Review Article

International Journal of Research in Pharmaceutical Sciences

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Effect of short-term memory and working memory in diabetes with comorbidities condition

Anand Vijayakumar P R*, Seema A, Kokul Rajan P

Department of Pharmacology (A DST FIST sponsored department), JSS College of Pharmacy (JSS Academy of Higher Education & Research), Rocklands, Udhagamandalam-643001, Tamil Nadu, India

Article History:

Received on: 09 Apr 2020
Revised on: 07 May 2020
Accepted on: 22 Jul 2020

Keywords:

Cognition,
Dementia,
Hippocampal damage,
Memory,
Type 2 diabetes

Abstract

Cognitive function refers to the ability of humans to function normally which includes physical as well as mental interpretation like ability to focus, concentrate, learn, plan, determine, execute, manipulate and problem solving. Etiologic of cognitive dysfunction includes AD, depression, anxiety and vascular dementia, hippocampal sclerosis etc., Diabetes associated with cognitive decline are related to short fall of learning and memory. Cognitive impairment/dysfunction in diabetic patients has been divided into three stages, stage one, stage two and stage three. Stage one, occur in all groups of different ages and it is characterized by mild and subtle changes in cognition. Deficit in short-term memory and working memory leads to major problems like Alzheimer disease and dementia. The pathophysiology of cognitive decline associated involves microvascular injury, hyperglycaemia, insulin resistance and oxidative stress. Diabetes associated with comorbidities condition leads to decrease in short-term memory and working memory. From this review we observed short term memory retains small amount of data in cognizance which are readily available state for short period of time whereas working memory manipulates the information through visual and auditory storage and it is important in understanding and improving the memory. Conclusion of this review is that, there is a decrease in short-term memory and working memory in type 2 diabetes patient condition. But there is no evidence of which type comorbidity condition affects more in short-term memory and working memory. So, further research study to be carried out.

*Corresponding Author

Name: Anand Vijayakumar P R
Phone: 9443181573
Email: ootyanand2004@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i4.3158

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Cognition has been referred as "the intellectual process or action of obtaining understanding and knowledge via thoughts, experiences and senses. Etiologic of Cognitive dysfunction/disorder includes degenerative disorders including AD, depression, anxiety and vascular dementia, medication side effects, hormones fluctuation, disturbed sleep, hippocampal sclerosis, lyme disease, diabetes, metabolic disorders, alcohol abuse, subdural and epidural hematomas, seizures, vitamin B12 deficiency, HIV associated neurodegenerative disorder, hashimoto's encephalopathy (Saedi *et al.*, 2016).

Cognitive function refers to the ability of humans to function normally in everyday life ranging from their personal, occupational and social point of view. These includes, physical as well as mental interpretation of the things surrounding them like the ability to focus, concentrate, learn, plan, determine, act,

execute, express, retain the information, manipulate and solving the problems (Sharma and Antonova, 2003).

Theories of cognition aging and work

Cognitive impairment/dysfunction in diabetic patients has been divide into three stages, stage one, stage two and stage three. Stage one, occur in all groups of different ages and it is characterized by mild and subtle changes in cognition. Periodic assessment of one's ability to perform crucial self-management task should be carried out. Stage two is a mild to moderate cognitive impairment stage. It is most commonly occurred in patients above the age of 60. In these patients the impairment is in one or two domains that impaired the daily living activity. Stage three or stage of Dementia which is commonly characterized by forgetfulness and decline in executive functions like reasoning, planning and problem solving (Hopkins *et al.*, 2016).

The different factors that are known to act as essential part in cognitive dysfunction in some diabetic patients are hyperglycaemia, hypoglycaemia, macrovascular disease, insulin resistance, absence of C-Peptide and absence of Apoε4 Allelle (Kodl and Seaquist, 2008).

Aspects of cognition consists of the term such as sensation, thinking, retention, recall, perception, imagery, problem-solving and many more (Neisser, 2014).

