

Subdural Pharmacotherapy Device Adapted to the Treatment of Alzheimer's Disease

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Abstract

The more than 20-year clinical experience with the inefficiency of systemically administered drugs for Alzheimer's disease (AD) justifies the extension of preclinical and clinical tests to new approaches. This author's opinion is that these new approaches should include tests with intracranial drug delivery devices, such as the Subdural Pharmacotherapy Device (SPD). The SPD, an implantable drug delivery – neurotoxin drainage device currently in the preclinical phase, has the following 5 main advantages over other anti-AD methods [1]. Ability of treating the diseased hippocampal–association cortical memory circuitry site-specifically and through the overlying subarachnoid space without tissue-penetrating cannulas [2]. The related ability of eliminating the risk of systemic pharmacological side-effects [3]. The other related ability of bypassing the Blood-Brain Barrier (BBB) with the delivered drugs, allowing the use of small molecules in combination with neurotrophic, gene-modulating, and other beneficial proteins [4]. The unique ability of enhancing local pharmacological efficacy via differentially clearing the affected tissue from endogenous neurotoxic products [5]. The additional unique ability of producing these four critical pharmacological/neurochemical actions with the long-term automatic precision of a clog-free engineered device.

Keywords: Intracranial drug delivery; Intracranial neurotoxin drainage; Subdural device; Blood-Brain Barrier; Nonhuman primates

According to the World Alzheimer Report 2014 [1], dementias, mostly Alzheimer's disease (AD), affect about 44 million people worldwide with the global annual costs exceeding \$600 billion. Yet, none of the approved drugs for AD is effective to even significantly alleviate its devastating cognitive symptoms. To change this “flat line of progress” in AD therapy [2], the following fundamental problems of systemic (e.g., oral, intravenous, transdermal) drug treatments for dementias need to be considered. First, drugs that can improve the efficacy of deficient neurotransmitter systems (e.g., the cholinergic system) cause often severe systemic side-effects when given systemically in effective doses, due to the unnecessary distribution of these drugs in the entire body. Second, potentially beneficial neurotrophic proteins, such as Nerve Growth Factor (NGF) or Brain-Derived Neurotrophic Factor (BDNF), do not cross the BBB upon systemic administration in pharmacologically significant quantities. Third, even those compounds that cross the BBB cannot be selectively directed via systemic administration to the hippocampal – association memory circuitry responsible for the predominant symptom, memory impairment, of AD. Fourth, no systemic drug application can clear the hippocampal–association cortical extracellular space from the wide spectrum of potentially neurotoxic molecules ranging from amyloid beta oligomers and proinflammatory cytokines to excess glutamate and extracellular tau.

These problems can be eliminated with the neurosurgical implantation of the SPD and its use as long as needed. The efficacy and safety of the antiepileptic version of this new intracranial drug delivery device have been proved in comprehensive studies in nonhuman primates [3-7]. These studies suggest that the device could be adapted to the treatment of other neurological disorders with predominantly cerebral cortical pathology, including AD. The essential components and features of the SPD for AD therapy are summarized in Figure 1 The device comprises < 1.0 mm thick silicone strips, placed bilaterally on the pia mater covering both the output-generating regions

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of the hippocampal formation (CA1, subiculum and entorhinal cortex) and the frontal, parietal and temporal association cortices. Each strip integrates multiple fluid-ports, with each port serving for both drug delivery and neurotoxin drainage to and from all layers of the contacted cortical tissues, respectively. Subdural EEG electrodes are added to the strips so that feedback electrophysiological data on this localized treatment can be obtained. Fluid-movements through the ports are directed by a battery-powered, microprocessor-controlled, delivery/drainage minipump. This control unit is also able to wirelessly transmit the recorded EEG waves along with hardware-status data while receiving external instructions to adjust device parameters when needed [3-7].

As Figure 1 indicates, the first advantage of the SPD over traditional systemic drug treatments is that it can apply the anti-AD compounds site-specifically into the hippocampal-association cortical memory system, the very circuitry responsible for the predominant symptoms of AD. In fact, as the SPD essentially irrigates the diseased neural tissue "transmeningeally", it causes no damage in the treated cortex with tissue-penetrating cannulas or catheters.

