ABSTRACTS OF

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1. A Brief Overview of Tyrosine Hydroxylase and alpha-Synuclein in the Parkinsonian Brain

*Khan W* (Khan, Wajihullah); *Priyadarshini M* (Priyadarshini, Medha); *Zakai HA* (Zakai, Haytham A.); *Kamal MA* (Kamal, Mohammad A.); *Alam Q* (Alam, Qamre)

**Abstract**

Parkinson's disease (PD) is associated with neurodegeneration of the nigrostriatal tract and is accompanied with loss of tyrosine hydroxylase (TH) and dopamine (DA). Development of neuroprotective strategies targeting PD is often undermined by lack of proper understanding of processes contributing to the pathology. In this mini review we have tried to briefly outline the involvement of TH and alpha-synuclein in PD. Aberrant expression of alpha-synuclein is toxic to dopaminergic neurons. It interacts with ubiquitin-proteasomal processing system, implicated in oxidative injury and mitochondrial dysfunction which ultimately induce neurodegeneration and cell death. The contributions of DJ-1 in TH regulation have also been discussed. Brain specific TH expression with the combined use of the pegylated immunoliposome (PILs) gene transfer technology and brain specific promoters as a new approach to treat PD has also been included.
A Synopsis on the Role of Tyrosine Hydroxylase in Parkinson's Disease

Tabrez S (Tabrez, Shams); Jabir NR (Jabir, Nasimudeen R.); Shakil S (Shakil, Shazi); Greig NH (Greig, Nigel H.); Alam Q (Alam, Qamre); Abuzenadah AM (Abuzenadah, Adel M.); Damanhouri GA (Damanhouri, Ghazi A.); Kamal MA (Kamal, Mohammad A.)

Abstract

Parkinson's disease (PD) is a common chronic progressive neurodegenerative disorder in elderly people. A consistent neurochemical abnormality in PD is degeneration of dopaminergic neurons in substantia nigra pars compacta, leading to a reduction of striatal dopamine (DA) levels. As tyrosine hydroxylase (TH) catalyses the formation of L-dihydroxyphenylalanine (L-DOPA), the rate-limiting step in the biosynthesis of DA, the disease can be considered as a TH-deficiency syndrome of the striatum. Problems related to PD usually build up when vesicular storage of DA is altered by the presence of either alpha-synuclein protofibrils or oxidative stress. Phosphorylation of three physiologically-regulated specific sites of N-terminal domain of TH is vital in regulating its kinetic and protein interaction. The concept of physiological significance of TH isoforms is another interesting aspect to be explored further for a comprehensive understanding of its role in PD. Thus, a logical and efficient strategy for PD treatment is based on correcting or bypassing the enzyme deficiency by the treatment with L-DOPA, DA agonists, inhibitors of DA metabolism or brain grafts with cells expressing a high level of TH. Neurotrophic factors are also attracting the attention of neuroscientists because they provide the essential neuroprotective and neurorestorative properties to the nigrostriatal DA system. PPAR-gamma, a key regulator of immune responses, is likewise a promising target for the treatment of PD, which can be achieved by the use of agonists with the potential to impact the expression of pro- and anti-inflammatory cytokines at the transcriptional level in immune cells via expression of TH. Herein, we review the primary biochemical and pathological features of PD, and describe both classical and developing approaches aimed to ameliorate disease symptoms and its progression.
3. Alzheimer's Disease And Type 2 Diabetes: Exploring The Association To Obesity And Tyrosine Hydroxylase

Priyadarshini M (Priyadarshini, Medha); Kamal MA (Kamal, Mohammad A.); Greig NH (Greig, Nigel H.); Reale M (Reale, Marcella); Abuzenadah AM (Abuzenadah, Adel M.); Chaudhary AGA (Chaudhary, Adeel G. A.); Damanhouri GA (Damanhouri, Ghazi A.)

