Stress and AD: Does One Beget the Other?

20 December 2011. Conventional wisdom says too much stress is a dangerous thing, weakening the heart, immune system, and perhaps the brain. But how bad is it, really? Does stress increase the risk of developing Alzheimer's disease, or worsen dementia? If so, what kind of stress, how long, how severe? While clear answers are not in, emerging data do link stress and AD more tightly together. For example, epidemiological studies finger stress as a risk factor for cognitive decline. Stress hormones can impair memory and damage the hippocampus over time, and people with AD tend toward higher levels of circulating cortisol, the main human stress hormone. Recent animal data show that psychological distress can worsen the pathology of AD.

"Overall, the evidence is accumulating that chronic adverse stress is bad for the brain during aging," said Mark Mattson at the National Institute on Aging in Baltimore, Maryland. However, it is uncertain if stress somehow causes decline, and if it does, what the mechanisms might be. "I think the best evidence is for stress and cortisol as exacerbative, rather than causative factors, and it is unclear what the magnitude of the effect is. It seems to me to be important work to follow up on," Robert Sapolsky at Stanford University, Palo Alto, California, wrote to ARF. One possibility is that stress acts as a "second hit," pushing vulnerable brains toward dementia faster, suggested Osborne Almeida at the Max Planck Institute of Psychiatry, Munich, Germany. One thing the experts agree on: The relationship between stress and dementia is complex.

As people around the world plunge into the busyness—some say stress—of the pre-holiday countdown, this series offers an overview of the topic. After all, stress is a life factor adults can control, at least in some measure. This series covers human data that connect stress and dementia, and describes a new longitudinal study that may help clarify that link; summarizes animal studies, including new papers on tau, that demonstrate stress accelerates neuropathology; and elves into recent work uncovering specific mechanisms and implicating particular receptors in good and bad effects of stress, as well as possible therapeutic approaches under consideration.

First, the basics: The body's response to stress is controlled by the hypothalamic-pituitary-adrenal (HPA) axis. In response to external stressors, cells in the hypothalamus release corticotrophin-releasing factor (CRF). This hormone then acts on pituitary cells to stimulate the secretion of adrenocorticotropic hormone (ACTH), which circulates through the blood to the adrenal glands on the kidneys. The adrenal glands then dump glucocorticoids, the primary mediators of stress, into the bloodstream. In humans, the main glucocorticoid is cortisol; in rats, it is corticosterone. Glucocorticoids feed back on the hypothalamus and pituitary to dial down production of CRF and ACTH, and also mediate many of the physiological effects of stress, such as raising blood glucose and depressing the immune system.

In healthy people, cortisol levels rise and fall throughout the day, peaking in the morning and again in the afternoon. They also vary from one day to the next, depending on activities. Glucocorticoids play crucial physiological roles, for example, in maintaining arousal and in memory encoding and consolidation (see, e.g., Roozendaal, 2000; Wilhelm et al., 2011). The steroids bind to two different brain receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), which activate distinct signaling pathways. Being transcription factors, the receptors allow glucocorticoids to turn genes on or off. But glucocorticoids are not

the only mediators of stress effects in the brain. For example, CRF itself and its receptors are widely expressed in brain tissue (see Baram and Hatalski, 1998), and may also play a role. The takeoff point for researchers' interest in stress and AD is the observation that the short-term stress response is healthy and adaptive, but the effects of long-term, chronic stress may be a different story.

Does Stress Make Us Vulnerable to Dementia?

