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A Derangement of the Brain Wound Healing Process May Cause Some Cases of Alzheimer's Disease

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Abstract: A derangement of brain wound healing may cause some cases of Alzheimer's disease. Wound healing, a highly complex process, has four stages: hemostasis, inflammation, repair, and remodeling. Hemostasis and the initial phases of inflammation in brain tissue are typical of all vascularized tissue, such as skin. However, distinct differences arise in brain tissue during the later stages of inflammation, repair, and remodeling, and closely parallel the changes of Alzheimer's disease. Our hypothesis -- Alzheimer's disease is brain wound healing gone awry at least in some cases -- could be tested by measuring progression with biomarkers for the four stages of wound healing in humans or appropriate animal models. Autopsy studies might be done. Chronic traumatic encephalopathy might also result from the brain wound healing process.
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Various causes have been postulated for Alzheimer's disease. Among them are genetic defects, extracellular amyloid beta (Aβ) deposits, tau protein abnormalities, reduced acetylcholine synthesis, vascular abnormalities, and mitochondrial dysfunction (Querfurth and LaFerla, 2010; Carvalho *et al*., 2015; Coyle *et al*., 1983). Another cause of some cases may be a derangement of the brain wound healing process.

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Wound Healing in the Brain

Recent studies of implanted electrodes have elucidated differences in brain wound healing versus wound healing in non-neural tissue (Stroncek and Reichert, 2008). Implanted electrodes have many therapeutic uses. For example, they can monitor neural signals in the brain and can be used for the treatment of Parkinson's disease, obsessive-compulsive disorder, Tourette syndrome, and the control of prosthetics in patients with full to partial paralysis. But chronically implanted sensors and electrodes frequently, unpredictably fail as a result of complications arising from the wound healing response.

Wound healing, a highly complex process, has four stages: hemostasis, inflammation, repair, and remodeling. The initial phases of inflammation in brain tissue are typical of all vascularized tissue, such as skin. However, distinct differences arise in brain tissue during the later stages of inflammation, repair, and remodeling, and closely parallel the changes of Alzheimer's disease. The functioning of the blood brain barrier, as well as the action of microglia and astrocytes, makes brain wound healing unique. Most important, the repair of a wound in the central nervous system is not followed by neural regeneration.

Four Stages of Wound Healing

1. *Hemostasis*. In non-brain tissue, platelet adhesion and activation occur, with fibrin formation, to stem blood flow with a hemostatic plug. In brain tissue, a similar process occurs. In Alzheimer's disease, a prothrombotic state is associated with increased clot formation, decreased fibrinolysis, and elevated levels of coagulation factors and activated platelets. Abnormal deposition and persistence of fibrinogen may result from Amyloid β-fibrinogen binding and altered hemostasis (Cortes-Canteli *et al*., 2012). The characteristic

breach of the blood brain barrier in Alzheimer's disease probably occurs at this stage of brain wound healing (Bell and Zlokovic, 2009).

2. *Inflammation*. In non-brain tissue, macrophages mediate inflammation. In brain tissue, microglia are the principal mediators. Microglia, the immune cells of the brain, are implicated in cascades leading to inflammation, neuronal loss and cognitive decline in Alzheimer's disease (Crehan *et al*., 2012). Inflammation is a fundamental feature of both wound healing and Alzheimer's disease.

3. *Repair*. In partial thickness skin wounds, where only the epidermis is damaged and the basement membrane remains intact, the wound can heal by keratinocyte regeneration and migration alone.In the brain, microglia and macrophages migrate into the lesion, secreting cytokines and growth factors. Macrophages, microglia, and astrocytes are strongly involved in the pathogenesis of Alzheimer's disease, as well as HIV-associated dementia and multiple sclerosis (Minagar *et al*., 2002).

4. *Remodeling*. In skin, fiber alignment and wound contraction take place, along with tissue strengthening. In brain wound healing, gliosis occurs. Gliosis is a non-specific reactive change of glial cells in response to damage to the central nervous system. In most cases, gliosis involves the proliferation or hypertrophy of several different types of glial cells, including astrocytes, microglia, and oligodendrocytes. Gliosis is a well documented finding in Alzheimer's disease (Gylys *et al*., 2004). The brain atrophy of Alzheimer's disease could correspond with skin wound contraction.

Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) increases the risk of Alzheimer's disease in men treated for prostate cancer, and there is a statistically significant increased risk of Alzheimer's disease with increasing duration of ADT (Nead *et al*., 2015). Moreover, endogenous testosterone inhibits the cutaneous wound healing response in males (Ashcroft and Mills, 2002). Therefore, ADT could enhance the brain wound healing process and increase Alzheimer's disease susceptibility.

Aspirin and Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Aspirin and NSAIDs significantly reduce the risk of Alzheimer's disease but have no value as a treatment (Jaturapatporn *et al*., 2012; Fotuhi *et al*., 2008). One explanation for this discrepancy is that because of tight plasma protein binding, the amount of NSAID reaching the brain is quite low: enough to prevent Alzheimer's disease but not enough to treat it (Parepally *et al*., 2006; Lehrer, 2014).

