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Bipolar Network News

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A Common Variant of BDNF Predicts Lack of Response to Intravenous Ketamine

Brain-derived neurotrophic factor (BDNF) is a protein in the brain that protects neurons and is necessary for long-term memory and learning. Different people have different genetic variations in BDNF depending on which amino acid the gene that codes for it inserts into the protein, valine or methionine. There are three possible combinations that vary in their efficiency. The Val66Val allele of BDNF is the most efficient for secreting and transporting BDNF within the cell body to synapses on dendrites, and is also a risk factor for early onset of bipolar disorder and rapid cycling. Twenty-five percent of the population has a Met variant (either Val66Met or Met66Met), which functions less efficiently. These people have mild decrements in some cognitive processing.

Increases in BDNF are necessary to the antidepressant effects of intravenous ketamine. In animals, ketamine also rapidly changes returns dendritic spines that had atrophied back to their healthy mushroom shape in association with its antidepressant effects.

Depressed patients with the better functioning Val66Val allele of BDNF respond best to ketamine, those with the intermediate functioning Val66Met allele respond less well, and those with the poorest functioning Met66Met allele virtually do not respond at all.

Researcher Ronald S. Duman of Yale University recently found that increases in BDNF in the medial prefrontal cortex are necessary to the antidepressant effects of ketamine. If antibodies to BDNF (which block its effects) are administered to the prefrontal cortex, antidepressant response to ketamine is not observed.

Duman also found that calcium influx through voltage sensitive L-type calcium channels is necessary for ketamine's antidepressant effects. A genetic variation in CACNA1C, a gene that codes for a subunit of the dihydropiridine L-type calcium channel, is a well-replicated risk factor for bipolar disorder. One might predict that those patients with the CACNA1C risk allele, which allows more calcium influx into cells, would respond well to ketamine.

Also in this issue:

Ketamine and the Nucleus Accumbens in Depression

Brain-derived neurotrophic factor (BDNF) keeps neurons healthy and is critical for long-term memory and synapse formation. BDNF levels increase in the nucleus accumbens (the brain's reward center) and decrease in the hippocampus during clinical depression and chronic cocaine use. In rodents, the same changes in BDNF levels occur during defeat stress (which resembles human depression).

Rodents who are repeatedly defeated by a larger rodent exhibit behaviors such as social withdrawal, lethargy, and decreased interest in sucrose. The increases in BDNF in the nucleus accumbens of these rodents could reflect the learning that takes place during the repeated defeat stress and the depression-like behaviors that follow it. Blocking the BDNF increases in the nucleus accumbens prevents these behaviors from developing.

Chadi Abdallah and other researchers at Yale University recently found that the left nucleus accumbens of patients with treatment-resistant depression is enlarged compared to normal controls, and **the drug ketamine, which produces rapid-onset antidepressant effects, rapidly decreases the volume of the nucleus accumbens in the depressed patients**. The mechanism by which it does so is unknown, but could reflect some suppression of the depressive learning.

Any relationship between the volume of the nucleus accumbens and its levels of BDNF is unknown, but ketamine's effect on the size of this brain region could be linked to a decrease in the defeat-stress memories.

Thank you to our many readers who informed us that you received issues of the *BNN* addressed to an incorrect first name. We apologize for the error in our database. It has been fixed.

Therapeutic Potential of Neurosteroids for Seizures and Bipolar Depression

Neurosteroids have shown promise in the treatment of anxiety and depression.

Allopregnanolone, a natural metabolite of the gonadal steroid progesterone, is a neurosteroid that acts as a positive modulator of synaptic and extrasynaptic GABA-A receptors and exerts effects without the development of tolerance.

Traumatic Brain Injury and Seizures

Researcher Mike Rogawski at the University of California, Davis developed an intravenous formulation of allopregnanolone that is being studied as a treatment for traumatic brain injury. The formulation was provided on an emergency-use basis to stop treatment-resistant status epilepticus (non-stop seizures) in patients in intensive care who had been unresponsive to all medications and were placed in a barbiturate coma. When barbiturates were stopped, their seizures returned. **All four intensive care patients who were treated with allopregnanolone had their status epilepticus cease and were able to go home.** This included a 23-year-old who had been hospitalized with refractory status epilepticus for over 90 days.

Bipolar Depression

Sherman Brown of the University of Texas Southwestern reports that allopregnanolone has positive effects in bipolar depression. Patients in Brown's study received 100mg capsules twice daily during the first week, then one capsule in the morning and two capsules in the evening during the second week, and two capsules in the morning and three capsules in the evening during the third week.

Neurosteroids can change the excitability of neurons through their interactions with the neurotransmitters that carry signals from neurons across synapses. Among the various types of neurotransmitters, GABA plays an inhibitory role, while glutamate is responsible for excitability. Allopregnanolone, which is naturally produced in the body, has positive effects on GABA receptors and inhibitory effects on glutamate NMDA receptors, so that it increases the balance of inhibition (GABA) over excitation (glutamate).