For people, a body of evidence hints that excess stress could contribute to the development of dementia. Numerous epidemiological studies, many from Robert Wilson at Rush University, Chicago, Illinois, indicate that people who are more prone to psychological distress face a higher risk for cognitive decline and AD (see, e.g., ARF related news story on Wilson et al., 2007; Simard et al., 2009; Johansson et al., 2010; and Wilson et al., 2011). Research has also turned up some genetic links between stress and AD. For example, a rare single nucleotide polymorphism that increases expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), an enzyme that regenerates glucocorticoids and thus amplifies their effects, confers a sixfold increased risk for sporadic AD (see de Quervain et al., 2004 and AlzGene entry). Au contraire, a genetic variant of the glucocorticoid receptor in about 7 percent of the population seems to protect its carriers from the harmful effects of the steroids, and greatly lowers their risk of dementia (see ARF related news story and van Rossum et al., 2008). Cortisol levels are higher in people who carry the ApoE4 AD risk allele than in non-carriers (see Peskind et al., 2001).

Some clues exist as to how stress might harm the brain. Small studies have shown that prolonged cortisol elevation correlates with reduced brain volume in the hippocampus and prefrontal cortex, two areas affected early in AD (see Lupien et al., 1998; Pruessner et al., 2010). Intriguingly, some animal studies appear to tie into this human observation by showing that chronic stress represses hippocampal neurogenesis and makes cells more vulnerable to damage and death, suggesting a possible mechanism behind brain shrinkage (see, e.g., Stein-Behrens et al., 1994; Mirescu and Gould, 2006; and Joëls et al., 2007). Could one culprit behind lessened neurogenesis in stressed brains be a lack of brain-derived neurotrophic factor (BDNF)? Some evidence hints at this. "It's interesting that many of the neurons that are vulnerable in AD, such as hippocampal CA1 neurons, express high levels of glucocorticoid receptors," Mattson noted. "Cortisol acting through GR has been shown to reduce expression of BDNF [in hippocampal neurons]. That's generally thought to be a bad thing, because BDNF has important roles in learning and memory."

Stress exacerbates other disorders that drive up risk for AD, such as depression (see Ownby et al., 2006; Aznar and Knudsen, 2011), diabetes (see AlzRisk summary; Pavlatou et al., 2008), and metabolic syndrome (see Tamashiro et al., 2011). Diabetic rats and mice maintain higher levels of blood glucocorticoids after a stressful situation than normal animals do, and reducing these levels improves learning and normalizes neurogenesis and synaptic plasticity (see ARF related news story and ARF related news story).

Metabolic syndrome, which is characterized by insulin resistance and abdominal fat, correlates with a higher risk of cognitive problems and AD (see, e.g., Craft, 2007; Whitmer et al., 2007; and García-Lara et al., 2010). A recent study by Philip Landfield's group at the University of Kentucky, Lexington, showed that monkeys with metabolic syndrome are more sensitive to

glucocorticoids than controls are (see Blalock et al., 2010). Monkeys with some degree of metabolic syndrome also dialed down insulin pathway genes and had poorer mitochondrial function and increased neuroinflammation, all of which have been linked to AD.

"We really need to understand the relationship of glucocorticoids to insulin in the brain, and to metabolic syndrome. That's because in many systems throughout the body, glucocorticoids and insulin have antagonistic roles in energy metabolism. It's possible that some of the decline in insulin function [in AD] is related to glucocorticoid activity," Landfield told ARF. Intranasal insulin is currently under investigation as an AD treatment (see ARF related news story).

AD and Cortisol: The Chicken and the Egg

Whether or not stress leads to AD, people with the disease typically have higher levels of cortisol in their blood than healthy people do (see, e.g., Davis et al., 1986; Masugi et al., 1989; Hartmann et al., 1997; Swanwick et al., 1998; Umegaki et al., 2000). Some studies have correlated high plasma cortisol levels and other HPA abnormalities in AD with faster disease progression and worse memory problems (see Weiner et al., 1997; Csernansky et al., 2006; Elgh et al., 2006; Peavy et al., 2011). It is not known how common elevated blood cortisol is in AD. To answer this, Kim Green at the University of California, Irvine, plans to screen about 300 patient samples collected at the UC Irvine Alzheimer's Disease Research Center. He will correlate cortisol levels with neuropathology data. AD patients with elevated cortisol might be good candidates for trials of anti-glucocorticoid-based therapies, Green noted.

