SECTION 9

PUBLICATIONS AND ORAL PRESENTATIONS
9. Publications and Oral Presentations

9.1. List of Publications


9.2. List of Oral Presentations

1. Sharma Bhupesh and Singh Nirmal. Salubrious Role of Modulator of Nicotinamide Adenine Dinucleotide Phosphate-Oxidase (NADPH-Oxidase) in Experimental Hypertension Induced Vascular Dementia. 44th Indian Pharmacological Society, KMC, Manipal, December, 2011 (Prof. Manjeet Singh Award Session for the Best Paper Presentation in Molecular Pharmacology).

2. Sharma Bhupesh and Singh Nirmal. Modulation of Nuclear Factor Kappa-B in Experimental Diabetes Induced Endothelial Dysfunction and Vascular Dementia. 43rd Indian Pharmacological Society, NIN, Hyderabad, December, 2010 (Prof. Manjeet Singh Award Session for the Best Paper Presentation in Molecular Pharmacology).
Behavioral and biochemical investigations to explore pharmacological potential of PPAR-gamma agonists in vascular dementia of diabetic rats

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A B S T R A C T

Vascular dementia (VaD) is the second most common dementing illness. We have recently reported that diabetes induces VaD in rats. The present study has been designed to investigate the potential of peroxisome-proliferator-activated receptors-gamma (PPAR-γ) agonists in diabetes induced VaD of Wistar Albino rats. The rats were administered, single dose of streptozotocin (STZ) for the induction of diabetes. Morris water-maze (MWM) test was employed for testing learning and memory. Serum glucose, bodyweight, vascular endothelial function, serum nitrite/nitrate levels, aortic and brain oxidative stress levels (viz. aortic superoxide anion levels, brain thiobarbituric acid reactive species and brain glutathione levels) and brain acetylcholinesterase activity were also tested. STZ treated animals performed poorly on MWM hence reflecting impairment of learning and memory behavior with a significant reduction in body weight, impairment of vascular endothelial function, and decrease in serum nitrite/nitrate levels, increase in serum glucose, aortic and brain oxidative stress levels and brain acetylcholinesterase activity. Treatment of PPAR-γ agonists, pioglitazone as well as rosiglitazone significantly reversed, diabetes induced impairment of learning and memory behavior, endothelial function, and changes in various biochemical parameters. It is concluded that PPAR-γ modulators pioglitazone and rosiglitazone may be considered as potential pharmacological agents for the management of diabetes induced VaD.

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1. Introduction

Diabetes and dementia have become a major public health concern worldwide due to being common diseases in the elderly population. Vascular dementia (VaD) a dementia of vascular origin is considered to be the second most common cause of dementia after Alzheimer’s disease (AD) (Liu et al., 2010). Diabetes has been found to be consistently associated with the risk of VaD and there is the significant association between glucose intolerance and the risks of both VaD and AD (Sekita and Kiyohara, 2010). Diabetic people had a 1.5 to 4 fold risk for AD as well as VaD. High glucose concentration, a major pathological characteristic of diabetes, may have toxic effects on neurons in the brain through osmotic insults and oxidative stress. The insulin resistance (i.e., hyperinsulinemia) in people with impaired glucose tolerance has been one of risk factors for cognitive decline (Araki, 2010). Furthermore, diabetes is associated with an increased release of inflammatory cytokines, and the excess inflammation may be neurotoxic (Umegaki, 2010). Oxidative stress and vascular endothelial are recognized as important contributing factors in the pathogenesis of AD and dementia of vascular origin (de la Torre, 2008; Viswanathan et al., 2009). Only limited therapeutic interventions are available to reduce the incidence of VaD.