Abstract

Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) are two debilitating health disorders affecting millions worldwide. Recent research has revealed similarities between AD and T2DM. Both these protein conformational disorders are associated with obesity, insulin resistance, inflammation and endoplasmic reticulum stress, en-route initiation and/or stage aggravation. In this mini review we have tried to summarize studies describing obesity, insulin resistance and glucocorticoid imbalance as common patho-mechanisms in T2DM and AD. A reduction in tyrosine hydroxylase (TH) in the brain has been found to occur in Parkinson's disease (PD). AD, T2DM and PD share common risk factors like depression. Thus, whether TH is involved in the 'state of cognitive depression' that is the hallmark of AD and often accompanies PD and T2DM is also explored.

Sheikh IA (Sheikh, Ishfaq Ahmed); Ali R (Ali, Riyasat); Dar TA (Dar, Tanveer A.); Kamal MA (Kamal, Mohammad Amjad)

Abstract

Alzheimer's disease (AD) is one of the major neurodegenerative diseases affecting almost 28 million people around the globe. It consistently remains one of the major health concerns of present world. Due to the clinical limitations like severe side effects of some synthesized drugs, alternative forms of treatments are gaining global acceptance in the treatment of AD. Neuroprotective compounds of natural origin and their synthetic derivatives exhibit promising results with minimal side effects and some of them are in their different phases of clinical trials. Alkaloids and their synthetic derivatives form one of the groups which have been used in treatment of neurodegenerative diseases like AD. We have further grouped these alkaloids into different sub groups like Indoles, piperdine and isoquinolines. Polyphenols form another important class of natural compounds used in AD management.
5. Antigenotoxic ketosteroid from the red algae Jania adhaerens

Alarif WM (Alarif, Walied M.); Ayyad SEN (Ayyad, Seif-Eldin N.); El-Assouli SM (El-Assouli, Sufian M.); Al-Lihaibi SS (Al-Lihaibi, Sultan S.)

Abstract

A new ketosteroid, 6 beta,16 beta-dihydroxycholest-4-en-3-one (1), in addition to the known 6 beta-hydroxycholest-4-en-3-one (2), 6 beta-hydroxycholest-4, 22-dien-3-one (3) and 16 beta-hydroxy-5 alpha-cholestan-3,6-dione (4), was isolated from the red alga Jania adhaerens. The structures were assigned on the basis of H-1-and C-13-NMR experiments. The new compound (1) was evaluated for its genotoxic and cytotoxic activities and found to possess protective antigenotoxicity in human peripheral blood cells.
6. Brain Region Specific Monoamine and Oxidative Changes During Restraint Stress

Ahmad A (Ahmad, Ausaf); Rasheed N (Rasheed, Naila); Ashraf GM (Ashraf, Ghularn Md); Kumar R (Kumar, Rajnish); Banu N (Banu, Naheed); Khan F (Khan, Farah); Al-Sheeha M (Al-Sheeha, Muneera); Palit G (Palit, Gautam)

Abstract

Background and Purpose: Stress-induced central effects are regulated by brain neurotransmitters, glucocorticoids and oxidative processes. Therefore, we aimed to evaluate the simultaneous alterations in the monoamine and antioxidant systems in selected brain regions (frontal cortex, striatum and hippocampus) at 1 hour (h) and 24h following the exposure of restraint stress (RS), to understand their initial response and possible crosstalk. Methods and Results: RS (150 min immobilization) significantly increased the dopamine levels in the frontal cortex and decreased them in the striatum and hippocampus, with selective increase of dopamine metabolites both in the 1h and 24h RS groups compared to control values. The serotonin and its metabolite levels were significantly increased in both time intervals, while noradrenaline levels were decreased in the frontal cortex and striatum only. The activities of superoxide dismutase, glutathione peroxidase and the levels of lipid peroxidation were significantly increased with significant decrease of glutathione levels in the frontal cortex and striatum both in the 1h and 24h RS groups. There was no significant change in the catalase activity in any group. In the hippocampus, the glutathione levels were significantly decreased only in the 1h RS group. Conclusions: Our study implies that the frontal cortex and striatum are more sensitive to oxidative burden which could be related to the parallel monoamine perturbations. This provides a rational look into the simultaneous compensatory central mechanisms operating during acute stress responses which are particular to precise brain regions and may have long lasting effects on various neuropathological alterations.
7. Comparison of phenotypic and virulence genes characteristics in human and chicken isolates of Proteus mirabilis