A tough question is, Which comes first, high plasma cortisol or AD? In other words, does a malfunctioning stress system lead to AD, or does the neuropathology of dementia disrupt normal stress physiology? While both could be true, some evidence supports the latter idea. In Green's studies on triple transgenic AD mice (3xTgAD), pathology preceded abnormalities in the HPA axis (see Green et al., 2006). Green and colleagues propose that glucocorticoid feedback to the hippocampus, which dampens the stress system, may be lost as the hippocampus degenerates in AD. They speculated that increasing glucocorticoid levels may accelerate pathology and further damage the hippocampus, leading to a vicious cycle of disease progression. This hypothesis leaves open the possibility that midlife stress may precipitate AD, Green noted. He believes both processes may occur, perhaps by different mechanisms. One way to address whether high blood cortisol levels increase risk would be to look at people with Cushing's disease, whose hyperactive pituitary glands elevate their cortisol throughout life, and see if they are more prone to cognitive problems in late life, suggested Jenna Carroll at the University of Pennsylvania, Philadelphia.

Searching for Answers In Longitudinal Data

To clarify the question of midlife stress and dementia risk, Scott Moffat at Wayne State University is making use of data collected by the Baltimore Longitudinal Study of Aging, run by the NIA. He has analyzed the cortisol content in some 6,000 urine samples obtained from about 2,000 people over the course of 20 years, with a few samples going back as far as 40 years. To minimize the effect of daily cortisol fluctuations, each sample was collected over 24 hours. Moffat will correlate urine cortisol with cognitive test results over time, and imaging data in a subset of the group.

Susan Resnick at NIA works on the cognitive and imaging parts of the Baltimore study. She told ARF they have MRI measures of brain volume and positron emission tomography (PET) measures of brain function for about 150 people, as well as amyloid imaging in a smaller group. This study will be one of the largest to look at the relationship among longitudinal cortisol levels, brain imaging, and cognition, Resnick noted. She expects to publish the data next year, and hopes they will shed some light on what effects, if any, midlife cortisol levels have on late-life cognitive outcomes. Resnick points out, however, that cortisol is but one important factor to consider. "The next steps are to understand the effect that cortisol has on other physiological parameters," she said, for example, on lipids, inflammatory markers, and glucose utilization. "You're not going to understand cortisol in isolation."

Glucocorticoids Accelerate Neuropathology in Animals

Researchers have been interested in the connections between stress and Alzheimer's disease for years, but hard data remained elusive at first. "It's only been in the last decade, with more sensitive assay techniques and more insight into the mechanisms of AD, that supportive evidence has emerged," Robert Sapolsky at Stanford University, Palo Alto, California, wrote to ARF. Researchers now have better tools, such as knockout mice and pharmacological manipulations, to investigate the mechanisms and pathways involved in stress, agreed John Trojanowski at the University of Pennsylvania, Philadelphia. In the last five years in particular, mounting animal data indicate that stress hormones have the ability to worsen both Aβ and tau pathology. At this point, "There's pretty good evidence that the impact of glucocorticoids on the brain is somehow intimately involved with the development of unhealthy brain aging, and maybe AD," said Philip Landfield at the University of Kentucky, Lexington.

Early studies showed that acute stress could trigger AD pathology, as administering glucocorticoids to wild-type rodents raises amyloid-β precursor protein (APP) levels and tau phosphorylation in the brain (see Elliott et al., 1993; Budas et al., 1999). Kim Green and Frank LaFerla at the University of California, Irvine, extended this finding to the triple transgenic AD mouse (3xTgAD), reporting that treating young mice for seven days with glucocorticoids raised levels of BACE1, APP, and Aβ, and, as a downstream consequence of Aβ changes, boosted total tau (see Green et al., 2006 and ARF related news story).

