NEW TREATMENT STRATEGIES FOR DIABETES-RELATED COGNITIVE DECLINE IN GLOBAL HEALTHCARE

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ABSTRACT
The epidemic of type 2 diabetes (T2DM) is spreading around the globe and challenging the unprecedented success of health sciences in increasing longevity. T2DM has been linked to accelerated brain aging and functional decline in older adults and dementia. Intranasal insulin (INI) therapy has emerged as a potential new treatment for T2DM-related cognitive decline. Insulin resistance and glycemic variability are potential mechanisms underlying T2DM-related brain damage. Wearable technologies now allow better monitoring of behaviors and glycemic levels over several days, and may be used in the future to deliver real time feedback and new therapies for T2DM complications.

Keywords: type 2 diabetes, intranasal insulin, glycemic variability, wearable technology

1. INTRODUCTION
Healthcare sciences have achieved an unprecedented success in continuing increase in longevity, decrease of birth death rates and diminishing or eliminating the impact of many infectious diseases. Large health inequalities between countries around the globe shape differences in lifespan from < 50 to > 80 years of age. At the same time, non-communicable diseases, and in particular diabetes, hypertension and cardiovascular diseases have become the most common causes of death. Over the last twenty years, the obesity epidemic has been sweeping across the globe, and many countries face a dilemma of fighting both hunger and obesity at the same time. Type 2 diabetes mellitus (T2DM) is a complex metabolic disease that affects multiple organ systems and interactions among them (Figure 1). T2DM accelerates brain aging (Xu et al., 2004), alters neurovascular coupling (Mogi and Horiuchi, 2011, Last et al., 2007, Novak and Hajjar, 2010, Novak et al., 2011, Tiehuis et al., 2008), and increases the risk for dementia and Alzheimer's disease (de Bresser et al., 2010a, de Bresser et al., 2010b, van den Berg et al., 2010). The long-term diabetes complications have a major impact on the high prevalence of cognitive impairment, depression, and disability in older adults. (Saczynski et al., 2008, Novak et al., 2011, Manor et al., 2012). Memory loss further deteriorates self-care and glycemic control and accelerates disease progression, worsening a vicious cycle of functional decline. Currently, there is no cure for DM-related cognitive impairment.

Figure 1: T2DM—a complex multi-organ disease

In T2DM, glucose levels fluctuate over various timescales, from minutes to days, exposing the organs (including the brain) to adverse effects of prolonged hyperglycemia (elevated blood sugar levels) and hypoglycemia (low blood sugar levels) during the day and night (Figure 2A). In contrast, in a healthy person blood sugar levels remain tightly regulated during daily activities and during the sleep (Figure 2B). As a result, even a strict glycemic control did not improve cognitive function in participants of the large clinical trials (Cukierman-Yaffe et al., 2009, Launer et al., 2011).

Figure 2: A. Glycemic variability in T2DM, B. Control
Insulin resistance, altered transport and insulin signaling in the brain may be a potential pathway for DM-related cognitive decline. Therefore, there is an urgent need to develop new therapies to target insulin delivery to the brain to treat cognitive impairment in older diabetic adults. This need for new therapies is also important as cognitive impairment poses a significant barrier for self-care, increasing further the risk for diabetic complications, disability, and dementia in this age group (Xu et al., 2004), (Reijmer et al., 2011), (Korf et al., 2006).

2. INSULIN A KEY MODULATOR IN THE BRAIN

Insulin has emerged as a key neurotrophic factor in the central nervous system, and as a promising therapeutic for treatment of amnestic cognitive impairment and Alzheimer’s disease (AD) (Figure 3). Insulin’s role in the brain is different from its actions in the periphery (Lioutas et al., 2015).

