tap water at 23^0C and 15 cm in depth. Animal behavior was recorded with a video camera for office manual analysis by an expert observer who was blind to the experimental conditions and recorded the duration of immobility during the 5 min of the test [62].

Antagomir

A locked Nucleic Acid (LNA) oligonucleotide with a sequence targeting miR-218 (Ant-miR-218) was used to downrange the expression of miR-218 *in vivo*. A scrambled LNA was utilized as a control. Ant-miR-218 was liquefied in sterile PBS at a final concentration of 0.3mM as indicated by [66,67]. The effectiveness and attentiveness of Ant-miR-218 were established through PCR as in [67].

Viral Construct

The viral construct was obtained from Vector Biolabs. Adeno-Associated Virus (AAVB) demonstrating a prior-mmu-miR-218-GFB fusion protein under the control of the calcium/calmodulin kinase II alpha promoter was used to overexpress miR-218 in pyramid neurons particularly. A scrambled construct combined with CaMKII alpha GFB was utilized as a control virus [62].

Stereotaxic Surgery

All the surgeries were executed under aseptic conditions as described in [70]. Adult male C57BL/6 wild type mice were deeply anesthetized with isoflurane and positioned in stereotaxic apparatus.

Wakeful intranasal administration of Ant-miR-218 or Anti-Scrambled

Adult male mice were held by the skin of their necks in the palm to decrease movement as indicated by [63]. A total of 5 microlitres of anti-scrambled were delivered per nostril with 10XL pipette tip attached to a P10 micropipette. Mice were placed in their home cage to detect free movement.

For neuro feedback training

The technique used: Magnetic Resonance Imaging (MRI)
MRI helps individuals to have access to their own brain activity in real time and quickly gain control over it.

Method

36 healthy subjects participated in the study which aimed to increase the activity of brain regions involved in hand movements. Instead of actually moving their hand, participants were asked to only imagine the movement in total rest. 19 individuals received real brain training and 17 individuals received placebo neurofeedback training immediately before and after 30 minutes of training. The neural networks were scanned to observe the impact of the neurofeedback (or placebo) on brain wiring (structural connectivity) and communication (functional connectivity) [42].

For ketamine in remission of depression

The technique used: Magnetic Resonance Imaging (MRI)

Method

Studies revealed that ketamine-induced brain-related changes that are responsible for maintaining the cancellation of behaviors related to depression in mice. Ketamine treatment restored dendritic spines and rescued organized neural activity in the prefrontal cortex in mice. Ketamine is a fast-acting antidepressant that can be used for potentially transformational alternative treatments for depression [44].

To understands the mechanisms underlying the transition from active depression to the cancellation of depression in humans researchers examined behaviors related to depression in mice. They obtained high-resolution images of dendritic spines in the prefrontal cortex before and after they were exposed to the stressor. Dendritic spines are projections in the part of neurons that receive communication input from other neurons [44].

RESULTS AND DISCUSSION

For ARC Genes Association with Empathy in ACC

They found that the rat ACC actually contains emotional mirror neurons. Most of these show a partiality for one of their first-hand experiences, with the majority responding more to Laser than CS. Spike decoding confirms common coding across observed and experienced pain. Deactivating this region lessens freezing while witnessing footshocks but not while hearing the CS. Together, this proposes that the rat ACC maps the experience of another animal onto a mosaic of pain- and fear-sensitive neurons in the observer and this region are necessary for emotional contagion to trigger freezing [20].