Other studies showed that Aβ levels also rise in models of chronic stress, such as extended periods of restraint and isolation (see Jeong et al., 2006; Lee et al., 2009; and Huang et al., 2011). John Csernansky and David Holtzman at Washington University, St. Louis, Missouri, reported that chronic isolation stress decreased hippocampal neurogenesis, impaired memory, and accelerated Aβ plaque deposition in Tg2576 transgenic mice (see Dong et al., 2004; Kang et al., 2007; and ARF related news story). Administering corticotrophin-releasing factor (CRF), but not glucocorticoids, mimicked this effect, suggesting it is mediated by CRF, the authors noted.

Osborne Almeida at the Max Planck Institute of Psychiatry, Munich, Germany, wanted to see how chronic stress would affect very early pathological events in AD. He decided to use wild-type animals to better model sporadic disease. As described in the May 25 Journal of Neuroscience, first authors Ioannis Sotiropoulos and Caterina Catania subjected healthy, middle-aged rats to a month of daily stresses, including overcrowding, restraint, or rocking motion.

Serum corticosterone levels shot up approximately sevenfold. Then, the researchers examined tau hyperphosphorylation in the hippocampus and prefrontal cortex, areas that show early AD pathology, and found that stressed animals developed about 50 percent more tau phosphorylation and insoluble tau aggregates than did controls. They also showed memory problems. Administering exogenous glucocorticoids led to similar changes in tau as the stressors did, suggesting hormones were mediating the harmful effects of stress (see Sotiropoulos et al., 2011).

Almeida told Alzforum that previous in-vitro studies performed by his group suggest that glucocorticoid treatment leads to tau hyperphosphorylation through an Aβ-mediated mechanism (see Sotiropoulos et al., 2008). Although the wild-type rats did not develop Aβ plaques, Almeida believes tau phosphorylation in these animals also occurs downstream of changes in soluble Aβ. To test if glucocorticoids exacerbate Aβ pathology, the authors injected wild-type rats with both Aβ and corticosterone and saw higher levels of tau phosphorylation than in rats receiving Aβ alone. The effect was greatest in animals that had been previously stressed. The results suggest that stress can accelerate AD pathology, even in otherwise healthy animals, Almeida said.

Trojanowski and colleagues at UPenn took a different approach. They looked at chronic stress in a tau mutant background. As reported in the October 5 Journal of Neuroscience, first author Jenna Carroll subjected Tg2576 APP mutant mice and PS19 tau mutant mice to one month of severe stress by housing the animals in isolation (mice like company) and restraining them in a small conical tube for six hours each day. As expected from previous studies, this treatment increased Aβ levels in the Tg2576 mice and worsened fear and spatial memory. Similarly, in the tau mice, but not in wild-type, chronic stress increased tau hyperphosphorylation, tau aggregation, memory problems, and neurodegeneration. This showed that stress is equally harmful on a tau mutant background as in APP mutant mice. Moreover, both Tg2576 and PS19 mice were more sensitive to stress than were wild-type animals; they released more corticosterone, and chronic stress did not blunt the response as it does in normal mice. The authors found that glucocorticoid receptor expression stayed high in the hippocampus of tau mice during chronic stress, not falling as it does in wild-type mice. In toto, these data suggest that AD pathology can alter the way the brain responds to stress. Other lines of evidence also indicate that AD disrupts the normal functioning of the hypothalamic-pituitary-adrenal (HPA) axis.

Carroll and colleagues wondered if glucocorticoids were mediating the effects of stress in this tau model. However, administering exogenous glucocorticoids did not mimic stress. In contrast, when the researchers blocked CRF receptors with an antagonist, they prevented tau accumulation and neurodegeneration, and rescued learning in the PS19 mice. This suggested to them that local CRF might bring about tau pathology. Strengthening this idea, the researchers found that transgenic mice that overexpress CRF in the brain produce more hyperphosphorylated tau than their wild-type littermates do.