Barbour EK (Barbour, Elie K.); Hajj ZG (Hajj, Zahi G.); Hamadeh S (Hamadeh, Shadi); Shaib HA (Shaib, Houssam A.); Farran MT (Farran, Mohamad T.); Araj G (Araj, George); Farou O (Farou, Obaid); Barbour KE (Barbour, Kamil E.); Jirjis F (Jirjis, Faris); Azhar E (Azhar, Esam); Kumosani T (Kumosani, Taha); Harakeh S (Harakeh, Steve)

Abstract

The objective of this work is to compare the phenotypic and virulence genes characteristics in human and chicken isolates of Proteus mirabilis. The bacterial examination of 50 livers of individual broilers, marketed by four major outlets, revealed a high recovery of P. mirabilis (66%), and a low recovery frequency of Salmonella spp. (4%), Serratia odorifera (2%), Citrobacter brakii (2%), and Providencia stuartii (2%). The phenotypic biochemical characterization of the recovered 33 chicken isolates of P. mirabilis were compared to 30 human isolates (23 urinary and six respiratory isolates). The comparison revealed significant differences in the presence of gelatinase enzyme (100% presence in chicken isolates versus 91.3 and 83.3% presence in human urinary and respiratory isolates, respectively, P < 0.05). The H2S production occurred in 100% of chicken isolates versus 95.6 and 66.7% presence in human urinary and respiratory isolates, respectively, P < 0.05). The other 17 biochemical characteristics did not differ significantly among the three groups of isolates (P > 0.05). Two virulence genes, the mrpA and FliL, were having a typical 100% presence in randomly selected isolates of P. mirabilis recovered from chicken livers (N=10) versus isolates recovered from urinary (N=5) and respiratory specimens of humans (N=5) (P > 0.05). The average percentage similarity of mrpA gene nucleotide sequence of poultry isolates to human urinary and respiratory isolates was 93.2 and 97.5-%, respectively. The high similarity in phenotypic characteristics, associated with typical frequency of presence of two virulence genes, and high similarity in sequences of mrpA gene among poultry versus human P. mirabilis isolates justifies future investigations targeting the evaluation of adaptable pathogenicity of avian Proteus mirabilis isolates to mammalian hosts.
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<th>Research Areas</th>
<th>Public, Environmental &amp; Occupational Health; Parasitology; Tropical Medicine</th>
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8. Cost effective surface functionalization of silver nanoparticles for high yield immobilization of Aspergillus oryzae beta-galactosidase and its application in lactose hydrolysis

Ansari SA (Ansari, Shakeel Ahmed); Satar R (Satar, Rukhsana); Alam F (Alam, Fahad); Alqahtani MH (Alqahtani, Mohammed Husein); Chaudhary AG (Chaudhary, Adeel Gulzar); Naseer MI (Naseer, Muhammad Imran); Karim S (Karim, Sajjad); Sheikh IA (Sheikh, Ishfaq Ahmed)