Bipolar Network News

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Another Blocker of Glutamate Receptor Function with Rapid Antidepressant Effects

Certain drugs such as ketamine and memantine that work by blocking activity at the NMDA receptor for the excitatory neurotransmitter glutamate have antidepressant effects. D-cycloserine is a drug that has a related mechanism and is being studied as an antidepressant. At high doses the drug acts as an antagonist at the glycine site of the NMDA receptor, blocking glycine's ability to facilitate glutamate transmission through the receptor.

Joshua Kantrowitz, a researcher at Columbia University, reported at a recent scientific meeting that **the rapid-onset antidepressant effects of D-cycloserine could be maintained for eight weeks**. Similar findings were published in the *Archives of General Psychiatry* in 2010 and were reported in another study by Uriel Heresco-Levy in a 2013 article in the *Journal of Neuropsychopharmacology*.

Glutamate is the major excitatory neurotransmitter in the brain and is important for the development of long-term memory. However, glutamate overactivity may contribute to depression. Decreasing this overactivity (with ketamine, memantine, or D-cycloserine) may produce antidepressant effects.

Conditioned Fear Can Be Transmitted Transgenerationally in Rodents

Scientists often use fear conditioning to study rodents' learning and behavior. If a particular stimulus (such as a light, a sound, or an odor) is presented paired with the delivery of a mild shock, the animal begins to associate the stimulus

Continued on Page 3

Buspirone and Melatonin Together May Treat Unipolar Depression

The combination of the anti-anxiety drug buspirone (trade name Buspar) and melatonin, a hormone that regulates cycles of sleep and waking, may be effective for depression. Researcher Maurizio Fava and other researchers at Massachusetts General Hospital report that **low-dose buspirone (e.g. 15 mg/day) combined with a 3 mg dose of melatonin produced significant antidepressant effects in a six-week study of patients with unipolar depression**.

While buspirone is not a potent antidepressant at low doses, the combination of buspirone and melatonin exerted significant effects, leading to better antidepressant response than did either placebo or 15 mg of buspirone by itself. Another benefit of the combination is that the low dose of buspirone minimizes side effects.

Buspirone is a serotonin 5HT1A receptor partial agonist, meaning that it produces weak activity at this serotonin receptor, but does not allow it to get overstimulated.

Conditioned Fear

Continued from Page 2

with the shock and will freeze when it is presented and avoid the stimulus.

New research shows that **if a pregnant rat (known as a dam) goes through fear conditioning that pairs an odor with a shock, the rat's offspring will also avoid that odor into adolescence**. Even if the pups are raised by a different mother who never went through the fear conditioning, they still avoid the odor into adolescence, showing that they do not learn the behavior through watching their mother.

The conditioning is specific to the particular odor, such that a different odor not used in the fear conditioning does not evoke a heightened reaction from the pups. It appears that the pup learns the fear through chemical signals, such as alarm pheromones that can pass through the placenta.

Transgenerational Transmission of PTSD From Parents to Children

At a recent scientific meeting, Rachael Yehada showed that PTSD-like traits could be passed transgenerationally. **Mothers in New York City who were pregnant when they experienced the events of September 11, 2001 and went on to develop post-traumatic stress disorder (PTSD) produced children with low cortisol in their blood (a sign of PTSD). If the fathers had PTSD during the mother's pregnancy, the children had high cortisol**.

These gender-related findings have some parallels in studies of rodents. When a rat pup is separated from its mother for 15 minutes, the mother is overjoyed to see the pup return and licks and grooms it excessively. This maternal overprotection yields an animal with lifelong low cortisol through an epigenetic process. The glucocorticoid receptor gives a feedback message to suppress cortisol, and glucocorticoid receptors are increased in the pups' brains because of lower methylation of the DNA promoter for glucocorticoid receptors.

If a father has PTSD, there is more methylation of the promoter for glucocorticoid receptors and less expression of them in the forebrain. There is also less feedback suppression of cortisol and the baby exhibits high cortisol.

The methylation of the glucocorticoid receptors in the offspring's white blood cells is highly correlated ($r=0.57$, $p<0.005$, $n=23$) with methylation in the parent's white blood cells.

Types of Epigenetic Modifications

The environment impacts not your inherited genes (based on the DNA nucleotides that encode amino acids to be sequenced in the production of proteins), but how easy it is to activate gene transcription or repress gene transcription.

There are various epigenetic modifications that can occur:

1. DNA Methylation (usually repressive)
2. Histone Methylation (usually repressive)
3. Histone Acetylation (usually activating)
4. DNA hydroxymethylation
5. Micro RNAs (si-mRNA) (repressing or activating)
6. Nucleosome remodeling by chromatin regulatory enzymes.

If the histone spools around which DNA is wrapped are moved further apart, this is activating. If the histones are moved closer together, this is repressing.