Peroxisome-proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptors super family which are present in three isoforms as α, β/δ and γ (Arck et al., 2010). PPAR-γ is present on vascular cells, exert protective role in the vascular endothelial dysfunction (Beyer et al., 2008). Disruption or down regulation of these receptors have been reported to result in vascular endothelial dysfunction (Kleinhenz et al., 2009). PPAR-γ receptors are distributed broadly in central nervous system (Sarruf et al., 2009), and activation of these receptors prevents neuronal death by reduction of oxidative stress (Zhao et al., 2009) and inflammatory mechanisms (Glatz et al., 2010). PPAR-γ agonists in addition to their anti-diabetic activity have been shown to provide beneficial effect in various CNS disorders (Chaturvedi et al., 2009; Jain et al., 2009; Kiae et al., 2008; Kumari et al., 2010; Schintu et al., 2009; Zhang et al., 2010a, 2010b). Furthermore, PPAR-γ agonists have the potential to modulate various signaling molecules/pathways, including mitogen-activated protein kinases, signal transducer and activator of transcription, amyloid precursor protein degradation, beta-site amyloid precursor protein cleaving enzyme 1 and Wnt signaling (Kaundal and Sharma, 2010). Moreover, it has been recently reported that, PPAR-γ is involved in improvement of memory and...
Attenuation of vascular dementia by sodium butyrate in streptozotocin diabetic rats

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Abstract
Rationale Vascular dementia is the second leading cause of dementia, which is strongly associated with diabetes. Diabetes and dementia have become a major public health concern worldwide. At this point of time, it is very important to find the possible pharmacological agents which may be useful in management and therapy of dementia including Alzheimer’s disease, vascular dementia, etc.

Objectives To investigate the effect of sodium butyrate on streptozotocin (STZ) diabetes induced vascular dementia in rats.

Methods Diabetes and subsequent endothelial dysfunction and dementia were induced in rats by administration of single dose of STZ. Drug treatment was started after 1 month of STZ administration and treatment was continued until the end of the study. Morris water maze (MWM) test was employed for testing learning and memory. Endothelial function was measured on isolated aortic rings using student physiograph. Serum glucose, body weight, serum nitrite/nitrate, aortic superoxide anion generation, brain thiobarbituric acid reactive species (TBARS), reduced glutathione (GSH) levels, and acetylcholinesterase activity were also tested.

Results STZ treatment produced endothelial dysfunction, impairment of learning and memory, reduction in body weight and serum nitrite/nitrate, and increase in serum glucose, aortic and brain oxidative stress (increased superoxide anion, TBARS, and decreased GSH levels), and brain acetylcholinesterase activity. Treatment of sodium butyrate attenuated diabetes induced impairment of learning, memory, endothelial function, and various biochemical parameters.

Conclusions Sodium butyrate may be considered as potential pharmacological agent for the management of diabetes induced vascular dementia.

Keywords Alzheimer · Dementia · Diabetes · HDAC · Endothelial dysfunction · Streptozotocin · Morris water maze · Nitrite/nitrate · Oxidative stress · Acetylcholinesterase activity

Introduction
Optimal cognitive function is vital to independence, productivity, and quality of life, and the debilitation associated with dementias makes them the most feared of conditions related to aging. Effective preventive measures are key components of any response to the potentially overwhelming problem of dementias (Desai et al. 2010). The prevalence of dementia is expected to increase dramatically over the upcoming decades due to the aging population. Since treatment is still short of a cure, preventative strategies are of the utmost importance (Middleton and Yaffe 2010). Individuals with old age represent the most rapidly growing segment of the population; late-life dementia (Fotuhi et al. 2009) and diabetes (Grünblatt et al. 2010) have become a major public health concern worldwide.

Dementia of vascular origin, i.e., vascular dementia (VaD), has gained much attention in recent times. Vascular dementia is the second leading cause of
**Pitavastatin and 4’-Hydroxy-3’-Methoxyacetophenone (HMAP) Reduce Cognitive Dysfunction in Vascular Dementia During Experimental Diabetes**