Abstract

The present study demonstrates synthesis, characterization and surface functionalization of silver nanoparticles (AgNPs) via glutaraldehyde for high yield immobilization of Aspergillus oryzae beta-galactosidase. Soluble beta-galactosidase (S beta G), enzyme adsorbed on unmodified AgNPs (U beta G) and surface modified AgNPs (M beta G) showed same pH-optima at pH 4.5. However, it was observed that M beta G exhibited enhanced pH stability toward acidic and alkaline sides, and increased temperature resistance as compared to S beta G and U beta G. Michaelis constant, K-m was increased nearly three-folds for M beta G while V-max for soluble and M beta G was 0.515 mM/min and 0.495 mM/min, respectively. Furthermore, M beta G showed greater resistance to product inhibition mediated by galactose as compared to it soluble counterpart and exhibited excellent catalytic activity even after its fourth successive reuse. The remarkable bioconversion rates of lactose from milk in batch reactors further revealed an attractive catalytic efficiency of beta-galactosidase adsorbed on surface functionalized AgNPs thereby promoting its use in the production of lactose free dairy products. Crown Copyright (C) 2012, Published by Elsevier Ltd. All rights reserved.
9. Genotoxicity of trichloroethylene in the natural milieu

Tabrez S (Tabrez, Shams); Ahmad M (Ahmad, Masood)

Abstract

Trichloroethylene (TCE) is a suspected genotoxic and carcinogenic compound which is usually present in the air, soil and water as pollutant. To estimate the genotoxic potential of TCE in a pure chemical form as well as an ingredient of the complex sample, Ames fluctuation test using TA98 and TA100 strains and Allium cepa genotoxicity assay were performed. For the genotoxicity analysis of TCE in natural milieu, the above mentioned tests were performed on the waste waters collected from two different stations of northern India namely Saharanpur and Aligarh, UP., and these waste waters were supplemented with 50 and 100 mg/l of trichloroethylene. TCE alone was found to be non-genotoxic by both the testing system up to the range of 1000 mg/l concentration (data not shown). However, the test water samples supplemented with 100 mg/l of TCE, exhibited a significant increase in the genotoxicity compared with control by both the testing systems. In Ames fluctuation test, Mi(f) value was found to be increased by 41% and 53% with 100 mg/l of TCE supplemented Saharanpur and Aligarh waste water samples respectively, in the presence of S9 fraction compared with their respective controls. Allium cepa genotoxicity test also showed around 25% increase in total chromosomal aberration frequency following 100 mg/l TCE supplementation. However, supplementation of 50 mg/l TCE to the test water samples could not enhance the genotoxicity to a significant extent. From these results, we can conclude that ICE itself was non-genotoxic but it may promote mutation and/or DNA damage at a concentration of 100 mg/l under certain environmental conditions. We suggest that some chemicals in the test water samples might be interacting with ICE and/or metabolite(s) to cause the enhancement in genotoxicity. The mechanism of these synergistic effects should be explored further. (C) 2011 Elsevier GmbH. All rights reserved.
Methylation of the Polycomb Group Target Genes Is a Possible Biomarker for Favorable Prognosis in Colorectal Cancer

Dallol A (Dallol, Ashraf); Al-Maghrabi J (Al-Maghrabi, Jaudah); Buhmeida A (Buhmeida, Abdelbaset); Gari MA (Gari, Mamdooh A.); Chaudhary AG (Chaudhary, Adeel G.); Schulten HJ (Schulten, Hans-Juergen); Abuzeadah AM (Abuzeadah, Adel M.); Al-Ahwal MS (Al-Ahwal, Mahmoud S.); Sibiany A (Sibiany, Abdulrahman); Al-Qahtani MH (Al-Qahtani, Mohammed H.)