Gene for Calcium Channel Linked to Bipolar Disorder in Several Ways

No one gene explains the risk of developing bipolar disorder. Many genes are involved, each with a small effect. However, **the effects of one particular gene have been validated in multiple different ways. The gene is called CACNA1C, and it codes for one subunit of the dihydropyridine L-type calcium channel. Calcium channels are structures on the membranes of neurons that allow calcium to enter cells and alter their excitability**.

Different people can have different variants of the CACNA1C gene, depending on which nucleotides appear there: valine (Val) or methionine (Met). One particular variant (known as the Met/Met single nucleotide polymorphism, rs1006737) has been associated with executive function deficits compared to the Val/Val variant in multiple tests in patients with bipolar disorder. Executive function refers to abilities like planning, organizing, and retaining information. This was reported by Soeiro-de-Souza et al. in the journal *Acta Psychiatrica Scandinavica* in 2013.

Importantly, CACNA1C has also been linked to risk of bipolar disorder, a finding that was replicated in several large genome-wide association studies (GWAS). Autopsy studies of people who had been diagnosed with bipolar disorder show more calcium channels in their brains. The Met/Met variant of the CACNA1C gene also lets more calcium ions into cells. Those who have the gene variant also show differences in some brain structures known to be involved in the modulation of emotions compared to those without the variant.

In addition to these findings, more than a dozen studies report increased intracellular calcium in the white blood cells of people with bipolar disorder compared to controls. To the extent that these increases in intracellular calcium reflect changes in neurons, this would be consistent with the findings about CACNA1C. High levels of calcium influx and the associated intracellular calcium may increase cellular excitability and potentially dysregulate normal neuronal functioning.

Nimodipine

The final piece of evidence linking altered calcium channel regulation to bipolar disorder is a direct therapeutic test of a drug that blocks calcium influx through the dihydropyridine L-type calcium channel. **There is evidence that nimodipine, which selectively blocks dihydropyridine L-type calcium channels, has therapeutic effects in bipolar disorder.**

Double-blind off-on-off-on studies by Pazzaglia et al. (1993, 1998) and this editor Post and Leverich (2008), in which patients' mood is rated while alternating between taking either placebo or nimodipine on a double-blind basis, have shown that the drug has both antimanic and antidepressant efficacy, including in patients with ultra-rapid and ultra-ultra rapid or ultradian cycling (cycling multiple times within one day).

Other open case studies in adults (Brunet et al. 1990, Goodnick 1995) and one in a teenager (Davanzo et al. 1999) with ultradian cycling support the double blind findings, as these patients also responded to nimodipine when other treatments had failed.

The combination of nimodipine and lithium may be particularly effective. A randomized study by Chaudhry et al. (2010) observed several different treatments including lithium alone, lithium plus nimodipine, valproate plus nimodipine, and carbamazepine with nimodipine, with about 50 participants in each group. Chaudhry found about a 50% response rate to lithium alone, but a 73% response rate on the combination of lithium plus nimodipine. (In two other randomized groups of about 50 patients each, those receiving nimodipine in combination with either valproate or carbamazepine only showed about a 50% response rate.) An earlier retrospective series showed that a year on the combination of nimodipine and lithium was more effective than a year on either drug alone, also suggesting additive effects of the drugs in combination.

Very early evidence had suggested that nimodipine had some positive effects on cognition in advanced Alzheimer's disease compared to placebo (a finding that was never pursued further). Nimodipine increases levels of the peptide somatostatin in cerebrospinal fluid, which are low in both depression and Alzheimer's disease.

Implications for Treatment

Nimodipine is worth a try in patients who respond well to lithium but cannot tolerate it or cannot take full therapeutic doses of it because of renal dysfunction. In research by Stephen Dubovsky, a history of a good prior response to lithium actually predicted a positive response to L-type calcium channel blockers. However, as noted above, nimodipine is also effective in some patients with a history of nonresponse to lithium.

Nimodipine might be useful in those with treatment-resistant ultra-rapid and ultradian cycling, although further studies with these groups are needed.

Nimodipine should also be tested in clinical trials to see if it could help prevent or reverse some of the cognitive deficits associated with bipolar disorder.

In a young person who is at high risk for bipolar disorder because they have a parent with the disorder, a test for high intracellular calcium or the CACNA1C variant Met/Met (neither of which is readily available at this time) could provide added

Continued on Page 6

Information from Environmental Experiences Can Be Passed on in Dad's Sperm

Researcher Brian Dias has shown that **when rats that would later be fathers learned to associate an odor with a shock, this learning could be passed on to the next generation when the father mated with a female rat that had not learned the same association**.

It turns out that the next generation of rat pups shows increased behavioral reactivity to the odor in a process different from the fear conditioning they might exhibit if they learned to avoid the odor through their own experiences.

Presumably, the pup is somehow programmed through an epigenetic modification of the father's sperm to grow more neurons from the nose to the olfactory bulb that specifically react to the odor its father feared, and not to other odors. Miraculously, when the second generation pup grows up and fathers a third generation pup, the new pup also shows increased behavioral sensitivity to that specific odor. How the odor information from the first generation is represented in the fathers' sperm and passed on to their descendants is still a complete mystery.

