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ANIMAL STUDIES SUGGEST NEW PATHS TO TREATING DEPRESSION

Research into immunity, stress, and key cellular molecules may lead to more effective therapies

SAN DIEGO — New animal research has identified factors, such as the stress response and immune system, that may play important roles in depression. Scientists have also found that the regulation of nerve cell signals influences depression in animals, and that new drug combinations may more effectively treat it. The findings were presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news on brain science and health.

Depression is a common mental disorder that affects more than 121 million people worldwide, according to the World Health Organization. Studies show the most effective treatment for moderate or severe depression is a combination of antidepressant medication and psychotherapy. However, 20 to 40 percent of people with depression are not helped by existing therapies, highlighting the need for new treatment targets and approaches.

Today's new findings show that:

- An inability to cope with stress may play a role in depression. When placed in stressful situations, zebrafish with a mutation in a receptor important in stress management displayed depression-like behavior, which was reversed when the fish were given Prozac (Herwig Baier, PhD, abstract 884.1, see attached summary).
- The immune system may be a factor in depression. When an immune hormone that carries "sickness" signals to the brain was blocked in mice, the animals showed fewer depression symptoms (Simon Sydserff, PhD, abstract 666.24, see attached summary).
- Mice that lack a molecule involved in regulating nerve cell signals are more active and resilient to stressful situations, behaving the same way as animals given antidepressant drugs. The discovery offers a new target for controlling brain chemicals involved in mood regulation (James Bibb, PhD, abstract 741.9, see attached summary).
- Two antidepressants may be better than one. A new animal study shows that when drugs that alter two mood-regulating brain chemicals are combined, they produce a greater antidepressant response (Marina Picciotto, PhD, abstract 769.9, see attached summary).

Other recent findings discussed show that:

- Two brain molecules, p11 and brain-derived neurotrophic factor, are key to making antidepressants work. In time, these results might lead to the development of faster-acting antidepressants with fewer side effects (Jennifer Warner-Schmidt, PhD, see attached speaker's summary).

"Finding treatments for disorders of the nervous system is a social imperative," said press conference moderator Robert Greene, MD, PhD, of the University of Texas Southwestern Medical School, an expert in psychiatric disorders. "Basic neuroscience research has formed the basis for significant progress in discovering potentially powerful strategies for new, more effective therapies to combat depression."

This research was supported by national funding agencies, such as the National Institutes of Health, as well as private and philanthropic organizations.

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Abstract 884.1 Summary

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Depression-like Behavior Identified in Zebrafish

Study suggests inability to cope with stress plays a role in depression

Disrupting the stress response in zebrafish generates behaviors that resemble depression, according to new research presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Our findings offer a molecular basis for the intuition that long-term emotional well-being depends on an individual's ability to cope with stress," said Herwig Baier, PhD, of the University of California, San Francisco, who led the study.

Zebrafish are popular model systems in many areas of biomedical research, but this is the first discovery of a zebrafish mutant with an apparent psychiatric disorder. When faced repeatedly with a stressful situation — isolation from others— the mutant fish stop swimming and hide in the corner of the tank for many minutes. This abnormal behavior was reversed by bathing the fish in water containing fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI) commonly prescribed for people with depression.

Baier and his colleagues found that the "depressed" zebrafish had a genetic mutation in the glucocorticoid receptor (GR) gene. One of the functions of GR is to "dial down" the secretion of stress hormones from the brain. Both too much and too little GR activity has been implicated in depression. The zebrafish mutant had little to no GR activity.

"We do not know yet if all this also holds true for people. But if it does, then strategies aimed at finding new antidepressant therapies should try to resurrect, rather than block, GR activity," Baier said.

Research was supported by the National Institutes of Health.