Abstract

Background: Colorectal cancer (CRC) is the second most common cancer in the Kingdom of Saudi Arabia with ever increasing incidence rates. DNA methylation is a common event in CRC where it is now considered an important phenomenon in CRC carcinogenesis and useful for the classification and prognosis of CRC. Methods: To gain insight into the molecular mechanisms underpinning CRC in Saudi Arabian patients, we profiled the DNA methylation frequency of key genes (MLH1, MSH2, RASSF1A, SLIT2, HIC1, MGMT, SFRP1, MYOD1, APC, CDKN2A, as well as five CIMP markers) in 120 sporadic CRC cases. CRC tumors originating from the rectum, left, and right colons are represented in this cohort of formalin-fixed paraffin-embedded tissues. Results: The most common methylation frequency was detected in the polycomb group target genes (PCGT) including SFRP1 (70%), MYOD1 (60.8%), HIC1 (61.7%), and SLIT2 (56.7%). In addition, MGMT methylation was detected at a high frequency (68.3%). RASSF1A, APC, and CDKN2A methylation frequencies were 42.5%, 25%, and 32.8%, respectively. K-means clustering analysis of the methylation events results in the clustering of the CRC samples into three groups depending on the level of methylation detected. Conclusion: Group II (PCGT methylation and CIMP-negative) methylation signature carried a favorable prognosis for male patients, whereas older patients with group 1 rare methylation signature have a potentially poorer clinical outcome. Impact: Methylation of the PCGT genes along with RASSF1A, APC, and MGMT can be potentially used as a new biomarker for the classification and prognosis of CRC tumors and independently of where the tumor has originated. Cancer Epidemiol Biomarkers Prev; 21(11); 2069-75. (C)2012 AACR

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Mitochondria as an Easy Target to Oxidative Stress Events in Parkinson's Disease

Reale M (Reale, Marcella); Pesce M (Pesce, Mirko); Priyadarshini M (Priyadarshini, Medha); Kamal MA (Kamal, Mohammad A.); Patruno A (Patruno, Antonia)

Abstract

Parkinson's disease (PD) is related to excess production of reactive oxygen species (ROS) or inadequate and impaired detoxification by endogenous antioxidants, alterations in catecholamine metabolism, alterations in mitochondrial electron transfer function, and enhanced iron deposition in the substantia nigra. The concept that oxidative stress is an important mechanism underlying the degeneration of dopaminergic (DAergic) neurons is reinforced by data documenting that high levels of lipid peroxidation, increased oxidation of proteins and DNA and depletion of glutathione are observed in postmortem studies of brain tissues of PD patients. Tyrosine hydroxylase (TH) is an important neuronal enzyme that, in the presence of tetrahydrobiopterin, catalyzes the initial and rate-limiting step in the biosynthesis of the catecholamine neurotransmitters dopamine (DA) and norepinephrine, and is frequently used as a marker of DAergic neuronal loss in animal models of PD. The role for TH as generators of ROS are highly relevant to PD because ROS have been proposed to contribute to the neurodegeneration of DA neurons. Oxidants and superoxide radicals are produced as byproducts of oxidative phosphorylation, making mitochondria the main site of ROS generation within the cell and the site of the first line of defence against oxidative stress. ROS can affect mitochondrial DNA (mtDNA) causing modulation in synthesis of electron transport chain (ETC) components, decreased ATP production, and increased leakage of ROS.
Molecular Docking Study of Catecholamines and [4-(Propan-2-yl) Phenyl] Carbamic acid with Tyrosine Hydroxylase

Parveen Z (Parveen, Zahida); Nawaz MS (Nawaz, Muhammad Sulaman); Shakil S (Shakil, Shazi); Greig NH (Greig, Nigel H.); Kamal MA (Kamal, Mohammad A.)

Abstract

Parkinson's disease is a major age-related neurodegenerative disorder. As the classical disease-related motor symptoms are associated with the loss of dopamine-generating cells within the substantia nigra, tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of catecholamines has become an important target in the development of Parkinson's disease drug candidates, with the focus to augment TH levels or its activity. By contrast, TH inhibitors are of relevance in the treatment of conditions associated with catecholamine over-production, as occurs in pheochromocytomas. To aid characterizing new drug candidates, a molecular docking study of catecholamines and a novel hypothetical compound [4-(propan-2-yl) phenyl] carbamic acid (PPCA) with TH is described. Docking was performed using Autodock4.2 and results were analyzed using Chimera1.5.2. All the studied ligands were found to bind within a deep narrow groove lined with polar aromatic and acidic residues within TH. Our results corroborated a 'hexa interacting amino acids unit' located in this deep narrow groove crucial to the interaction of PPCA and the studied catecholamines with TH, whereby the 'His361-His336 dyad' was found to be even more crucial to these binding interactions. PPCA displayed a binding interaction with human TH that was comparable to the original TH substrate, L-tyrosine. Hence PPCA may warrant in vitro and in vivo characterization with TH to assess its potential as a candidate therapeutic.