There are also new data that a father rat fed a diet deficient in folic acid (vitamin B9) will sire offspring with more congenital malformations. Additionally, an obese father rat fed a diet that includes extra fat calories will sire pups that become obese as adults even when fed a normal milk diet from a svelte mother before weaning and then fed a normal diet after weaning.

Mothers' behavior usually gets most of the credit and/or blame for her children's behavior, but now it looks like fathers' diet or behavior (even before they have children) may have lasting consequences for their offspring.

Epigenetic Regulation of Social Attachment: Genes May Dictate Partner Preference

Prairie voles, which form monogamous bonds for life, are often studied as a source of information about social attachment. New findings indicate that these mating choices are regulated by epigenetics.

Epigenetics refers to changes in genes that do not affect the inherited sequence of DNA, but affect how easily the DNA is transcribed to produce proteins. Environmental events such as stress or exposure to chemicals can bring about epigenetic changes by adding or subtracting acetyl or methyl groups from strands of DNA or the histones around which it is wound.

When prairie voles mate naturally, levels of oxytocin, often thought of as the "bonding hormone," increase in the reward area of the brain, the nucleus accumbens. When voles are given a drug that increases histone acetylation, their behavior mimics natural partner preference. The drug, known as a histone deacetylase (HDAC) inhibitor, blocks the removal of acetyl groups, and researchers Wang et al. reported in the journal *Nature Neuroscience* in 2013 that oxytocin levels increase in the nucleus accumbens. The voles receive the drug and mate for life, suggesting that social bonding is epigenetically regulated.

Similar epigenetic alterations may play a role in human social bonding and vulnerability to depression. Depressed mothers and their offspring have low levels of oxytocin in their blood, and maternal depression is a risk factor for depression in the offspring, as reported by Apter-Levy et al. in the *American Journal of Psychiatry* in 2013.

Editor's Note: Perhaps depressed moms who show reduced physical and verbal interactions with their newborns should receive special training in holding, cuddling, cooing, and other social bonding activities that could increase their infants' oxytocin levels and potentially also decrease their own anxiety and depression.

Gene Mutation Induces Bipolar-Like Symptoms

A mutation in a gene related to circadian rhythms may help explain bipolar disorder. Animals with a mutation in the gene, known as CLOCK, typically exhibit behaviors that mimic human mania, such as increased locomotor activity and decreased anxiety.

Stress can lead to depression in bipolar patients, so **researcher Nicole Edgar et al. exposed animals with the mutated "manic" version of the CLOCK gene to unpredictable chronic mild stress. The stress brought about decreased locomotor activity and increased anxiety, mimicking a switch into depression**. These data suggest that alterations in CLOCK genes may provide a useful model for both mania and depression.

The research was presented at the 2013 meeting of the Society of Biological Psychiatry, and the abstract (#471) can be found in the meeting supplement, Volume 73, Number 9S of the journal *Biological Psychiatry*.

In another abstract (#472) at the same meeting, researcher Wilbur Williams et al. reported that alterations in related clock genes (that result in decreases in the proteins CRY-1 and SIRT1) are associated with manic-like behavior that could be reversed using lithium. These data further suggest that clock genes may provide a useful model for bipolar disorder.

Fear Memories Can Be Erased or Provoked in Animals

Researchers have identified neurons responsible for remembering conditioned fear in the amygdala of rodents, and can turn them on and off. At the 2013 meeting of the Society of Biological Psychiatry, Sheena A. Josselyn gave a breathtaking presentation on this process.

When animals hear a tone they have learned to associate with the imminent delivery of a shock in a given environment, they learn to avoid that environment, and they reveal their learning of the tone-shock association by freezing in place.

Josselyn was able to observe that 20% of the neurons in the lateral nucleus of the amygdala were involved in this memory trace. They were revealed by their ability to increase the transcription factor CREB, which is a marker of cell activation.

Using cutting-edge molecular genetic techniques, the researchers could selectively eliminate only these CREB-expressing neurons (using a new technology in which a diphtheria toxin is attached to designer receptors exclusively activated by designer drugs, or DREADDs) and consequently erase the fear memory.

The researchers could also temporarily inhibit the memory, by de-activating the memory trace cells, or induce the memory, so that the animal would freeze in a new context.

Josselyn and colleagues were able to identify the memory trace for two different tones in two different populations of amygdala neurons.

The same molecular tricks with memory also worked with cocaine cues, using what is known as a conditioned place preference test. A rodent will show a preference for an environment where it received cocaine. Knocking out the selected neurons would remove the memory of the cocaine experience, erasing the place preference.

The memory for cocaine involved a subset of amygdala neurons that were also involved in the conditioned fear memory trace. Incidentally, Josselyn and her group were eventually able to show that amygdala neurons were in competition with each other as to whether they would be involved in the memory trace for conditioned fear or for the conditioned cocaine place preference.