The second advantage of the SPD is that, as a consequence of its site-specific action, the delivered drugs do not spread to the rest of the body in concentrations high enough to cause clinically significant side-effects. This site-specific efficacy without side-effects enables the device to increase the concentration of the therapeutic agent only where it is needed to effective levels without inducing side-effects that interfere with treatment.

The third advantage of the SPD is that as it delivers the anti-AD compounds transmeningeally, thus directly into the cortical extracellular space, bypassing the BBB. This immediately offers the full utilization of proteins, including neurotrophic factors and modulators of gene transcription, which otherwise do not cross the BBB. It has yet to be determined whether or not the local efficacy and safety of these SPD-delivered molecules can be further increased by encapsulating them and administered as nanoparticles.

The fourth advantage of the SPD is that its unique, bidirectional fluid-moving function can also execute local cerebrospinal fluid (CSF) drainage. This makes possible to clear the cortical extracellular space from at least some of the AD-inducing/maintaining endogenous neurotoxins that diffuse into the CSF. Certainly, these harmful molecules include amyloid-beta oligomers, extracellular tau, excess glutamate and some proinflammatory cytokines. In our pending US patent Pub. No. 20150038948 (available at: <http://www.google.com/patents/US20150038948>) we described a method for differentially facilitating the clearance of these harmful molecules without the unwanted drainage of such crucial neuromodulators as acetylcholine, norepinephrine and serotonin (5-HT). Essentially, in this method "the neurochemical composition of the artificial CSF solvent, which is used for the delivered drugs and fills the treated cortical area's subarachnoid space, is adjusted to increase or decrease the chemical concentration gradient for specific cortical molecules or molecular sets and thereby allow the differential removal of potentially harmful endogenous molecules from the diseased cortical extracellular space."

Finally, the fifth advantage of the SPD is that as an engineered, microprocessor-controlled device it performs the above functions automatically, with the precision of digital electronics.

However, the SPD has the disadvantage of being an implanted system, thus its use requires an invasive neurosurgical procedure in the first place. But this disadvantage, in this author's view, is actually the price to be paid for site-specificity: the prerequisite of (a) directing drugs to the diseased brain areas only, where pharmacological assistance is needed; (b) draining endogenous molecules from the diseased brain areas only, which benefit from this treatment; (c) avoiding the unnecessary exposure of healthy tissues to drugs, and (d) accessing the subarachnoid space to bypass the BBB and unleash the therapeutic potential of the used agents. Is, then, neurosurgery a price worth paying to help AD patients to regain their cognitive power and personality, indeed, the life they had before stricken with the disease? In this author's view the answer is YES, even though the limits of neurosurgical care in the US would make SPD therapy accessible to only a fraction of the approximately 5 million people suffering from AD.

Implants for NGF administration into the cerebral ventricles or the basal forebrain were tested in clinical trials [8,9] just as ventroperitoneal shunting to drain neurotoxic molecules from the brain of AD patients [10]. None of these treatments led to breakthrough results. However, the used methods differed significantly from the outlined SPD strategy (Figure 1). For example, they did not target site-specifically the hippocampal – association cortical memory circuitry. Nor did the used ventroperitoneal shunt prevent the unwanted drainage of acetylcholine, norepinephrine or 5-HT. Further, the cited studies did not capitalize on the synergistic action of drug delivery and neurotoxin drainage, nor did they intervene into more than one neurochemical pathways involved in AD pathology.

Nanoparticles, including drug-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles dispersed in hyaluronan/methylcellulose hydrogel [11], hold great promise to regenerate tissue in the central nervous system [11]. Indeed, these and other ingenious techniques using nanoparticles can be adapted to the specific needs of AD therapy and may well open a new chapter in the care of this disease. But in order to demonstrate that systemically administered nanoparticles effectively cross the BBB and selectively act in the hippocampal-association cortical memory circuitry while remain free of side-effects, extensive safety studies like ours [3-7] would be prudent to pursue with nanotechnological applications, as well. The necessity of such *in vivo* studies has also been emphasized by other investigators [12]. Using SPDs and other drug delivery devices for administering AD drugs encapsulated in nanoparticles is one reasonable avenue for such studies.