Scientific Presentation: Wednesday, Nov. 17, 1–2 p.m., Halls B–H

884.1, Depression-like behavior in zebrafish mutants with disruption of the glucocorticoid receptor
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TECHNICAL ABSTRACT: Physiological stress leads to the sequential release of corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary gland, and cortisol from the adrenal gland. Cortisol feeds back on the brain by binding the glucocorticoid receptor (GR) and suppressing synthesis and release of CRH and ACTH. Chronic hyperactivation of the hypothalamo-pituitary-adrenal (HPA) axis in mammals may predispose psychiatric disorders, particularly major depression, but the mechanisms underlying this association are still a matter of debate. Both too much and too little GR activity have been implicated in depression. Insensitivity to cortisol and reduced GR activity lead to a lack of negative feedback on the post-GR stress response. Conversely, excessive cortisol signaling, apparently through an active GR, has detrimental effects on emotional brain areas, including the hippocampus where it impairs neurogenesis and plasticity. Here we have identified a zebrafish GR mutant (grs357), which suffers from a depression-like syndrome. The point mutation disrupts DNA binding of this transcription factor. Surprisingly, the mutant fish are adult viable. Cortisol, CRH, and proopiomelanocortin (POMC), the precursor of ACTH, are all chronically elevated, whereas the serotonin transporter Sert-a is reduced. When placed in an isolated arena, mutants stop swimming ('freeze'), and their ability to adapt to repeated exposure to this stressful environment is impaired. Acute (diazepam) and chronic (fluoxetine) antidepressant treatments restore normal swimming (see Figure) without influencing cortisol levels. Visual interactions with other fish have the same beneficial effect, suggesting social buffering. Together our results show that GR-mediated feedback has an evolutionarily conserved, protective function in the emotional responses to stress.

Abstract 666.24 Summary

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Immune System Involved in Depression, Animal Study Suggests

Study may lead to new treatments for depression

A new animal study suggests the immune system plays a role in depression. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Activation of the immune system caused mice to learn to run less on wheels in their cages — an activity they normally like. The mice resumed their normal activity when the action of interleukin-6, an immune hormone that carries "sickness" signals to the brain, was blocked.

"Our findings suggest that blocking the action of interleukin-6 might reduce depression symptoms, like fatigue or loss of interest in pleasurable activities, in people who are depressed and who have elevated levels of interleukin-6," said Simon Sydserff, PhD, a senior research scientist at BrainCells Inc., who conducted the research while with AstraZeneca Pharmaceuticals.

Scientists previously observed that some people became depressed due to an immune response to illness or stress. Elevated levels of immune hormones like interleukin-6 have been found in some depressed patients who are otherwise healthy. In addition, people who have never had a mental illness, but who are treated for other illnesses with immune-stimulating cytokines, often become depressed.

"These observations support the idea that depression may be caused in part by a breakdown in the normal communication between the immune system and the brain, causing people to experience the feelings associated with sickness even when they are medically healthy," Sydserff said.

Research was supported by AstraZeneca Pharmaceuticals.

Scientific Presentation: Tuesday, Nov. 16, 3–4 p.m., Halls B–H

666.24, The therapeutic effect of an IL -6 antibody on depression-like behavior following BCG inoculation in mice
S. SYDSERFF, J. ARRIZA, T. PISER; AstraZeneca Pharmaceuticals, WILMINGTON, DE