Central insulin plays a role as an important neuromodulator in key processes such as cognition (Shemesh et al., 2012, Freiherr et al., 2013), energy homeostasis, food intake, sympathetic activity, neuron-astrocyte signaling, synapse formation, and neuronal survival (Plum et al., 2005, Plum et al., 2006). Furthermore, insulin has been shown to reinforce signaling in the brain—reward dopamine–mediated limbic system and modulate behavioral responses to natural food and other reward stimuli (Figlewicz, 2003, Figlewicz and Benoit, 2009, Stice et al., 2012). Insulin receptors (IRs) are expressed in numerous brain regions, namely in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, and hippocampus (Hopkins and Williams, 1997, Albrecht et al., 1981), (Banks, 2004). Even wider IR distribution overlaps with expression of downstream proteins and isoforms in insulin-related pathways (Horsch and Kahn, 1999) (Banks, 2004). Insulin also contributes to cortical blood flow regulation, as evidenced by the presence of IRs within the neurovascular unit, e.g., in neurons, astrocytes, and capillaries (Hopkins and Williams, 1997), (Albrecht et al., 1981), (Cersosimo and DeFronzo, 2006), (Girouard and Iadecola, 2006) and the wall of small vessels (Abbott et al., 1999). We anticipate that cerebral insulin may directly modulate neuron-astrocyte signaling through neurovascular coupling and autonomic control of vascular tone and thus enable better regulation of local and regional perfusion (Lok et al., 2007) and neuronal activity in response to various stimuli (Amir and Shechter, 1987), (Cranston et al., 1998), (Kim et al., 2006), (Reger et al., 2006), (Muniyappa et al., 2007).

Intranasal insulin (INI) enters the brain, where it rapidly propagates through perivascular channels and binds to the receptors in the limbic system and memory networks including the hippocampus, hypothalamus, and insular cortex (Thorne et al., 2004), (Hanson and Frey, 2008), (Hallschmid et al., 2008). INI increases blood flow and energy metabolism and improves functional connectivity in these regions. More efficient neuronal signaling within memory networks improves visuospatial memory, learning, and other cognitive functions associated with these areas. It may also improve mood, regulate feeding behavior, and increase amyloid-beta clearance (Craft et al., 2013), (Morrison and Burns, 2012), (Craft et al., 2012) (Figure 3). Ten minutes after INI administration (dose 40 IU) insulin began to rise and peaked at 30 to 45 minutes as compared to placebo (insulin 1091±219.8 vs. placebo 603.2±34.6 AUC (pmol/l/min), p=0.02), with no change in serum levels (insulin 3410±276.8 vs. placebo 3410±106.1 AUC (pmol/l/min), p=0.22). After that insulin in CSF began to decline, but remained mildly elevated even 80 minutes after INI. (Born et al., 2002) INI administration safe without triggering hypoglycemia, but INI does not effectively control hyperglycemia because it results only in about 1-2% bioavailability in the serum as compared to the intravenous route (Moses et al., 1983).

3. INTRANASAL INSULIN IMPROVES COGNITION IN CLINICAL STUDIES

The insulin resistance syndrome, characterized by chronic peripheral insulin elevations, reduced insulin activity, and reduced brain insulin levels, is associated with age-related memory impairment and AD (Craft, 2005a, Craft, 2005b). These mild forms of insulin resistance may precede AD pathology for years (Freiherr et al., 2013), (Messier and Teuntenberg, 2005). The risk of T2DM for dementia and AD in late life has been increasingly recognized (Xu et al., 2004), (Reijmer et al., 2011), (Korf et al., 2006) and impaired insulin signaling in the hippocampus and hypothalamus, as seen in both conditions, may provide a common link between DM and AD (Cedernaes et al., 2013). The evidence that INI could be a promising treatment for improving cognitive function is growing (Banks et al.,...
INI Effects on Memory in Type 2 Diabetics

Our proof-of-concept (Novak et al., 2013; Zhang et al., 2014), randomized, double-blind, placebo-controlled intervention evaluated the effects of a single 40-IU dose of insulin (Novolin® Novonordisk) on vasoreactivity and cognition in 15 type 2 DM patients (60.1±9.9 years old, HbA1c 7.4±1.4%, DM duration 11.3±4.7 years, 7 F), and 14 age- and sex-matched healthy controls (62.0±7.9 years old, 10 F). A ViaNase device was used to administer INI or sterile saline in random order with cross-over assignment on Day 2 or Day 3. Perfusion MRI using 3-D CASL at 3 Tesla and cognitive test were done < 2 hr after INI.

**Brief Visuospatial Learning and Memory Test Revised (BVMT):** INI improved BVMT performance in both groups. Controls on INI performed better than diabetics on either INI or placebo on immediate recall Trials 2-3 (T2, T3) [(least squares model adjusted for age R^2 = 0.1, p<0.03), T3 (R^2 adj = 0.14, p<0.03), and Total Recall. These effects remained significant after adjusting for education (T2: R^2 adj = 0.1, p=0.02; T3: R^2 adj = 0.1, p=0.03). INI improved performance on T2 (p=0.04) and Total Recall (paired t-test, p=0.05). **Verbal Fluency Task (timed word generation using letters F,A,S)** INI improved verbal fluency. Controls on INI performed better than diabetics on the FAS (R^2 adj = 0.26, p=0.0045), switching (R^2 adj = 0.2, p=0.006), and composite verbal fluency (R^2 adj = 0.12, p=0.02).