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**Abstract:** Diabetes has been found to increase the probability of vascular dementia in humans. We have investigated the effect of 4’-hydroxy-3’-methoxyacetophenone (HMAP), a NADPH oxidase inhibitor and Pitavastatin, a HMG Co-A reductase inhibitor, on Streptozotocin (STZ) diabetes induced vascular dementia in rats. Donepezil served as a positive control. The rats were administered with single dose of STZ for the induction of diabetes. Drug treatment was started after one month of STZ administration and treatment was continued till the end of the study (i.e. 56th day). On 52nd day onwards, the animals were exposed to Morris water-maze (MWM) for testing learning & memory. Serum glucose, body weight, vascular endothelial function, serum nitrite / nitrate levels, aortic & brain oxidative stress levels and brain acetylcholinesterase activity were also tested. STZ treated animals performed poorly on MWM hence reflecting impairment of learning & memory. Further STZ treatment also produced a reduction in body weight, impairment of vascular endothelial function, decrease in serum nitrite / nitrate levels, along with increase in serum glucose, aortic & brain oxidative stress levels and brain acetylcholinesterase activity. Treatment of HMAP, Pitavastatin and Donepezil significantly reversed diabetes induced impairment of learning and memory, endothelial dysfunction, and changes in various biochemical levels. It may be concluded that STZ induces vascular dementia. 4’hydroxy-3’-methoxy acetophenone and Pitavastatin may be considered as potential pharmacological agents for the management of diabetes induced vascular dementia.

**Keywords:** Diabetes, NADPH oxidase, statin, endothelial dysfunction, dementia, donepezil, streptozotocin, morris water maze.

**INTRODUCTION**

There is a progressive increase in the number of people reaching old age. Dementia and diabetes mellitus are both common in later life and often co-exist. Dementia is an organic brain disease defined as “loss of intellectual ability of sufficient severity to interfere either with occupational functioning, usual social activities or relationship of a person in the absence of gross clouding of consciousness or motor involvement [1]. Dementia of vascular origin i.e. vascular dementia (VaD) has gained much attention in the recent time. VaD (30-40%) is the second main cause of dementia after Alzheimer's disease (AD) which accounts for 50-70% of the cases, followed by mixed dementia (15-20%) [2].

VaD is characterized by loss of executive function with milder memory loss and is associated with cerebral brain infarction or hemorrhage [3]. Vascular lesions often coexist with Alzheimer disease (AD) [4]. There is a high frequency of Alzheimer disease (AD) in those with clinically diagnosed vascular dementia, and the frequent findings of vascular disease in those with clinically diagnosed AD [5].

The well-established risk factors of endothelial dysfunction and subsequent vascular dementia such as hypertension, history of stroke, diabetes mellitus and hypercholesterolemia are all associated with high risk of AD [6, 7]. The noted vascular dysfunction (vascular deformities) in AD and common risk factor of AD and VaD suggest that, there is a great overlap between AD and vascular dementia [8-10]. Diabetes mellitus is a well-known risk factor for cardiovascular disease. Diabetes is also associated with cognitive decline and an increased risk of dementia in the elderly [11, 12]. Diabetes has been found to increase the probability of vascular dementia, both in early as well as late life vascular dementia in humans. The impact of diabetes was more in case of late life vascular dementia as compared to early life vascular dementia [13]. Further it has been observed that, there is a significant association of midlife impaired glucose metabolism with late life incidence of vascular dementia, but not with ‘any dementia' or Alzheimer's disease [14]. But other reports suggest a significant increased risk of any dementia including Alzheimer's disease associated with impaired glucose metabolism [15, 16].

The association of dementia with over production of reactive oxygen species (ROS) by NADPH oxidase (Nox) enzymes has been noted which may results in oxidative stress that damages tissues over time [17]. NADPH oxidase is an enzymatic complex that catalyzes superoxide anion O₂⁻ production from O₂ and NADPH. Further it has also been
Salutary effect of NFκB inhibitor and folacin in hyperhomocysteinemia–hyperlipidemia induced vascular dementia

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A R T I C L E   I N F O

Keywords: Alzheimer’s disease; Cholesterol; l-methionine; Morris water maze; Natrium diethyl dithio carbamate trihydrate; Vitamin-B9