TECHNICAL ABSTRACT: Exposure to pro-inflammatory cytokines produces a range of sickness behaviors comprising neuropsychological symptoms such as anhedonia and confusion as well as physiological symptoms such as anorexia, fever, fatigue, increased pain and sleep disturbances. Inoculation with Bacillus Calmette Guerin (BCG) produces a 2-5 day sickness behavior in mice, characterized by anorexia, weight loss and pyrexia, which is followed by a set of behaviors that may represent core symptoms of depression - fatigue and anhedonia. We have harnessed the natural propensity for rodents to run on a freely accessible wheel and have introduced wireless running wheels to the home cages of mice following the resolution of sickness behavior but at the outset of depression behavior. We have shown that we can capture and characterize both the development and maintenance of the motivational behavior that is manifested in wheel running. Male CF-1 mice were inoculated with 108 CFU BCG or PBS. The mice were monitored for sickness behavior for 1 week after inoculation before being given unrestricted access to wireless low profile running wheels (Med Associates) streaming activity data every 30 seconds. MAB406, a peripherally restricted anti-mouse IL-6 antibody or IgG control was administered as a single I.P. injection of 20 mg/kg, 2 weeks after BCG inoculation. The pattern of running wheel behavior was recorded for a further 2.5 weeks. Mice inoculated with BCG developed a distinctly different behavioral activity pattern compared to normal mice. BCG mice showed both a diminished overall circadian activity profile as well as a change in the pattern of nocturnal running behavior. The activity that typically occurs in the first 2-3 hours following lights out is semi normal in appearance but later activity bouts coinciding with the 3-12 hour dark cycle pattern are severely compromised suggesting the presence of a fatigue component that is absent in normal mice. MAB406 significantly increased overall activity but more importantly increased late evening and early morning activity. We suggest that targeting the inflammatory pathway directly 10 or so days after the resolution of sickness behavior can have a significant impact on depression-like behavior patterns. This of course implies that there is a significant continuing contribution of an ongoing inflammatory response weeks after BCG inoculation that is not manifest in peripheral physiological sickness behavior.

Abstract 741.9 Summary

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Nerve Cell Molecule Has Antidepressant Effect

Animal study may lead to more effective treatments for depression

Mice that lack a molecule involved in regulating nerve cell signaling are more active and resilient to stressful situations, a new study shows. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Mice lacking the molecule — known as Cdk5 — exhibited the same behaviors seen in mice given antidepressant drugs. "We immediately realized that these mice could teach us something important about depression and that we could use them to study new pathways that might serve as targets to treat the disease," said senior author James Bibb, PhD, of the University of Texas Southwestern Medical Center, who directed the study.

When dopamine and serotonin, brain chemicals involved in mood regulation, act at brain cells, a "wave" of the signaling molecule cyclic adenosine monophosphate (cyclic AMP) is generated. Normally, another molecule, phosphodiesterase, breaks down the cyclic AMP. However, Bibb and his colleagues discovered that phosphodiesterase did not do its job — the wave of cyclic AMP did not stop — in mice that lacked Cdk5. Without Cdk5, the mice behaved with more resilience to stress and showed strong antidepressant-like behavior. The discovery that Cdk5 regulates phosphodiesterases opens up new opportunities to target them.

"Our hope is that the conceptual advances these findings represent will contribute to the development of new depression therapeutics," Bibb said.

Research was supported by the National Institute of Mental Health, the National Institute on Drug Addiction, and the Department of Psychiatry at the University of Texas Southwestern Medical Center.

Scientific Presentation: Wednesday, Nov. 17, 8–9 a.m., Halls B–H

741.9, Cdk5 regulates camp phosphodiesterase 4 and serves as a potential target for the treatment of depression
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TECHNICAL ABSTRACT: The regulation of intracellular signaling pathways in the brain that mediate emotional state and susceptibility to depression remain poorly understood. Work to date has emphasized the importance of key neurotransmitters and neuropeptides upstream of cAMP signaling in the control of mood and behavior. We previously found that Cdk5 regulated dopamine neurotransmission by converting the protein phosphatase 1 inhibitor DARPP-32 into an inhibitor of PKA. In order to better understand how Cdk5 regulates cAMP/PKA signaling downstream of dopamine receptors, a pharmacological study was conducted to assess the relationship between Cdk5 inhibition and PKA activation. Cdk5 inhibition activated PKA-dependent phosphorylation of both pre- and post-synaptic targets in striatal slices, increased cAMP levels and reduced PDE activity in striatal lysates, while the addition of Cdk5 activated PDE. In cultured cells, inhibition of Cdk5 prevented PKA dependent activation of PDE4, reducing the activity of PDE4 and the decay rate of cAMP. We found that Cdk5 phosphorylates PDE4B1 at Ser145, close to the Ser133 PKA-dependent activation site, and that S145A mutant PDE4 showed decreased PKA-dependent phosphorylation compared to wild type PDE4. Cdk5 conditional knockout in adult mice induced increased cAMP levels and PKA activity. Furthermore, loss of Cdk5 in adult mice resulted in an anti-depressant-like phenotype and resistance to social defeat stress in behavioral paradigms. Our results identify Cdk5 as a novel regulator of cAMP metabolism in the brain and implicate its regulation of PDE4 as a potential therapeutic target for the treatment of mood disorders.