A second explanation is the inhibitory effect of aspirin and NSAIDs on wound healing (Lee, 1968). Aspirin inhibits healing by reducing 12-hydroxyheptadecatrienoic acid production (Yokomizo *et al*., 2013; Liu *et al*., 2014; Gus-Brautbar and Panigrahy, 2014). In animal models, systemic ibuprofen has an anti-proliferative effect on wound healing, resulting in decreased numbers of fibroblasts, weakened breaking strength, reduced wound contraction, delayed epithelialization, and impaired angiogenesis (Guo and Dipietro, 2010). Both aspirin and NSAIDs act early enough to stop the brain wound healing process from initiating and prevent Alzheimer's disease from starting. But by the time Alzheimer's disease becomes clinically apparent, wound healing is too far along to be affected by these drugs.

Intranasal Insulin

Intranasal insulin has two potentially antagonistic effects in Alzheimer's disease, promotion of both brain insulin signaling and brain inflammation.

Insulin signaling is impaired in Alzheimer's disease (Candeias *et al*., 2012). Moreover, insulin treatment has a potent protective effect on spatial learning and memory ability of diabetic rats (Yang *et al*., 2015).

In the SNIFF Trial, Claxton *et al*. (2015) reported that Long-Acting Intranasal Insulin Detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease. But insulin glulisine (Apidra) failed to have an acute impact on cognition in ApoE4 carriers with mild-moderate Alzheimer's disease. Other intranasal insulin preparations were also ineffective in ApoE4 carriers in four trials (Rosenbloom *et al*., 2014; Reger *et al*., 2006). ApoE4 carriers demonstrated a relative decline in verbal memory when treated with regular recombinant human insulin (Novolin) (Reger *et al*., 2008). Only insulin detemir (Levemir) in the SNIFF trial improved verbal episodic memory in ApoE4 carriers, although it had no effect on working memory (Claxton *et al*., 2015).

ApoE4 carriers may not respond to intranasal insulin because of increased inflammation. ApoE4 exacerbates neuro-inflammation, much more so than apoE3 (Guo *et al*., 2004).

Topical insulin promotes wound healing (Pierre *et al*.,

1998) by augmenting wound inflammation, especially the quantity and function of macrophages (Chen *et al*., 2012). The brain insulin resistance in Alzheimer's disease, sometimes called type III diabetes, may be due to brain inflammation, since chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance (Xu *et al*., 2003).

Rapamycin (INN/USAN Sirolimus)

Rapamycin (Rapamune) is a macrolide immunosuppressant drug which is administered after transplantation to prevent organ rejection. In the brain, rapamycin benefits neuronal survival and plasticity, contributing to memory improvement (Santos *et al*., 2011). Some studies suggest that rapamycin might be a treatment for Alzheimer's disease (Caccamo *et al*., 2010; Spilman *et al*., 2010). If so, rapamycin's therapeutic benefit could be due to one of its principal side effects, impairment of wound healing (Schaffer *et al*., 2007; FDA and Pfizer, 2001).

In mice, the brain concentration of rapamycin after intraperitoneal administration is 2% of the liver and plasma concentration with very low passive penetration of the blood brain barrier (Meikle *et al*., 2008). Therefore, rapamycin might be administered intranasally to achieve an effective therapeutic brain dose.

Chronic Traumatic Encephalopathy

Some professional football players and boxers often develop symptoms of impaired cognition, mood, behavior, and motor skills. Repeated head trauma is followed by a lag period before Chronic Traumatic Encephalopathy (CTE) symptoms become evident. The pathologic changes are similar to Alzheimer's disease but show a predominance of tau protein deposition over amyloid (Yi *et al*., 2013). Some cases of CTE, like Alzheimer's disease, might result from the brain wound healing response.

Conclusion

We propose that some cases of Alzheimer's disease are due to the initiation of the brain wound healing process, often in the absence of any actual wound. The pathologic hallmarks of Alzheimer's disease, plaques and tangles, are a non-specific result of the disease process, not a cause (Lee *et al*., 2007). Alzheimer's begins in the hippocampus and rhinencephalon, then spreads throughout the brain (Braak *et al*., 2006). The hippocampus and rhinencephalon connect to the olfactory nerves and olfactory bulbs, which could serve as a portal of entry for substances that trigger the wound healing process. Wound healing is beneficial for skin and bone, but might not always be conducive to normal brain function or cognition. Once the wound healing process begins, brain deterioration proceeds unimpeded.

Our hypothesis -- Alzheimer's disease is brain wound healing gone awry in some cases -- could be tested by measuring progression with biomarkers for the four stages of wound healing in humans or appropriate animal models. Autopsy studies might also be done. Although autopsy studies are cross-sectional rather than longitudinal, they can be used to gauge Alzheimer's disease progression (Serrano-Pozo *et al*., 2011).

Better understanding of brain wound healing may lead to an effective treatment for Alzheimer's disease.

Disclosure

Dr. Lehrer has filed a patent application for nasal NSAID treatment of Alzheimer's disease.

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