A B S T R A C T

Dementia of vascular origin or vascular dementia (VaD) is considered as the second commonest form of dementia after Alzheimer’s disease (AD). In the last ten years various researchers have reported a strong association of hyperhomocysteinemia (HHcy); hyperlipidemia (HL) and dementia. This study investigates the salutary effect of natrium diethyl dithio carbamate trihydrate (NDDCT), a nuclear factor-kappaB (NFκ-B) inhibitor as well as folacin (Vitamin-B9) in HHcy-HL induced VaD, l-methionine was used to induce HHcy-HL and associated VaD. Morris water-maze (MWM) was used for testing learning and memory. Vascular system assessment was done by testing endothelial function. Biochemical estimations were performed to assess HHcy (serum homocysteine), HL (serum cholesterol), oxidative stress (aortic superoxide anion, serum and brain thiobarbituric acid reactive species and brain glutathione), nitric oxide levels (serum nitrite/nitrate) and cholinergic activity (brain acetyl cholinesterase activity). l-methionine treated animals have shown HHcy-HL, endothelial dysfunction, impairment of learning, memory, reduction in serum nitrite/nitrate levels and brain glutathione (GSH) along with increase in serum and brain thiobarbituric acid reactive species (TBARS), and brain acetylcholinesterase activity. NDDCT, folacin and donepezil (positive control) significantly improved HHcy-HL induced impairment of learning, memory, endothelial dysfunction, and changes in various biochemical parameters. l-methionine induced HHcy-HL has caused VaD in rats. NFκ-B inhibitors and folacin may be considered as potential agents for the management of HHcy-HL induced VaD.

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1. Introduction

Vascular dementia (VaD) is the second leading cause of dementia (Sharma and Singh, 2010, 2011a, 2011b) having a strong correlation with various vascular disorders such as diabetes, hyperhomocysteinemia (HHcy), hyperlipidemia (HL) etc. (Daviglus et al., 2011; Enciu et al., 2011). Epidemiological studies show a positive, dose-dependent relationship between mild-to-moderate increases in plasma total homocysteine concentrations (Hcy) and the risk of neurodegenerative diseases, such as Alzheimer’s disease (AD), VaD, cognitive impairment or stroke (Herrmann and Obeid, 2011). HL has been shown to cause memory impairment, cholinergic dysfunction, inflammation and microbleeding.

Abbreviations: VaD, Vascular dementia; HHcy, hyperhomocysteinemia; HL, hyperlipidemia; Hcy, homocysteine; AD, Alzheimer’s disease; NFκ-B, nuclear factor kappa-B; NDDCT, natrium diethyl dithio carbamate trihydrate; IAEIC, Institutional Animal Ethics Committee; CPCSEA, Committee for the Purpose of Control and Supervision of Experiments on Animals; DTNB, 5,5′-dithiobis (2-nitro benzoic acid); BSA, Bovine serum albumin; GSH, reduced form of glutathione; NBT, Nitroblue tetrazolium; CMC, sodium carboxy methyl cellulose; MWM, Morris water maze; ELT, escape latency time; KCl, potassium chloride; ACh, acetylcholine; SNP, sodium nitroprusside; TBARS, thiobarbituric acid reactive substances; AChE, acetyl cholinesterase; CHO/D; POD, cholesterol oxidase/peroxidase; ANOVA, analysis of variance; TSTQ, time spent in target quadrant; A/J, amyloid beta; LD, low dose; HD, high dose.

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Experimental hypertension induced vascular dementia: Pharmacological, biochemical and behavioral recuperation by angiotensin receptor blocker and acetylcholinesterase inhibitor

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2 Keywords: Endothelial dysfunction, Vascular dementia, Angiotensin receptor blocker, Morris water maze, Oxidative stress

1. Introduction

Cardiovascular risk factors, including hypertension, have been linked to subsequent increased incidence, onset and progression rate of dementia of vascular origin and other etiologies (Monsuez et al., 2011; Moretti et al., 2011). Vascular dementia (VaD) represents the second most common cause of dementia after Alzheimer’s disease (AD) in the elderly, and is referred to as the “silent epidemic of the twenty-first century” (Battistin and Cagnin, 2010). Optimal treatment of cardiovascular risk factors has been observed to prevent and slow down age-related cognitive disorders (Monsuez et al., 2011; Wehling and Groth, 2011).