Cognitive functioning impairment was known to be associated with syndromes like type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The ability and capacity to grasp and hold the stimuli for a short period of time and make use of it directly, process and manipulate it is called "Working Memory". Reasoning, learning and understanding are the cognitive tasks where working memory plays a pivotal and crucial role (Sharma and Antonova, 2003). Working memory was reported to be associated with the activation of dorsolateral prefrontal cortex (DLPF) (Stufflebeam and Rosen, 2007).

Working memory has limited capacity for processing the information of same data or other which are preserved and at the same time coordination of resources was suggested to be the key role of working memory (Bharadwaj *et al.*, 2015), (Swanson *et al.*, 2009).

There are three subcomponents in working memory. They are: a) It is assumed to be attention controlling system and important in skills and which is most susceptible to effect AD which is referred a central executive system; b) the second, processes and manipulates visual perception and action which is referred as visuospatial sketch pad; and c) the last it stores and rehearses speech based info and is required for both native and second language vocabulary (Swanson *et al.*, 2009).

Short-term memory (STM) that involve remembering novel information across brief intervals was observed to associate with medial temporal lobe (MTL) damage (Kumaran, 2008).

Unlike LTM, STM does not require the synthesis of proteins (Goelet *et al.*, 1986).

Microvascular dysfunction and hyperglycaemia

There is a tight link between microvascular and metabolic physiology. Many organs are affected by microvascular dysfunction in diabetes condition. Diabetes associated comorbidities such as depression and cognitive impairment. Microvascular damage can cause cerebral microbleeds, lacunar infarcts and white matter hyperintensities (WMHs), which are together called as cerebral small-vessel disease. It can also cause abnormal cerebral microvascular structure and function. Reduced cognitive performance, clinical cognitive impairment (dementia), leads to brain dysfunction. According to the data obtained from the cross sectional and prospective systematic reviews, it was found that risk towards dementia and depression is greater in patients with cerebral small vessel disease. (Rensma *et al.*, 2018). In individuals with or without T2D, microalbuminuria is also considered as one of the factors for cognitive impairment (Martens *et al.*, 2017). and depression (Martens *et al.*, 2016). Diabetic patients are susceptible to cerebral MVP and its clinical consequences, as it is related to large artery stiffening.

Pathophysiology

Central nervous system problem due to type1 and type2 diabetes, which have sensitive brain buildings and reactive to fluctuations in glucose homeostasis. Diabetic encephalopathy occurs due to interaction between direct and indirect metabolic significance of insulin deficit, enduring hyperglycaemia and additional components such as hereditary and eco-friendly causes (Stranahan, 2015).

Diabetes associated with cognitive decline are related to shortfalls of learning and memory. This may result in risk of AD, dementia and affecting disorder (Biessels *et al.*, 1994), (Talbot *et al.*, 2012).

Diabetes related cognitive deterioration linked with structural modifications in the brain. This modification along with brain atrophy and electrophysiological deficits, terminate in declined memory and mental act. The hippocampus region of brain involved in memory construction and associative learning.

It is mostly pretentious by this pathological condition because of its sensitivity variations in glucose and insulin homeostasis. The comparative degree of cognitive dysfunction and cognitive aberrations are established changes in both type of diabetes (Hershey *et al.*, 2004).

Mental, problem solving, learning, motor speed and memory impairments are associated with Type 1 diabetic patients. Declarative memory deficits are reported in children (Brands *et al.*, 2005), changes in intellectual performance and information processing speed, psychomotor functioning due to mild central brain atrophy in younger adult. (Ferguson *et al.*, 2005), (Kodl and Seaquist, 2008). Tasks involved in moderate impairment of verbal memory results in increase memory deficits and decreased executive function. This results in reduction of psychomotor speed in patients with type 2 diabetes present (Ryan *et al.*, 2006) , (Tomlinson and Gardiner, 2008) .