3.1.1. Cognitive Performance Correlates with Regional Vasodilation

Regionally, perfusion changes on INI were observed in the middle cerebral artery (MCA) territory and insular cortex, integrative areas for learning, memory, and language. The DM group had lower baseline perfusion than controls (p=0.039). In the DM group, INI increased perfusion in the right insular cortex compared to placebo (p=0.0001) and to the control group (p=0.0003). BVMT and verbal fluency performances correlated to perfusion and vasodilation within the MCA territory and the insular cortex, an area that regulates attention-related task performance (Novak et al., 2014). BVMT T3 and BVMT Delayed Recall (MCA: R^2 = 0.28, p=0.04; insula: R^2 = 0.22, p=0.04). In diabetics, better visuospatial memory after INI correlated with vasodilation in the MCA territory for BVMT immediate recall (T2: R^2 adj = 0.43, p<0.01; T3: R^2 adj = 0.39, p<0.035), and Total Recall (R^2 adj = 0.44, p=0.0098). These relationships were not observed after placebo. BVMT T2, T3 and Total Recall also correlated with vasodilation in the anterior cerebral artery territory (p=0.05-0.08). In controls on INI, FAS score (R^2 adj = 0.39, p=0.04) and the composite verbal fluency score (R^2 adj = 0.18, p=0.05) were associated with greater vasodilation in the right insular cortex. In the DM group on INI, FAS scores were also associated with greater vasodilation in the left (p=0.02) than in the right insular cortex (R^2 adj = 0.26p=0.04).
3.1.2. INI Improved Functional Connectivity of Hippocampus with Resting State Networks

For network correlation analyses we used a voxel-based approach to examine connectivity of the hippocampal regions with regions within the resting state DMN (Zhang et al., 2014). The DM subjects on INI demonstrated increased connectivity of hippocampus regions with DMN regions (MPC: medial prefrontal cortex [3.7, peak t score]; IPC: inferior parietal cortex [3.9]; PCC: posterior cingulate cortex [3.2]) than those on placebo (Figure 4 A-B) (p<0.05, voxel corrected).

Figure 4: A. Diabetes group on INI had better functional connectivity between hippocampus and default mode network. B. On placebo DM group had worse connectivity than controls.

On placebo, DM group had lower connectivity as compared to controls (p=0.02) but connectivity on INI was similar. In DM subjects, functional connectivity between hippocampus and anterior cingulate cortex was associated with better Verbal Fluency Score. BVMT showed a positive trend toward association between hippocampus and right IPC. INI may modify functional connectivity among brain regions regulating memory and complex cognitive behaviors.

4. TYPE 2 DM EPIDEMIC, PHENOTYPE AND HEALTHCARE SYSTEMS

As the epidemic of T2DM spans around the globe and different age groups, it presents complex health issues and care delivery that challenge the traditional health care systems. The major challenge is the increase of obesity and T2DM in children (18% of children in the U.S. are obese) and younger adults increasing their risk for cardiovascular complications in young adulthood (Lurbe et al., 2008),(Wild et al., 2004). Obesity is a “social phenomenon” that spreads along the social networks, and obese peers increase probability for their friends to become obese, e.g. up to 100% for male friends, 40% in siblings, and 37% in souses(Christakis and Fowler, 2007). Interestingly, social contagion phenomenon has been also observed for other health-related behaviors (Christakis and Fowler, 2013), such as drinking alcohol (Christakis, 2004). However, this social phenomenon may also support the spread of health-positive behaviors such as smoking cessation, and smokers are progressively found on the periphery of the networks. The probability of smoking decreased by 67% for the spouse, 36% for a friend and 25% for a sibling (Christakis and Fowler, 2008).