Both endothelial dysfunction and VaD are reported to have high probability of occurrence with hypertension (Lorenza Muiisan et al., 2011; Yang et al., 2011; Zhang et al., 2011). Aging-related structural and functional disturbances in the macro- or microcirculation of the brain make it vulnerable to cognitive dysfunction, leading to dementia illness (Kalaria, 2010). In previous reports from our lab, we have shown that endothelial dysfunction occurred due to different metabolic disorders results in VaD. Furthermore, we have observed impairment of learning and memory as the major behavioral alteration in VaD. We have also reported that in VaD, there is an enhancement of central & peripheral oxidative stress, brain acetylcholinesterase activity with reduction of serum nitrite levels (Koladiya et al., 2008, 2009; Sain et al., 2011; Sharma and Singh, 2010, 2011a, 2011b).

Since chronic hypertension is associated with an increased risk of both VaD and AD, the role of anti-hypertensive therapy for the prevention and delay of cognitive decline and dementia is of central importance. Most longitudinal studies have shown a significant inverse association between anti-hypertensive therapies and dementia incidence (Duron and Hanon, 2010). But the effect of experimental hypertension, in the genesis of VaD, is yet to be investigated.

The local renin–angiotensin system (RAS) in the brain is a multi-tasking system. Aside from its vasoactive actions, brain angiotensin II (AT-II) has also been implicated in the pathogenesis of cognitive decline, and beneficial effects of angiotensin receptor blockers (ARBs) in AD are suggested (Danieley et al., 2010). AT II type 1 receptor blockers (ARBs) have been demonstrated to reduce the onset of stroke, stroke severity, the incidence and progression of dementia, as ARBs provide protection against ischemic brain damage and associated cognitive
Defensive effect of natrium diethylidithiocarbamate trihydrate (NDDCT) and lisinopril in DOCA–salt hypertension-induced vascular dementia in rats

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Abstract
Rationale Vascular dementia and hypertension are increasing day by day, with a high degree of co-occurrence. Tremendous amount of research work is required so that new pharmacological agents may be identified for their appropriate therapeutic utility to combat different dementing disorders.

Objectives This study investigates the effect of natrium diethylidithiocarbamate trihydrate (NDDCT), a nuclear factor kappa-B (NF-κB) inhibitor, as well as lisinopril, an angiotensin converting enzyme (ACE) inhibitor, on deoxycorticosterone acetate (DOCA) hypertension-induced vascular dementia in rats.

Methods DOCA was used to induce hypertension and associated vascular dementia. Morris water maze (MWM) was used for testing learning and memory. Endothelial function was assessed by acetylcholine-induced endothelium-dependent relaxation of aortic strips. Different biochemical estimations were used to assess oxidative stress (aortic superoxide anion, serum and brain thiobarbituric acid reactive species, and brain glutathione), nitric oxide levels (serum nitrite/nitrate), and cholinergic activity (brain acetyl cholinesterase activity).

Results DOCA treatment significantly raised the mean arterial blood pressure of rats, and these hypertensive rats performed poorly on MWM, reflecting impairment of learning and memory. DOCA treatment also impaired vascular endothelial function and different biochemical parameters. Treatments of NDDCT as well as lisinopril significantly attenuated DOCA hypertension-induced impairment of learning and memory, endothelial dysfunction, and changes in various biochemical levels.

Conclusions DOCA–salt hypertension induces vascular dementia in rats. NF-κB as well as ACE inhibitors may be considered as potential pharmacological agents for the management of hypertension-induced vascular dementia.

Keywords Nuclear factor kappa-B · Angiotensin converting enzyme · Endothelial dysfunction · Morris water maze · Alzheimer’s disease · Oxidative stress

Introduction
Cardiovascular risk factors, including hypertension have been linked to subsequent incidence, onset, and progression rate of dementia of vascular origin and other etiology like Alzheimer’s disease (AD) (Monsuez et al. 2011). Vascular dementia (VaD) represents the second most common cause of dementia after AD in the elderly and is referred as the “silent epidemic of the twenty-first century” (Battistin and Cagnin 2010). Several epidemiological studies reported associations of hypertension, diabetes, obesity, and inflammation with VaD and in some cases, AD (Moretti et al. 2011). Optimal treatment of cardiovascular risk factors prevents and slows down age-related cognitive disorders (Monsuez et al. 2011). Further, it has been suggested that dementia prevention can become effective without delay if the vascular components of dementia are aggressively targeted through the treatment of vascular risk factors such as hypertension (Wehling and Groth 2011).