Diabetic complications which is generally considered due to hyperglycaemia, activating few metabolic and molecular modification. This leads to progressive neuronal dysfunction (Cherbuin *et al.*, 2012). Glucose is the main metabolic nutrient source, which is poorly controlled in diabetes cases (prolonged hyperglycaemia). Glucose transport is bothered and often lead to dysregulation of osmolarity and metabolism of the brain. Atrophy of the hippocampus and amygdala (Cherbuin *et al.*, 2012) (Gorelick *et al.*, 2011) are caused due to high glucose levels which suggest that a well control of blood glucose levels progresses cognitive performance in type 2 diabetic patients (Tomlinson and Gardiner, 2008).

In Hyperglycaemia

Blood brain barrier and its transport function are pretentious by increase in vascular permeability, lowering of perfusion rates, thickening of capillary walls and abnormal proliferation of endothelial cells which occurred in hyperglycaemic condition which consequently affect the transport function and integrity of blood brain barrier (Sochocka *et al.*, 2017).

The transport of choline is hinder by Vascular damage of BBB leading to brain deprivation of choline transmitter and it affects the brain homeostasis. cognitive damage produced by tau(τ)phosphorylation and disruption of brain homeostasis is promoted via vascular damage thereby decrease the clearance of amyloid- β(Aβ) protein. oxidative stress and inflammation production via chemicals induced CNS damage. Any damage in BBB elevate the penetration of free radicals and pro-inflammatory and further penetrate the CNS (Francis *et al.*, 1999) (Talbot *et al.*, 2012).

Insulin sensitivity

Two mechanisms are involved in the impairment of insulin-signalling pathway I) Inhibition of molecules (AMPK, JNK, GSK3β mPLK, IKKβ) from other pathways. II) Inhibition of the upstream components by the downstream component's pathway (mTOR/S6K, MAPK, PKC), identical to negative feedback mechanism. Serine phosphorylation of IRS is involved in the latter, blocking further signal propagation and further suggested that phosphorylation IRS by serine to be a biomarker of T2DM. Insulin resistance and activated insulin is an inducer of IRS kinases ((e.g., S6K1, PKC). Insulin receptors which are expressed by all organs, including the brain (Boucher *et al.*, 2014) (Zhao *et al.*, 1999) is conserved for insulin-signalling pathway and in the brain particularly hippocampus region insulin receptors are expressed which are accountable for recall and cognition (Droge, 2002).

Oxidative stress

Two mechanisms are involved in ROS modulation of insulin-signalling pathway I) To insulin response, ROS is produced where advanced organism have progressed the use of ROS and NO as signalling molecules for supplementary physiological function which includes signal transduction from membrane, monitoring of oxygen tension and regulation of vascular tone. II) ROS negatively controls the insulin pathway leads to decrease insulin secretion and subsequently insulin sensitivity (Butterfield *et al.*, 2014). Increased free radicals promotes loss of synapse, neuronal function disruption, apoptosis and cell damage results in cognitive impairment (Redish and Touretzky, 1997).

Effect of STM and WM

Working Memory

A part of Hippocampal region is a working memory (WM) which delivers brief storage and manipulation of the data which is required for cognitive task such as language understanding, Knowledge and perceptive. It is derived from the concept of unitary short-term memory system. There are three subcomponents of working memory, they are central executive, The visuospatial sketchpad and the phonological loop.

1. Central executive duplicates system concerned with the attentional regulator of behaviour with succeeding progresses almost certainly reliant on parallel growths in the study of attention and switch of action.

2. Visual perception and actions are processed by visuospatial sketchpad
3. The speech perception and production systems used for active memory which is represented by phonological loop. Thus, phonological loop is likely to overlay substantially with speech perception and production.

Short Term Memory (STM)

Active or primary memory are referred to be STM, the data are presently alert of or intellectual about. When sensory memory is considered it provides the information found in short term memory. If STM are not prepared or maintained, they last for few secs and the limit of STM it can hold seven plus or minus two items. STM stores data for approximately 20 to 30 seconds and few information lasts up to a minute, but most data deteriorate quickly. Old information is evacuated by new information when it enters the short-term memory. There is a variation in quantity of information which is stored in short term memory.