Other animal studies, such as the one from Holtzman's group mentioned above, implicate CRF as a key stress mediator as well (see also ARF related news story on Rissman et al., 2007). However, the picture is complicated because CRF has been shown to be neuroprotective (see, e.g., Bayatti and Behl, 2005), suggesting the effects of CRF may depend on the context. The CRF results also conflict with experiments in other animal models that have fingered

glucocorticoids as the main stress mediator. Mark Mattson at the National Institute on Aging in Baltimore, Maryland, noted that the Trojanowski study does not rule out the possibility that glucocorticoids affect tau, since global inhibition of CRF in the brain will also lower glucocorticoid levels. An interesting follow-up experiment would be to use adrenalectomized mice that cannot produce corticosterone, or to administer a CRF antagonist directly to the hippocampus, to more clearly exclude a glucocorticoid effect, Mattson suggested. Green speculated that perhaps CRF is the most important stress mediator early in the development of pathology, while glucocorticoids may be the more important hormone in established disease when cortisol levels are up.

Trojanowski told ARF that his study tried to dissect out which types of stress are most harmful. The scientists put a separate group of mice through a month of variable stress, where every day the animals randomly experienced one of several stressors. They were either forced to swim for 20 minutes, restrained for 15 minutes, in cold water for 2.5 minutes, housed alone all day, or had the lights on all day. These forms of stress increased glucocorticoid secretion just as much as the lengthy restraint and isolation paradigm did. However, in contrast to the latter, mice exposed to variable stressors showed few negative effects, and no increase in Aβ or phosphorylated tau compared to unstressed mice.

The results emphasize the idea that not all stressors are equally bad. In particular, acute stress may have very different effects than chronic stress, Carroll told ARF, noting that a single 15-minute period of restraint in an otherwise unstressed tau mouse actually lowered tau phosphorylation. This fits with the classic idea that acute stress is an adaptive response that benefits an organism, in contrast to the negative effects of chronic stress. It is also possible that certain behaviors or environmental factors can counteract the effects of stress, Carroll suggested. She speculated that the mice who had variable stress may have inadvertently experienced some benefits from exercise or novel environments. Exercise has been consistently linked to lower risk of AD (see tau mutant mice AlzRisk data), and environmental enrichment has been shown to lessen neuropathology in numerous animal models (see Nithianantharajah and Hannan, 2006). In follow-up work, Carroll is looking at whether housing the PS19 mice in an enriched environment can lessen tau phosphorylation, and whether this environment can counteract the effects of previous stress.

How do these findings in animal models relate to the stresses humans experience? People regularly face all kinds of psychological stress, for example, from deadlines, interpersonal conflict, traffic jams, and demanding jobs, but is any of this bad for you? The animal results suggest that pathological effects may come primarily from chronic exposure to very high-stress situations, Carroll said, such as active military duty in a war zone. Indeed, epidemiologic evidence has linked post-traumatic stress disorder (a dysregulation of the HPA system) to a twofold higher risk of getting dementia (see ARF related news story). This, then, might relegate everyday stress in what would be considered normal proportions to a rather marginal role in AD.

How the Brain Responds Makes All the Difference

Scientists believe that stress has a hand in Alzheimer's disease, and that stress hormones can nudge along the disease's pathology. However, many questions remain unanswered. For

example, what is it about stress and glucocorticoids that relates to normal aging? Some animal studies suggest that circulating glucocorticoid levels go up with age (see, e.g., Sapolsky et al., 1986), but others don't (see Sonntag et al., 1987). The classic glucocorticoid hypothesis of brain aging proposes that too much stress "ages" the brain. As an oft-quoted line from Hans Selye, the pioneering endocrinologist known as the "Father of Stress," goes: "Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older."