Applications

- ✓ Deactivating the cingulate cortex region: impairs the social transmission of distress using pharmacological analgesia and placebo
- ✓ Role in psychophysiological Disorders: to increase activation of cingulate cortex
- ✓ Modification of cingulate cortex: this form of empathy can be suppressed
- ✓ Treating depression by finding suppressor molecules and genes associated with activation of mirror neurons
- ✓ Personalized Neuro disease treatment by self-control in preventing the overexpression of cells in cingulate cortex
- ✓ Identification of antagonists (such as muscimol: psychoactive constituent in mushroom) against the activity of such cells

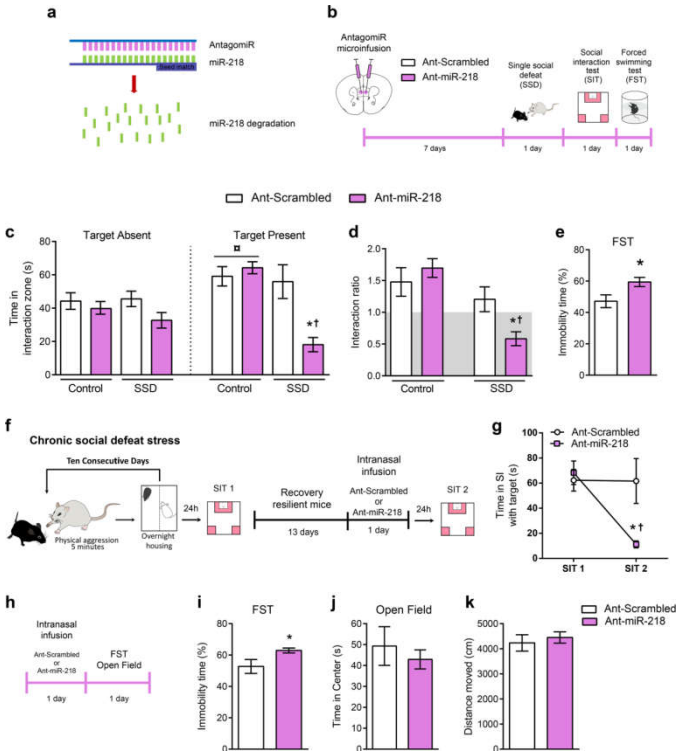
For miR-218 Genes as a Biomarker of Susceptibility to stress

Down-regulated expressions of miR-218 in the mPFC promotes susceptibility to depression-like behaviors
Reduced expression of miR-218 in the mPFC is related to depression in humans and susceptibility to CSDS in adult mice [63]. To address whether the down-regulation of mPFC levels of miR-218 directly causes increased vulnerability to CSDS, they used nucleic acid (LNA)-modified antisense oligonucleotides that hybridize miR-218 with high vulnerability *in vivo*, leading to its degradation [66] follows in (Figure 1a). For control microinfusions, they used LNA-modified antisense oligonucleotides carrying a scrambled sequence. One week after infusion, adult mice were exposed to an SSD, which comprised of 5 min of physical aggression by a novel CD-1 mouse, previously screened for hostile behavior follows in (Figure 1b). Twenty four hr after an SSD, adult mice were tested in the SIT and classified into receptive and strong populations according to the social interaction ratio, as described in [63]. They chose this pattern since a single defeat session does not induce social evasion in adult wild-type mice24. As expected, an SSD fails to induce social avoidance in mice that received the Antscrambled, indicated by the time spent in the interaction zone in the presence of a novel CD1 mouse follows in (Figure 1c) and the social interaction ratio higher than >1 follows in (Figure 1d). Indifference, an SSD is sufficient to induce high social avoidance in mice injected with Ant-miR-218 in the mPFC follows in (Figure 1c-d), indicating that the downregulation of miR-218 in the mPFC induces a defenseless phenotype. Furthermore, miR-218 downregulation in the mPFC increases immobility in the forced swimming test follows in (Figure 1e), another measure of increased stress susceptibility [62].