Abstract 769.9 Summary

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Combining Two Types of Antidepressants Produces Stronger Effect

Mouse study may help patients for whom existing antidepressants are not effective

When it comes to antidepressants, two may be better than one. When drugs that alter two mood-regulating brain chemicals — serotonin and acetylcholine — are combined, they work together to produce a greater antidepressant response, a new animal study shows. The research was presented at Neuroscience 2010, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

"Although we have many therapies available to help alleviate the symptoms of depression, current treatments, which include the popular selective serotonin reuptake inhibitor [SSRI] medications, are effective in only about 50 percent of patients," said Marina Picciotto, PhD, of Yale University, the study's senior author. "Our study suggests that combination therapies could be beneficial in patients non-responsive to SSRIs," she said.

SSRIs, which increase serotonin levels in the brain, have long been used to treat depression. More recently, animal studies and a few clinical trials have suggested that another brain chemical, acetycholine, plays an important role in regulating mood. Medicines that block some of the nerve receptors for acetylcholine can be antidepressant.

Picciotto and her colleagues found that combining the SSRI fluoxetine (Prozac) with cytisine, a drug that limits the effects of acetylcholine, produced greater antidepressant-like properties in mice than when the drugs were used alone. They also discovered that when serotonin was removed from the animals' brains, cytisine was no longer effective.

"This suggests that serotonin is critical for cytisine's antidepressant-like effects," Picciotto said.

Research was supported by the National Institute of Mental Health and NARSAD. Dr. Picciotto has a proprietary interest in developing several nicotinic partial agonists for the treatment of depression, none of which were used in the current study.

Scientific Presentation: Wednesday, Nov. 17, 8–9 a.m., Halls B–H

769.9, Interactions between the cholinergic and monoaminergic systems in mediating antidepressant-like responses in animal models
Y. S. MINEUR, E. B. EINSTEIN, **M. R. PICCIOTTO**; Psychiatry, Yale Univ. Sch. Med., NEW HAVEN, CT

TECHNICAL ABSTRACT: Previous studies have shown that compounds that limit activity at α4/β2* nicotinic acetylcholine receptors (nAChRs) can have robust antidepressant-like (ADL) effects in mice and patients with selective serotonin reuptake inhibitor (SSRI)-resistant major depressive disorder. In addition, stimulation of serotonin signaling is thought to be an important component of the therapeutic action of currently used antidepressants since SSRIs are clinically effective in treating human depression. Thus, while both SSRI and nAChR blockers can have ADL effects, it is not known whether these effects are independent or whether the two neurotransmitter systems could act synergistically to induce an antidepressant response. In this study, we first determined that the SSRI fluoxetine and the nicotinic partial agonist cytisine had significant antidepressant-like effects when subthreshold (behaviorally inactive) doses of each compound were combined. We then used 5HT agonists to identify downstream effects of SSRI-mediated increases in serotonin mediating this interaction with nicotinic drugs, and found that 5HT1A agonism could also potentiate cytisine's ADL effects. In addition, serotonin signaling appeared to be necessary for the ADL response to cytisine, since an active dose of cytisine did not result in any effects in mouse models of antidepressant response following 5HT depletion. 5-HT1A receptors are located both presynaptically and postsynaptically on neurons throughout the brain, with the highest densities found in amygdala, hippocampus and prefrontal cortex. Presynaptic 5-HT1A receptors are involved in negative feedback of serotoninergic neurons, and are only found on the 5-HT neurons of the raphe nuclei; they also have higher affinity for serotonin than postsynaptic receptors. Thus, pharmacological methods cannot distinguish between the ability of pre- or postsynaptic 5HT1A agonism to potentiate the ADL response to nicotinic drugs. We therefore used adeno-associated virus (AAV) to deliver small hairpin RNAs targeting 5HT1A receptors into the locus coeruleus and hippocampus to identify the loci critical for synergism between 5HT1A and nAChR effects in tests of antidepressant efficacy. Taken together, our results show that monoaminergic and cholinergic modulation can have synergistic ADL effects and that 5HT tone is required for the effects of nicotinic drugs in mouse models of antidepressant response. The data also suggest that antidepressant-like effects induced by an increase in 5HT activation can be potentiated by a reduction of cholinergic tone through α4/β2* nAChR blockade, and that these effects involve 5HT1A receptors.