BDNF in Learning and Memory

Brain-derived neurotrophic factor (BDNF) is involved in various aspects of learning and memory. The DNA for BDNF contains nine different regulatory sites, each of which is involved in different aspects of learning. Researcher Keri Martinovich studied each site by selectively knocking each one out with a genetic manipulation. She found that **blocking the e1 site increased acquisition of new learning and recall in mice, while e2 did the opposite**. Blockade of e4 had no effect on these memory functions but markedly blocked the process of extinction, which involves a different kind of new learning.

A mouse that learned to associate a particular cue with a shock (a process known as conditioned fear) will stop reacting to the cue after it is presented many times without a shock. This learning that the cue is no longer associated with the shock is referred to as extinction. The animals with e4 blocked in their BDNF did not develop the new extinction learning, and continued to react to the cue as if it were still associated with the shock.

Editor's Note: These data may have clinical relevance for humans. The anticonvulsant valproate (trade name Depakote), a histone deacetylase inhibitor, selectively increases the e4 promoter site of BDNF and facilitates extinction of conditioned fear, according to research by Tim Bredy et al. published in 2010.

Clinical trails should examine whether valproate could enhance fear extinction in patients with post-traumatic stress disorder (PTSD).

Rats Learn Fear Conditioning From One Another

Rats who are taught to associate a light with an electric shock learn to avoid the light. This process is known as conditioned fear. New research shows that **if one rat watches another rat go through fear conditioning, the observing rat will also show the effects of fear conditioning**. It will also avoid the light, but only if it had previous experience with fear conditioning. It appears that rats have the ability to learn from other rats' painful experiences.

Calcium Channel

Continued from Page 4

evidence of risk, so that early intervention using family focused therapy (FFT) and/or medications might be considered if symptoms develop.

Whether early intervention with nimodipine could help prevent the onset of full-blown mania in a child who has bipolar illness not otherwise specified (BP NOS), which is often accompanied by multiple mood switches in a single day, and is at high risk for converting to bipolar I or II disorder within several years should also be studied.

Pharmacogenetic studies should assess whether those with the Met/Met variant of CACNA1C are more responsive than those without this variant to the effects of nimodipine on mood stabilization or cognition. If this proved to be the case, it would be a step toward "personalized medicine," i.e. predicting in advance what drugs might work best for a given individual based on genetic or other laboratory testing.

HDAC Inhibitor Facilitates Extinction of Fear Memories

Unwanted recall and re-experiencing of traumatic memories is thought to be a crucial mechanism leading to the onset of post-traumatic stress disorder (PTSD). The inability to diminish (extinguish) those memories contributes to the persistence of PTSD. A new study suggests that the extinction of fear memories can be enhanced by a drug that acts epigenetically to alter the structure of DNA and subsequent gene expression.

DNA is wound around structures called histones, and chemical changes can affect how loosely or tightly the DNA is wound. Johannes Graff et al. reported in the journal *Cell* in 2014 that application of a histone deacetylase (HDAC) inhibitor, which keeps acetyl groups on histones, ensuring that DNA is wrapped more loosely and is easier to activate (or transcribe), helps rodents revise both new and old fear memories after they have been actively recalled.

When a memory is actively recalled, the trace of that memory in the brain becomes more amenable to revision over the proceeding five minutes to one hour (a period known as the reconsolidation window). New learning and extinction training (to get rid of the memory) lasts much longer when it takes place during the reconsolidation window than when the same procedures are performed 6 hours later (after the reconsolidation window has closed) or if the procedures are performed in the absence of active recall of the memory (when the reconsolidation window is never opened).

We have previously described the 2013 work of Xue et al. published in the journal *Science*, which showed that this specific procedure could yield long-lasting extinction of a patient's craving for cocaine or heroin, and could reduce amygdala activation (as observed via functional magnetic resonance imaging) in response to an experiment that produces conditioned fear (Agren et al. *Science*, 2013).

Editor's Note: This new work by Graff et al. adds another twist. Older long-term memories are more stable and less amenable to new learning than more recent (but still long-term) memories. The application of an HDAC inhibitor changes this and makes even very old memories amenable to lasting revision. The HDAC inhibitor that Graff et al. used was a specific inhibitor for HDAC type II. However, the anticonvulsant valproate (Depakote) is a potent although nonspecific HDAC inhibitor, and presumably could have the same facilitating effect as the more selective drug.

EMDR (Eye Movement Desensitization and Reprocessing), which has been widely used for the treatment of PTSD, includes active memory recall, immediately followed by an attempt to re-interpret and construct new memories of the trauma. These elements could open the reconsolidation window. However, EMDR works less well with older memories compared to more recent traumatic memories.

The Graff et al. data would suggest that adding an HDAC inhibitor such as valproate to EMDR-like work might make it more effective in revising more remote memories. Graff et al. encourage controlled clinical trials with a type II inhibitor to confirm that their findings in rodents would generalize to humans. While awaiting such validation through controlled clinical trials, it would not be surprising if clinicians started trying out the paradigm on their own using valproate.