Comparison STM and WM

This takes place by withholding of memories which needs shifting of information from short term stores to long term memory, where capacity and duration are limited in short term memory. There are limited unlike methods that the content can be transferred to long term memory given below.

Adaptation of short-term memory to long term memory

Practice helps to convert the information into long term memory. Chunking is one of method by breaking smaller segment data into long term memory data. But mechanism is mysterious. STM can be improved by doing exercise has shown in the recent research work.

Comorbidities condition

Hyperglycaemic condition

Decreased cognitive function due to chronic raised glucose concentration which lead to poor learning and memory power. Cognitive function in elder adults is improved by pharmacological improvement of glycaemic control (Gradman *et al.*, 1993). In animal studies there is an evidence that streptozotocin induced hyperglycaemia leads to decreased Ach synthesis and release in rats' brain (Welsh and Wecker, 1991) leads to loss of cortical neurons, results in impaired memory (Baura *et al.*, 1993).

Hyperinsulinemia

A numeral of mechanisms can be hypothesized by which cognitive functioning can be modified by insulin. Since the insulin transportation occur via BBB, insulin concentration in the serum is closely related to insulin present in the cerebrospinal fluid (Shibata *et al.*, 1986). Hypothalamus and hippocampal region are rich in insulin receptors. Reduction in cholinergic transmission is also mediated by insulin receptors (Palovcik *et al.*, 1984) (Perlmuter *et al.*, 1990).

Dyslipidaemia condition

Dyslipidaemia is linked with the insulin resistance syndrome. Only few studies have recommended for cognitive impairment by increased triglyceride level and they are inversely linked with verbal fluency test (Meneses *et al.*, 1996) in diabetic patients. In ageing patient with T2D showed decline reaction time in hypertriglyceridemia condition.

Hypertension condition

Increased blood pressure is linked with type 2 diabetes and insulin sensitivity syndrome. It is focused on many researches on deviation in cognitive function. Rats with hypertensive related with age, there is a drop-in learning. Mechanism that can be hypothesized is that hypertension is linked with brain white matter lesions, cerebrovascular disease and lacunar brain infarct Hypertension associated with white matter lesion cause cognitive impairment during assessment of magnetic resonance imaging (Breteler *et al.*, 1994).

we observed short term memory retains small amount of data in cognizance which are readily available state for short period of time whereas working memory manipulates the information through visual and auditory storage, and it is important in understanding and improving the memory. There is a substantial evidence to support that the T2D is associated with cognitive impairment. Thus, long term diabetes and its comorbidities leads to dysfunction of working memory and short-term memory which further may lead to chronic disorder like Alzheimer, dementia and brain dysfunction. Since the specific mechanism for hippocampal region is unclear and further studies should be carried out.

CONCLUSIONS

Short term and working memory were found to decrease in the presence of diabetic condition, which was further deteriorated in the presence of comorbid conditions like hypertension, hyperinsulinemia, hyperlipidaemia and depression. There is no evidence to know which type of comorbidity effects severely this condition. So, further research should be carried out to find which type of comor-

bidity will affect short-term and working memory severely in diabetic condition.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

Funding Support

The authors declare that they have no funding support for this study.

REFERENCES

Baura, G. D., Foster, D. M., Porte, D., Kahn, S. E., Bergman, R. N., Cobelli, C., Schwartz, M. W. 1993. Saturable transport of insulin from plasma into the central nervous system of dogs in vivo. A mechanism for regulated insulin delivery to the brain. *Journal of Clinical Investigation*, 92(4):1824–1830.

Bharadwaj, S. V., Maricle, D., Green, L., Allman, T. 2015. Working memory, short-term memory and reading proficiency in school-age children with cochlear implants. *International Journal of Pediatric Otorhinolaryngology*, 79(10):1647–1653.

Biessels, G. J., Kappelle, A. C., Bravenboer, B., Erkelens, D. W., Gispen, W. H. 1994. Cerebral function in diabetes mellitus. *Diabetologia*, 37(7):643–650.