Speaker's Summary

Speaker: Jennifer Warner-Schmidt, PhD (212) 327-8786
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New York, N.Y.

Abstract: **A role for p11 in the antidepressant action of brain-derived neurotrophic factor** (769.13)
Wednesday, Nov. 17, 8–9 a.m., San Diego Convention Center, Halls B–H

Antidepressant therapies are accompanied by a therapeutic delay of weeks or months and by a host of unpleasant side effects. This poses a serious clinical problem for the millions of Americans suffering with major depression. The mechanism underlying the therapeutic actions of antidepressants it not yet understood. Our work has identified a relationship between two key regulators of antidepressant responses, namely p11 and brain-derived neurotrophic factor (BDNF), allowing us to take a step forward in our understanding the mechanism by which antidepressants act. In time, this work could lead to faster acting antidepressants with fewer off target effects.

Our laboratory identified p11 as a key regulator of depressive-like states and antidepressant responses, at least in part due to its interactions with specific serotonin receptors (5HT1B and 5HT4). p11 is a small protein expressed in depression-related brain regions including the cerebral cortex and hippocampus. Chronic, but not acute treatment with multiple classes of antidepressants increases p11 levels in the brain. In models of depression, mice that over-express p11 behave as if they have received an antidepressant. Brain-derived neurotrophic factor (BDNF) is also induced by chronic, but not acute antidepressant treatments and has been reported to be linked to the therapeutic efficacy of antidepressants in many preclinical and clinical studies. Over-expression of BDNF also has antidepressant-like effects in rodent behavioral paradigms. Over the past decade, experimental evidence has supported a neurotrophic hypothesis of depression, suggesting a role for neurotrophins, including BDNF, in mediating the therapeutic actions of antidepressants. Therefore, we sought to determine whether BDNF could regulate p11.

The results of our study show that BDNF increases p11 messenger RNA (mRNA) and protein levels in cortical neurons. We find that BDNF also has downstream effects, increasing serotonin receptor 1B (5HT1B) expression at the plasma membrane of cortical neurons. This indicates that BDNF-induced increases in p11 protein have functional molecular consequences. Serotonin reuptake inhibitors block the serotonin transporter, thereby increasing serotonin levels in the brain. These compounds are widely prescribed for the treatment of depression and anxiety disorders. Therefore, we investigated the effect of serotonin reuptake inhibitors or serotonin on p11 levels. Results indicate (1) that serotonin reuptake inhibitors cause an even greater increase in p11 than tricyclic antidepressants do, (2) that serotonin itself increases p11, (3) that BDNF is required for serotonin-induced increases in p11, and (4) that BDNF is also necessary for maintaining basal levels of p11. Importantly, we also find that p11 is required for the antidepressant-like actions of BDNF in rodent behavioral models of depression.

The time course for therapeutic efficacy in humans treated with antidepressants (i.e., several weeks) coincides with the elevation of BDNF and p11 by antidepressants in rodents, consistent with the possibility that these two factors mediate the therapeutic antidepressant response. Our work underscores that p11 is a critical player in the actions of antidepressants. It also suggests the possibility that p11 is downstream of BDNF in the pathway of antidepressant action, and could be more directly responsible for the therapeutic effects of these drugs. This hypothesis will require further investigation. Future work will also be aimed at determining the brain region(s) and cell-type(s) that mediate the effects of BDNF and p11 on antidepressant-like responses. From the current work, we conclude that p11 plays a necessary role in the antidepressant-actions of neurotrophins.