Intranasal delivery of Ant-miR-218 induces susceptibility in mice

Recent confirmations reveal that intranasal delivery of antagomiRs can successfully alter stress-related behaviors in mice [37]. They, therefore, traveled an unfamiliar area and found the possibility that intranasal delivery of Ant-miR-218 could promote depression-like behaviors. Initially exposed adult wild-type mice to CSDS and tested them in the SIT as in [63]. Thirteen days after the first SIT (SIT 1), mice that exhibited a strong or resilience phenotype were infused intra-nasally with either Ant-miR-218 or Ant-Scrambled. Twenty-four h after infusion, mice

were tested in a second SIT (SIT 2) to evaluate social avoidance (Figure 1f). As



Follows in (Figure 1g), resilient mice infused with Ant-miR-218 spend less time to interact with the social target in the SIT 2 in consideration to SIT 1. This result was not observed in resilient mice infused with Ant-Scrambled intra-nasally in stress-naive mice and tested them 24 h later in the forced swimming test (FST) (Figure 1h). They established that intranasal infusion of Ant-miR-218 enhances the percentage of immobility time follows in (Figure 1i), again suggesting a defenseless effect. Importantly, two hours after the FST, mice were tested in the open field to evaluate anxiety-like behaviors and overall locomotion. They did not find notable differences between groups in the time mice spent in the center (Figure 1j) or the total distance traveled (Figure 1k) in the open field [62].

Applications

MiR-218 can acts as a reliable biomarker for regulation and determination of stress, acting as a novel preventive measure and allowing robust treatment against neurological diseases. Direct manipulation of the levels of miR-218 in mPFC pyramidal neurons, via viral injection or antagomiR microinfusion, correlates with circulating levels of miR-218, supporting the idea that mPFC might be an important source of miR-218 in blood.

Thus direct detection of miR-218 in the blood can play a vital role in the diagnosis of susceptibility or resilience against stress and also can be used in the determination of the effectiveness of cognitive therapies.

For Neurofeedback Training

In this present study by using neural network scanning it was seen that Corpus Callosum a part of the brain, major cerebral bridge that connects the right and left hemisphere exhibited increased integrity and the neural network controlling the movements of the body became stronger and the whole system became more robust. The training also had a positive impact on the default mode network (the region of the brain that is impaired after stroke). The general brain exercise here proves that the impacts are more robust than any other cognitive therapies. Even the hypnotherapies and mindfulness training are based on the rewiring of the brain and by using neurofeedback training one can become their own trainer of the brain. All the challenges related to mental health and behavior are deep-rooted with the deregulated brain activity [42].

Applications: Neurofeedback is an important mechanism that allows us to tackle the root of any problem by training the brain to better regulate itself. Neurofeedback is a personalized procedure of having an accurate indication over our brain's electrical signals that are measured with a device called electroencephalograph (EEG) which thus can help us to control our brain responses and that can be an ideal step towards preventing depression and all other neurological disorders that are originated from brain deregulation. By using this treatment an initial stage of brain's dysfunction can be monitored and prior treatment and solutions can be obtained.

For Ketamine in Remission of Depression

Studies revealed that mice displaying behaviors related to depression had increased the elimination of and decreased the formation of dendritic spines in the prefrontal cortex compared with the mice which were not exposed to a stressor. Liston's group found that ketamine treatment rapidly restored functional connectivity and assemble the activity of neurons and eliminated behaviors related to depression. After 24 hours of receiving a single dose of ketamine, mice were exposed to a stressor. Mice showed a reversal of behavior related to depression and an increase in dendritic spine formation compared to one which did not receive ketamine treatment. These new dendritic spines were functional, creating working connections with other neurons [44].

Demerits

Behavioral changes in neural activity in mice happened quickly (3 hours of treatment) but dendritic spine formation happened slowly (12-24 hours of ketamine treatment). Researchers found that selectively deleting there newly formed dendritic spines lead to the re-emergence of behaviors related to depression. As a solution, it was suggested that enhancing synapse formation and prolonging their survival could be useful for maintaining the anti-depressant effects of ketamine. Mode of administration is IV compared to other antidepressants that come in pill formSafety and efficacy of this drug are still not at its 100% efficacy state

Merits

Quick action, as compared to other antidepressants that take 2 to more weeks for positive result ketamine can transform the timeline of treatment for depression, with its efficient immediate results.

The drug i.e. ketamine in ketamine depression treatment is given in lower doses and an intravenous mode of delivery.
Proven to be useful in patients with the development of resistance to other antidepressants and also has a reduction in suicidal thoughts.

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