Exercise Helps Mice with Spacial Learning

Exercise increases brain-derived neurotrophic factor (BDNF), a protein that protects neurons and is important for learning and memory. In a study of mice who were trained to find objects, **sedentary mice could not discriminate between familiar object locations and novel ones 24 hours after receiving weak training, while mice who had voluntarily taken part in exercise over a 3-week period could easily distinguish between these locations after the weak training**.

Mice who received sodium butyrate (NaB) after training behaved similarly well to those who had exercised. Sodium butyrate is a histone deacetylase (HDAC) inhibitor, meaning it helps keep acetyl groups on histones, around which DNA is wrapped, making the DNA easier to transcribe. In this case the easy transcription of DNA enables learning under conditions in which it might not usually take place.

Both sodium butyrate and exercise promote learning through their effects on BDNF in the hippocampus. They make the DNA for BDNF easier to transcribe, suggesting that exercise can put the brain in a state of readiness to create new or more lasting memories.

Residue from Nuclear Bomb Testing Shows That Contrary to Earlier Reports, Neurogenesis Occurs in the Brains of Adults

In 2013 we reported that according to Pasco Rakic, professor of neuroanatomy at Yale University, neurogenesis (the production of new neurons) occurs only in rodents, and not in any significant amount in the brains of adult primates. However, a new carbon-dating procedure shows that the adult human brain does actually continue to create new neurons.

According to an article by Spalding et al. published more recently in the journal *Cell*, such neuroplasticity occurs to a much greater degree than previously thought. The authors base their research on levels of carbon isotope 14 (14C) that were released into the atmosphere during aboveground nuclear bomb tests between 1945 and 1963. **Dividing cells require carbon, so the 14C released into the atmosphere during the era of nuclear testing made its way into the cells of people who were alive at the time**. Levels of 14C that were incorporated into the DNA of dividing cells correlate with levels of 14C in the atmosphere at the time the cells divided, and since carbon levels have declined at a predictable rate since the nuclear tests, measuring the 14C in cells can show how old they are.

Spalding et al. show that **neurogenesis in humans occurs only in the hippocampus.** They found evidence that a subpopulation of hippocampal neurons continually renews itself at a rate of about 700 new neurons per day, while other hippocampal cells are non-renewing. The annual turnover rate of about 1.75% is the same for men and women and declines slightly with age.

The researchers were able to determine that the renewing cells play an important role in certain types of brain function. Long-term potentiation, the process by which learning and memory can occur, depends heavily on new cells produced in the part of the hippocampus knows as the dentate gyrus.

Glia Cells Prune Over-Abundant Neurons

The brain contains neurons, which transmit electrical impulses, and glia, which protect and support neurons. **New evidence suggests that some types of glia also play a role in pruning back overabundant neurons that are produced as the brain develops in utero**.

Researcher Beth Stevens reports that astrocytes secrete a protein called transforming growth factor beta (TGF-beta). TGF-beta is a cytokine, or regulating protein, that activates brain microglia to initiate a complement cascade (C1 to C3), a series of chemical changes that destroy unnecessary neurons and synapses.

The various proteins involved in a complement cascade are numbered. This complement cascade starts with C1q and is continued by C4, C2, and C3, which initiate phagocytosis (or eating up) of the axon terminals of the underutilized neurons, sparing those that are active.

Inflammation and other changes in glia could cause either deficient or excess pruning of neurons, which has been thought to occur in neuropsychiatric disorders such as autism or schizophrenia.

Blockade of Kappa Opiate Receptors Blocks Proneness to Relapse in Addiction

George Koob, the new director of the National Institute for Alcohol Abuse and Alcoholism (NIAAA), showed that animals with extended access to self-administered abuse substances like cocaine or morphine will escalate the amount of drug they self-administer. When the drug is no longer available starting after a delay of one to two weeks, the number of times they press a lever in the presence of a cue previously associated with drug availability progressively increases over a period of one to two months (even through no drug is available). This is called incubation and reflects a measure of "craving" or relapse potential.

This incubation effect, or increasing degree of craving for a drug, is also seen clinically in people who are heavy drug users and then achieve abstinence or are incarcerated and have a period of forced abstinence. As the duration of abstinence increases, they experience an increased proneness to relapse.

Dynorphin is a psychomimetic opiate peptide that is produced in the brain and causes anxiety and dysphoria when it is given to humans. While opiates like morphine and heroin that produce euphoria and antipain effects act at a mu opiate receptor, dynorphin acts at a kappa opiate receptor. Chronic cocaine use gradually increases levels of dynorphin in the brains of addicts and also increases kappa receptors, thus converting what is often initially a euphoric drug experience into an anxiety-producing and dysphoric one.

If kappa receptors are blocked, the incubation effects during abstinence described above do not occur, and presumably addicts would be less relapse-prone. **No kappa antagonist is currently available for human use, but if one combines buprenorphine (a mixed opiate agonist/antagonist) with naloxone or naltrexone (which selectively block the mu opiate receptors), one would in effect have a kappa receptor antagonist.** Koob showed that this drug combination could prevent the incubation effects in abstinent animals. Further study might lead to advances in the treatment of addition in humans.