In reality, the picture has been complicated considerably since Selye's days, Philip Landfield told Alzforum. Landfield, who is at the University of Kentucky, Lexington, ran microarray analyses using a panel of hippocampal genes on brain extracts from aged animals and those with high plasma corticosterone levels. He found that aging and elevated corticosterone shifted gene expression in opposite directions for the most part, rather than in the same direction, as predicted by the glucocorticoid aging hypothesis (see Landfield et al., 2007). Expression changes were also cell type-specific. It appears that aging magnifies the effects of glucocorticoids on some processes, for example, catabolism in neurons, while weakening their effects on other processes, such as inflammation in astrocytes, Landfield said. This latter finding fits with the observation that neuroinflammation increases with age, even in the presence of high levels of glucocorticoids that normally dampen inflammation. Landfield proposes that, rather than glucocorticoids "aging" the brain, the aging process instead changes the way glucocorticoids act in the brain.

Other researchers agree that the brain's response to stress may be the crucial factor. "We know that as people get older, the ability to turn off the endocrine response to stress gets slightly worse in general. The homeostatic mechanism is getting lost," said Osborne Almeida, Max Planck Institute of Psychiatry, Munich, Germany. He also noted that epigenetic changes in DNA, which often occur during early development, may play a role in an individual's response to stress. "Early life stress, for example, can have enormous repercussions for you throughout life," he said.

The idea that the brain's response is the key variable highlights the importance of receptors and specific signaling pathways. For example, a genetic variant of the glucocorticoid receptor (GR) lowers dementia risk. The downstream effectors of GRs are also very important. "Glucocorticoids work in large part by regulating other genes, and so [we need] to understand what those other genes are and how they build into a picture, a network that underpins both cognition and maybe pathogenesis," said Jonathan Seckl at the University of Edinburgh, U.K.

Work by Mark Mattson at the National Institute on Aging in Baltimore, Maryland, among others, has shown that caloric restriction, which extends lifespan and improves cognition, shoots up levels of circulating glucocorticoids (see also ARF related news story). This contradicts the idea that higher glucocorticoid levels always harm memory (see, e.g., Brown, 2009). What explains this seeming paradox? "What we think is happening is that the neurons respond to glucocorticoids differently," Mattson told ARF. "With dietary calorie restriction, the expression of glucocorticoid receptors (GRs) in hippocampal neurons decreases." (See Lee et al., 2000.) With chronic uncontrollable stress, by contrast, levels of the "good" mineralocorticoid receptor (MR) receptor go down instead. Mattson noted that GR activation suppresses brain-derived neurotrophic factor (BDNF) production, while MR activation does not. BDNF plays crucial roles

in learning, memory, and brain health. “The bottom line is, we think the signaling pathways by which neurons respond to glucocorticoids are very important in determining whether glucocorticoids have a good or bad effect on the neuron,” Mattson said.

Several recent studies implicate glucocorticoids in memory impairment via 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1). This enzyme converts inactive glucocorticoid metabolites to active forms in the brain, and so amplifies the effects of these hormones. Seckl and colleagues report that 11β-HSD1 is up in the brain of aged mice, and that inhibiting this enzyme improves memory. Overexpressing it, meanwhile, brings on premature memory problems (see Holmes et al., 2010 and Sooy et al., 2010). Seckl said that the high levels of glucocorticoids found in elderly wild-type mice saturate the high-affinity MRs and spill over onto the low-affinity GRs, so lowering glucocorticoid levels by knocking out 11β-HSD1 helps neurons make the switch from GR to MR. Joyce Yau, working in Seckl’s lab, used glucocorticoid receptor blockers in aged control and 11β-HSD1 knockout mice to investigate the roles of the GR and MR receptors in memory (see Yau et al., 2011). In the aged knockout mice, which are cognitively sharp, GR blockers had no effect, but MR blockers worsened memory. Conversely, in the elderly control mice, which have poor memory, MR blockers had no effect, and GR blockers sharpened memory. The results support the idea that when glucocorticoids act through GR receptors, they harm memory, but when they act through MR receptors, they enhance it. Similarly, researchers led by Lynne Rueter at Abbott Laboratories, Abbott Park, Illinois, report that 11β-HSD1 inhibitors can improve memory in wild-type rats (see Mohler et al., 2011). Rueter declined to speak with Alzforum for more information on these inhibitors.