Boucher, J., Kleinridders, A., Kahn, C. R. 2014. Insulin Receptor Signaling in Normal and Insulin-Resistant States. *Cold Spring Harbor Perspectives in Biology*, 6(1):a009191.

Brands, A. M. A., Biessels, G. J., de Haan, E. H. F., Kappelle, L. J., Kessels, R. P. C. 2005. The Effects of Type 1 Diabetes on Cognitive Performance: A meta-analysis. *Diabetes Care*, 28(3):726–735.

Breteler, M. M. B., van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., van den Hout, J. H., van Harskamp, F., Tanghe, H. L., de Jong, P. T., van Gijn, J., Hofman, A. 1994. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: The Rotterdam Study. *Neurology*, 44(7):1246–1246.

Butterfield, D. A., Domenico, F. D., Barone, E. 2014. Elevated risk of type 2 diabetes for development of Alzheimer disease: A key role for oxidative stress in brain. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1842(9):1693–1706.

Cherbuin, N., Sachdev, P., Anstey, K. J. 2012. Higher normal fasting plasma glucose is associated with hippocampal atrophy: The PATH Study. *Neurology*, 79(10):1019–1026.

Droge, W. 2002. Free radicals in the physiological control of cell function. Physiological reviews. 2002 Jan 1;82(1):47-95.

Ferguson, S. C., Blane, A., Wardlaw, J., Frier, B. M., Perros, P., McCrimmon, R. J., Deary, I. J. 2005. Influence of an Early-Onset Age of Type 1 Diabetes on Cerebral Structure and Cognitive Function. *Diabetes Care*, 28(6):1431–1437.

Francis, P. T., Palmer, A. M., Snape, M., Wilcock, G. K. 1999. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *Journal of Neurology, Neurosurgery and Psychiatry*, 66(2):137–147.

Goelet, P., Castellucci, V. F., Schacher, S., Kandel, E. R. 1986. The long and the short of long–term memory—a molecular framework. *Nature*, 322(6078):419–422.

Gorelick, P. B., Scuteri, A., Black, S. E., Decarli, C., Greenberg, S. M., Iadecola, C., Launer, L. J., Laurent, S., Lopez, O. L., Nyenhuis, D., Petersen, R. C. 2011. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 42(9):2672–2713.

Gradman, T. J., Laws, A., Thompson, L. W., Reaven, G. M. 1993. Verbal Learning and/or Memory Improves with Glycemic Control in Older Subjects with Non-Insulin-Dependent Diabetes Mellitus. *Journal of the American Geriatrics Society*, 41(12):1305–1312.

Hershey, T., Lillie, R., Sadler, M., White, N. H. 2004. A prospective study of severe hypoglycemia and long-term spatial memory in children with type 1 diabetes. *Pediatric Diabetes*, 5(2):63–71.

Hopkins, R., Shaver, K., Weinstock, R. S. 2016. Management of Adults With Diabetes and Cognitive Problems. *Diabetes Spectrum*, 29(4):224–237.

Kodl, C. T., Seaquist, E. R. 2008. Cognitive Dysfunction and Diabetes Mellitus. *Endocrine Reviews*, 29(4):494–511.

Kumaran, D. 2008. Short-Term Memory and the Human Hippocampus. *Journal of Neuroscience*, 28(15):3837–3838.

Martens, R. J., Kooman, J. P., Stehouwer, C. D., Dagnelie, P. C., van der Kallen, C. J., Koster, A., Kroon, A. A., Leunissen, K. M., Nijpels, G., van der Sande, F. M., Schaper, N. C., Sep, S. J., van Boxtel, M. P., Schram, M. T., Henry, R. M. 2017. Estimated GFR, Albuminuria, and Cognitive Performance: The Maastricht Study. *American Journal of Kidney Diseases*, 69(2):179–191.