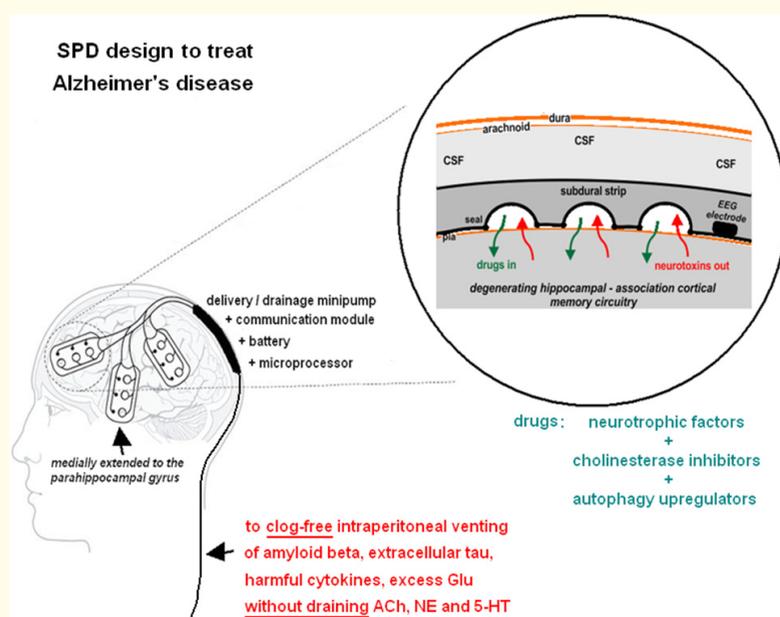


Figure 1: SPD design adapted for the treatment of AD. The subdural strips integrating fluid-ports for both drug delivery and neurotoxin drainage, as well as EEG electrodes for feedback data, are placed bilaterally over the hippocampal – association cortical memory circuitry. The functions of these strips are regulated by a control unit inserted in the cranial bone. In the preferred system (shown), drained local fluids are vented via a clog-free intraperitoneal shunt without removing physiologically functioning neuromodulators, while allowing the analysis of the withdrawn harmful molecules/neurotoxins for precision AD therapy. Alternatively, the drained local fluids can be collected in one of the reservoirs of the control unit minipump and emptied as needed via a subcutaneous port. The safety and pharmacological efficacy of this system, albeit not yet including this particular shunt, have been documented in nonhuman primates [3-7]; specific adaptation to AD therapy has yet to be completed.

In summary, the SPD has the potential to restore, or at least significantly improve, memory and cognitive functions in AD patients. The optimal timing of SPD implantation is likely the transition from the early to the middle stage of the disease, as by this stage it becomes clear whether systemic drugs are useful or inefficient for the patient and whether the costly, and in some cases undesired, institutionalization is already under consideration, while the patient's age and general condition still permit the necessary neurosurgical procedure. Since the safety and antiepileptic efficacy of the muscimol-delivering SPD version have already been extensively documented in nonhuman primates [3-6], a viable and realistic clinical trial could certainly include patients with both AD and diffuse fronto temporal focal epilepsy poorly responding to oral antiepileptic drugs, as the documented co-occurrence of these brain disorders [13,14] involves overlapping pathologies within the same neural circuitry. Preventing these patients' otherwise poorly controlled seizures with the SPD-delivered muscimol would likely optimize the local cellular/molecular conditions for the subsequently co-administered anti-AD treatment tailored to the patient's specific neurochemical abnormality (Figure 1). True, even in this narrowed patient population SPD implantation cannot be immediately performed in all who need it and give consent with his/her family, as gaining acceptance for this novel treatment in the medical community and building the necessary infrastructure, including specialized implantation centers, would take time. But the proposed extension of medical device applications to AD treatment with the SPD should yield, within a decade, clinically meaningful relief for tens of thousands of people suffering from AD and lead to considerable health care savings for the society, while reveal a new set of information on the neurochemistry of AD. This latter may well help to achieve the ultimate goal of curing the disease, perhaps with the cooperative, rational, and synergistic use of gene therapy, nanotechnology, device implantation and other emerging revolutionary techniques .

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