Transcranial Direct Current Stimulation Plus Zoloft Has Better Antidepressant Effects Than Either Treatment Alone

Transcranial direct current stimulation (tDCS), in which a barely perceptible level of electrical current is applied directly from one side of a patient's scalp to the other, is a promising treatment for patients with tought-to-treat depression. A 2013 study by Brunoni et al. in *JAMA Psychiatry* examined whether combined treatment using tDCS and the selective-serotonin reuptake inhibitor (SSRI) antidepressant sertraline (Zoloft) would be a safe and effective treatment for unipolar depression. The combination was better than either treatment alone and better than placebo.

The six-week study used what is called a 2x2 factorial design, in which 120 patients with unipolar depression received either 50 mg/day of sertraline or placebo and also received either real tDCS or a sham procedure. The tDCS was administered in twelve 30-minute sessions, one per day Monday through Friday during the first two weeks, followed by one every other week. TDCS consists of an anodal (positive) and cathodal (negative) current placed at particular positions on the head. This study used 2 microamps of anodal left/cathodal right prefrontal stimulation for the tDCS treatment.

While the combination of sertraline and tDCS was significantly better than all three other treatment options (sertraline plus sham procedure, placebo plus tDCS, and placebo plus sham procedure), sertraline by itself and tDCS by itself resulted in similar efficacies. However, TDCS by itself was also significantly better than placebo, while sertraline by itself was not.

Side effects among the different treatment options were similar, except those who received tDCS had more scalp redness. There were seven instances of patients developing mania or hypomania during the study, five of which occurred in the combined tDCS and sertraline treatment group, higher than the 1–2% rate that would be expected in a study of unipolar depression.

Learning to Change Brain Activity to Decrease Cocaine Craving

Colleen Hanlon, a researcher at the Medical University of South Carolina, has found that biofeedback can be used to decrease cocaine craving in people with substance abuse problems. In her research, patients were given real time feedback from functional magnetic resonance imaging (fMRI) and learned to decrease the activation of a part of the brain called the anterior cingulate when exposed to cocaine cues (reminders of their desire for cocaine). They were able to decrease drug craving as well as heart rate and skin conduction, which often accompany it.

Second RTMS Device Approved for Treatment-Resistant Depression

In 2008, the Federal Drug Administration approved the Neuronetics company's NeuroStar system for delivering repeated transcranial magnetic stimulation to patients with treatment-resistant depression. **In rTMS treatment, an electromagnetic coil is placed against the forehead and magnetic pulses that can penetrate the scalp are converted into small electrical currents that stimulate neurons in the brain.** Now the FDA has approved a second device manufactured by Brainsway Ltd.

In 2012, Brainsway released data from their double-blind, multicenter controlled trials of the device. After five weeks of treatment, 30.4% of the patients who received the rTMS treatment achieved remission of their depression, twice the rate of remission among the patients who received a sham procedure instead.

Editor's Note: These data showing slightly higher response rates than seen in two trials by Neuronetics confirm the efficacy of rTMS in patients whose depression persists after one or more trials with antidepressant medications. The efficacy of rTMS in those patients who have failed to respond to multiple antidepressant medications remains to be further defined, as do the optimal stimulation parameters to achieve the best results in this difficult-to-treat sub-group of patients.

IV Ketamine Produces Antidepressant Effects More Rapidly Than ECT

More and more evidence suggests that drugs such as ketamine that work by blocking the brain's NMDA receptors can produce rapid-acting antidepressant effects in patients with depression.

Ketamine produced antidepressant effects more quickly than ECT, and these effects were significantly better than baseline for the duration of the study, but not significantly different from those achieved through ECT by the end of the study.

In a recent study by Ghasemi et al. published in the journal *Psychiatric Research*, 18 patients with unipolar depression were divided into two groups, one that received intravenous infusions of ketamine hydrochloride (0.5 mg/kg over 45 minutes) three times (every 48 hours), and another that received electroconvulsive therapy (ECT) on the same schedule.

Ketamine produced antidepressant effects more quickly than ECT, and these effects were significantly better than baseline for the duration of the study, but not significantly different from those achieved through ECT by the end of the study.

Editors Note: These data continue to add to the already strong findings that ketamine produces rapid-onset antidepressant effects. When and where ketamine should be incorporated into routine clinical treatment of depression remains to be further clarified.

Inflammatory and Metabolic Abnormalities Predict Poor Response to Antidepressants

There is mounting evidence that inflammation and metabolic problems are related to depression. A recent study by Vogelzangs et al. in the journal *Neuropsychopharmacology* examined 313 patients with depression to see whether levels of inflammatory markers in the blood and metabolic factors such as cholesterol, blood pressure, and waist circumference predicted whether those patients would still (or again) be diagnosable with depression two years later.

Several factors predicted later depression, including high levels of the inflammatory marker interleukin-6, low HDL ("good") cholesterol, higher than normal triglycerides, and high blood glucose (hyperglycemia).