In the October 5 Journal of Neuroscience, researchers led by Steven Thomas at the University of Pennsylvania, Philadelphia, describe a mechanism by which acute stress impairs memory retrieval (a well-known effect of glucocorticoids). First author Keith Schutsky found that during acute stress, glucocorticoids and norepinephrine both act through the β2-adrenergic receptor to scramble memory. Activation of this receptor reduces cAMP signaling, known to be important for memory. Conversely, norepinephrine acting on the β1-adrenergic receptor increases cAMP and facilitates memory retrieval. Norepinephrine and glucocorticoids may therefore have a synergistic harmful effect in acute stress that is mediated by the β2 receptor, Thomas suggested. Identifying a particular receptor opens up possibilities for intervening in harmful pathways while sparing positive effects.

With specific enzymes and receptors being implicated in memory suppression, are any of them suitable targets for therapeutic trials? Several experts told ARF that they first need to understand more about the basic science and mechanisms behind stress. The stress system is enormously complicated, and perturbing it could do more harm than good. For example, the synthetic glucocorticoid prednisone worsened some behavioral symptoms when given to AD patients as an anti-inflammatory (see Aisen et al., 2000). In addition, Thomas noted that different types of stress may require distinct therapeutic approaches. One non-pharmacological way to lower stress is through relaxation techniques such as yoga and meditation, but very few studies have looked at the effects of these interventions on cognition and brain health (see Pagnoni and Cekic, 2007; Doraiswamy and Xiong, 2007).

Currently, some of the most promising therapeutic approaches include 11β-HSD1 inhibitors and CRF receptor antagonists. A small study by Seckl's group found that 11β-HSD1 inhibition improves cognition in elderly diabetic men (see Sandeep et al., 2004). Rueter at Abbott Laboratories is doing preclinical work on such inhibitors, and Merck is also in the hunt (see ARF related news story), but neither of them has listed any current dementia trials targeting this enzyme. Seckl noted, however, that 11β-HSD1 inhibitors have been "modestly successful" for several companies in metabolic disease and diabetes trials, and he predicted dementia trials might be next.

CRF receptor antagonists are similarly on the verge, with no dementia trials currently listed. However, several companies, such as Eli Lilly, Bristol-Myers Squibb Company, and SmithKline Beecham Limited, have filed patents for CRF1 antagonists in the last year or so, suggesting that preclinical work is ongoing. The patents cover conditions ranging from depression, anxiety, and irritable bowel syndrome to neurodegenerative conditions.

Other potential treatments also target receptors. Kim Green at the University of California, Irvine, points out that the glucocorticoid receptor antagonist tau mutant mice mifepristone (RU-486) may be a promising treatment for AD (see also Dhikav and Anand, 2007). Green sees encouraging results in AD animal models with mifepristone (paper submitted). The drug is currently in several clinical trials for conditions such as depression, post-traumatic stress disorder, and metabolic syndrome. A small AD trial in 2002 reportedly showed cognitive improvement (see Pomara et al., 2002; Pomara et al., 2006).

It seems clear that the study of stress and AD is still in its infancy, Landfield told ARF. "One thing we've learned, especially since we began working with microarray analyses, is that everything is enormously more complicated than we thought. I do think a major key to unhealthy brain aging and neurodegeneration may lie in the role of glucocorticoids in the brain, but it's not going to be a simple puzzle. We're going to need a Rosetta stone of some sort."—Madolyn Bowman Rogers.

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