The major challenge is that the increase of obesity and T2DM in children and younger adults still affects even countries that previously had very low rates of obesity and cardiovascular complications. At the same time the media impact on behavior in younger generation is much stronger, and therefore there is a greater opportunity for influencing both positive (activity) and negative behavior (e.g. obesity, drinking) via social networks and media and this phenomenon could be perhaps expanded to reinforcing the positive behaviors such as activity and healthy eating via web care (Christakis and Fowler, 2013),(Christakis, 2008)

The younger generation is at greater risk of developing T2DM complications, because the perception of its risks is lower than in older generation, and therefore younger people are less likely to receive more aggressive treatments that are needed for long-term health preservation. At the same time the older people with T2DM are living longer, and surviving cardiovascular complications. As a result, the number of people with disability due to diabetes is on the rise, however the perception of severity of its complications is declining. A phenotype of slow gait speed, depression and cognitive impairment has thus emerged that may be linked to abnormal vasoregulation. Altered regulation of perfusion during daily challenges may accelerate brain atrophy and correlate with slower gait speed, worse cognition and function,(Novak et al., 2006),(Novak et al., 2009) (Last et al., 2007) (Hu et al., 2008) and poor balance in older age (Manor and Li, 2009),(Manor et al., 2012). DM affects verbal learning, executive function, and memory,(Morra et al., 2013),(Hajjar et al., 2009) and thus poses a barrier to self-care in DM patients (Kuo et al., 2005) (Munshi et al., 2006). Furthermore, cardiovascular risk (Albert et al., 1988),(Munshi et al., 2006),(Kuo et al., 2007),(Kuo et al., 2009) and genetic(Zade et al., 2013) and lifestyle factors (Levine et al., 1997,Rudolph et al., 2006) may contribute or lead to cognitive decline in older adults. Cardiovascular risk factors increase exponentially with age and are often overlooked as a source of cognitive changes attributed to “normal” aging (Leritz et al., 2011)(Kuo et al., 2004). Therefore, there is a great need to reinforce the concept that long-term health-oriented behaviors are crucial for prevention of T2DM and its long-term complications.

4.1. The Self-Management and Mobile Technology

Look AHEAD long term clinical trial (Espeland et al., 2009) has shown that behavioral interventions are effective for short-term improvement of health status, but sustainability of healthy behaviors and prevention of long-germ complications still remains a challenge (Espeland et al., 2009),(Unick et al., 2011). Therefore, there is a need to bring novel non-traditional approaches
to reinforce healthy behaviors in people of all ages and improve prevention and management of cardiovascular risk factors that lead to T2DM and its complications.

Recent advancements of wearable technologies and web-based sites offer the new opportunity for self-monitoring of behaviors (e.g. gait, activity, sleep etc.) and have been effective in recording daily/weekly activities. However, accurate monitoring of food intake, food composition, metabolic rate and balance still remains a challenge. New sensors can be woven into fabrics (smart textile technology), clothing or even directly printed on human skin (Zheng et al., 2014), (Jadad et al., 2015),(Alam and Ben, 2014) thus allowing pervasive yet unobtrusive health monitoring and telemonitoring (Hung et al., 2004) for prolonged time periods. The feasibility of wearable technology applications is growing (Choi et al., 2013),(Barnard and Shea, 2004), (Buttussi and Chittaro, 2008), and some technologies are already achieving sustainable goals in combination with guided therapy e.g. for weight loss, diabetes control etc. that are comparable to the office visits and group therapy. In addition, these approaches would utilize only a fraction of the healthcare worker’s time, would be more cost effective, could reach larger population and would not require one-to-one contact.

The major challenge that remains in T2DM management is development of a closed loop system capable of real time monitoring of multiple physiological variables (e.g. activity, glucose, nutrients intake) and delivering treatments either behavioral notifications, feedback reinforcement or medications in a real time. Even better set-up would be preemptive modes that would predict glycemic fluctuations in real time and through a closed loop system maintain glycemic levels stable during daily activities, metabolic demands and challenges.

4.2. Conclusions
The utilization of wearable technologies, however, has not yet been adopted by the traditional systems, and there is a great need for education of a younger generation that is not spared from the risks of lifestyle related diseases and is facing a longer diseased life or even a shorter lifespan (Lurbe et al., 2008). At the same time, there is a need for better understanding of the impact of availability, sharing and potential misuse of health-related are information, mass data collection and a proper use of smart technology (Barnard and Shea, 2004). There is a growing need for further development of telemedicine and “guided self-diagnosics and monitoring using smart devices” that is becoming more feasible based upon the advances and availability of mobile technology and sensors. Therefore, non-traditional approaches based on wearable technologies combined with artificial intelligence that could provide real time feedbacks about behavior modifications would allow the design and implementation of new strategies and and novel paradigms to further improve well-being of younger as well as older population of diabetic people and those at risk for diabetes.

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