People who had four or more types of inflammatory or metabolic abnormalities had almost twice the odds of having chronic depression. Among those study participants who had only recently begun taking antidepressant medication, having four or more of these risk factors made them almost 7 times more likely to be depressed during follow-up.

One explanation is that inflammation and metabolic problems worsen and complicate a patient's depression and reduce the patient's responsiveness to traditional antidepressants. Alternative ways of treating these patients aimed at their inflammation and metabolism may be necessary.

Depression May Not Be All in Your Head

Repeated social defeat stress (when an intruder mouse is repeatedly threatened by a larger mouse defending its home territory) is often used as a model to study human depression. Animals repeatedly exposed to social defeat stress start to exhibit depression-like behaviors such as social avoidance and loss of interest in sucrose. Georgia Hodes, a researcher at Mount Sinai School of Medicine, reported at a recent scientific meeting that **repeated defeat stress–induced behavior was blocked when IL-6, an inflammatory cytokine released by white blood cells in the blood, was inhibited**. The central nervous system did not appear to be involved.

Interestingly, mice with more white blood cells and more IL-6 release at baseline (prior to the social defeat stress) were more likely to show the defeat-stress depressive behaviors.

Editor's Note: The higher number and greater reactivity of white blood cells seen in these mice could be a clinical marker of vulnerability to defeat stress, and such findings are worthy of study in human depression. White blood cells are critical to fighting infection and sometimes their overactivity can contribute to inflammation. In meta-analyses, a subgroup of depressed patients consistently show elevated inflammatory markers (including IL-1, IL-6, TNF alpha, and CRP), and it remains to be seen whether these markers of inflammation are generated in the central nervous system or come from white blood cells in the blood, and whether their targeted suppression could be a new route to antidepressant effects (as in the study of defeat stress in mice).

Individual Predictors of Response to Treatment

At a recent scientific meeting, researcher Andrew H. Miller presented data on infliximab, an inhibitor of inflammatory cytokine TNF alpha that is used to treat rheumatoid arthritis and is being explored for the treatment of depression. As previously reported in *BNN* Volume 16, Issue 2 from 2012, the drug was not effective overall among the depressed patients, but in a subgroup of patients with high levels of the inflammatory marker CRP, infliximab was highly effective. Miller emphasized that patients do not fail to respond to treatments; it is doctors who fail, or drugs that fail. He explained that **there is tremendous heterogeneity in people's illnesses, and doctors must get better at sorting out what treatments will work for each patient, striving toward personalized therapeutics**.

There are many clinical correlates or predictors of nonresponse to antidepressants used in unipolar depression. These include inflammation, obesity, stress in childhood, anxiety disorder comorbidity, substance abuse comorbidity, and medical comorbidity.

Editor's Note: How do we doctors target these clinical correlates of illness for better therapeutic effects? We are just starting to learn, and until we identify good markers for predicting illness, the best we can do is carry out carefully sequenced clinical trials of medications and therapies with different mechanisms of action.

Patients can assist their physicians and clinicians by engaging in precise, preferably nightly charting of their mood, functioning, medications, life events, side effects, and other symptoms such as anxiety on a personal calendar. Several of these are available for free download at our website (www.bipolarnews.org), and there are other longitudinal screening instruments, such as the app My Mood Monitor *(or* M3*).*

A good personal response to a novel treatment or a poor response to an Federal Drug Administration–approved treatment trumps anything that is written in the research literature. The best way to achieve the best outcome is to engage in excellent monitoring of symptoms and side effects that can guide the next steps in therapeutics.

How Inflammation Increases Glutamate Overexcitation And Neurotoxicity

Research has shown a link between inflammation and mental illness. Inflammation leads to a series of chemical changes that can overexcite neurons and interfere with the protection of neurons.

Inflammation increases the production of indoleamine-pyrrole 2,3-dioxygenase (IDO), an enzyme that breaks down the amino acid tryptophan into kynurenic acid and quinolinic acid. They in turn increase glutamate, the main excitatory neurotransmitter, and decrease brain-derived neurotrophic factor (BDNF), which keeps neurons healthy.

Kynurenic acid stimulates microglia, which clean up the central nervous system as a form of immune defense, to produce inflammatory cytokine proteins.

Quinolinic acid directly stimulates glutamate receptors and encourages glutamate release from astrocytes. Quinolinic acid also blocks glutamate removal that would normally occur through reuptake into the astrocytes, leading to more stimulation of extrasynaptic glutamate receptors and decreases in BDNF.

Quinolinic acid's effects are opposite to those of the antidepressant ketamine, which blocks glutamate NMDA receptors and increases BDNF. When people are given interferon protein for the treatment of cancers, quinolinic acid increases in cerebrospinal fluid, inducing depression. The severity of depression induced is correlated with the patient's levels of quinolinic acid.

It appears that ketamine has indirect anti-inflammatory effects through its ability to block glutamate receptors and increase BDNF.

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