Martens, R. J., Kooman, J. P., Stehouwer, C. D., Dagnelie, P. C., van der Kallen, C. J., Kroon, A. A., Leunissen, K. M., van der Sande, F. M., Schaper, N. C., Sep, S. J., Köhler, S., Schram, M. T., Henry, R. M. 2016. Albuminuria is associated with a higher

prevalence of depression in a population-based cohort study: the Maastricht Study. *Nephrology Dialysis Transplantation*, 33(1):gfw377.

Meneses, A., Castillo, C., Ibarra, M., Hong, E. 1996. Effects of aging and hypertension on learning, memory, and activity in rats. *Physiology and Behavior*, 60(2):341–345.

Neisser, U. 2014. Cognitive psychology: Classic edition. pages 1–20. Psychology Press.

Palovcik, R. A., Phillips, M. I., Kappy, M. S., Raizada, M. K. 1984. Insulin inhibits pyramidal neurons in hippocampal slices. *Brain Research*, 309(1):187–191.

Perlmuter, L. C., Goldfinger, S. H., Shore, A. R., Nathan, D. M. 1990. Cognitive function in non-insulin-dependent diabetes. In *Neuropsychological and behavioral aspects of diabetes*, pages 222–238. Springer.

Redish, A. D., Touretzky, D. S. 1997. Cognitive maps beyond the hippocampus. *Hippocampus*, 7(1):15–35.

Rensma, S. P., van Sloten, T. T., Launer, L. J., Stehouwer, C. D. 2018. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, 90:164–173.

Ryan, C. M., Freed, M. I., Rood, J. A., Cobitz, A. R., Waterhouse, B. R., Strachan, M. W. 2006. Improving Metabolic Control Leads to Better Working Memory in Adults With Type 2 Diabetes. *Diabetes Care*, 29(2):345–351.

Saedi, E., Gheini, M. R., Faiz, F., Arami, M. A. 2016. Diabetes mellitus and cognitive impairments. *World Journal of Diabetes*, 7(17):412.

Sharma, T., Antonova, L. 2003. Cognitive function in schizophrenia: deficits, functional consequences, and future treatment. *Psychiatric Clinics of North America*, 26(1):25–40.

Shibata, S., Liou, S. Y., Ueki, S., Oomura, Y. 1986. Inhibitory action of insulin on suprachiasmatic nucleus neurons in rat hypothalamic slice preparations. *Physiology and Behavior*, 36(1):79–81.

Sochocka, M., Diniz, B. S., Leszek, J. 2017. Inflammatory Response in the CNS: Friend or Foe? *Molecular Neurobiology*, 54(10):8071–8089.

Stranahan, A. M. 2015. Models and mechanisms for hippocampal dysfunction in obesity and diabetes. *Neuroscience*, 309:125–139.

Stufflebeam, S. M., Rosen, B. R. 2007. Mapping Cognitive Function. *Neuroimaging Clinics of North America*, 17(4):469–484.

Swanson, H. L., Zheng, X., Jerman, O. 2009. Working Memory, Short-Term Memory, and Reading Disabilities. *Journal of Learning Disabilities*, 42(3):260–287.

Talbot, K., Wang, H.-Y., Kazi, H., Han, L.-Y., Bakshi, K. P., Stucky, A., Fuino, R. L., Kawaguchi, K. R., Samoyedny, A. J., Wilson, R. S., Arvanitakis, Z., Schneider, J. A., Wolf, B. A., Bennett, D. A., Trojanowski, J. Q., Arnold, S. E. 2012. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. *Journal of Clinical Investigation*, 122(4):1316–1338.

Tomlinson, D. R., Gardiner, N. J. 2008. Glucose neurotoxicity. *Nature Reviews Neuroscience*, 9(1):36–45.

Welsh, B., Wecker, L. 1991. Effects of streptozotocin-induced diabetes on acetylcholine metabolism in rat brain. *Neurochemical Research*, 16(4):453–460.

Zhao, W., Chen, H., Xu, H., Moore, E., Meiri, N., Quon, M. J., Alkon, D. L. 1999. Brain insulin receptors and spatial memory correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *Journal of Biological Chemistry*, 274(49):34893–34902.