Shakil S (Shakil, Shazi); Kamal MA (Kamal, Mohammad A.); Tabrez S (Tabrez, Shams); Abuzenadah AM (Abuzenadah, Adel M.); Chaudhary AGA (Chaudhary, Adeel G. A.); Damanhour GA (Damanhour, Ghazi A.)

Abstract

This study describes molecular interactions between human brain acetylcholinesterase (AChE) and the well known anti-neoplastic drug, methotrexate (MTX) and its comparison to 'AChE-cyclophosphamide (CP) interactions' that we reported previously. Docking between MTX and AChE was performed using 'Autodock4.2'. Hydrophobic interactions and hydrogen bonds both play an equally important role in the correct positioning of MTX within the 'acyl pocket' as well as 'catalytic site' of AChE to permit docking. However, docking of CP to AChE is largely dominated by hydrophobic interactions. Such information may aid in the design of versatile AChE-inhibitors, and is expected to aid in safe clinical use of MTX. Scope still remains in the determination of the three-dimensional structure of AChE-MTX complex by X-ray crystallography to validate the described data. The current computational study supports our previous experimental study which concluded a mixed inhibition model for AChE-inhibition by MTX. Furthermore, the present report confirms that MTX is a more efficient inhibitor of human brain AChE compared to CP with reference to K-i and Delta G values.

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Center Name: Center of King Fahd for Medical Research
Department: King Fahd Center for Medical Research
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14. New ursane-type triterpenes from the root bark of Calotropis procera

Ibrahim SRM (Ibrahim, Sabrin R. M.); Mohamed GA (Mohamed, Gamal A.); Shaala LA (Shaala, Lamiaa A.); Banuls LMY (Banuls, Laetitia Moreno Y.); Van Goietsenoven G (Van Goietsenoven, Gwendoline); Kiss R (Kiss, Robert); Youssef DTA (Youssef, Diaa T. A.)

Abstract

As a part of our continuing interest in identifying anticancer drug leads from natural sources, we have investigated the in vitro growth inhibitory effects of the hexane fraction of the root bark of Calotropis procera (Ait) R. Br. (Asclepiadaceae). This study reports the isolation and structure elucidation of four new ursane-type triterpenes named calotroprocerol A (1), calotroproceryl acetate A (2), calotroprocerone A (3) and calotroproceryl acetate B (4) in addition to five known compounds including pseudo-taraxasterol acetate (5), taraxasterol (6), calotropursenyl acetate B (7), stigmasterol (8) and (E)-octadec-7-enoic acid (9). Their structures were established on the basis of 1D and 2D NMR studies (H-1-H-1 COSY, HSQC, and HMBC) and HRMS spectral data. The in vitro growth inhibitory activity of the isolated compounds was evaluated against three human cancer cell lines including the A549 non-small cell lung cancer (NSCLC), the U373 glioblastoma (GBM) and the PC-3 prostate cancer cell lines. (C) 2012 Phytochemical Society of Europe., Published by Elsevier B.V. All rights reserved.

Ahmad A (Ahmad, Ausaf); Rasheed N (Rasheed, Naila); Gupta P (Gupta, Prasoon); Singh S (Singh, Seema); Siripurapu KB (Siripurapu, Kiran Babu); Ashraf GM (Ashraf, Ghulam Md); Kumar R (Kumar, Rajnish); Chand K (Chand, Kailash); Maurya R (Maurya, Rakesh); Banu N (Banu, Naheed); Al-Sheeha M (Al-Sheeha, Muneera); Palit G (Palit, Gautam)

Abstract

Therapies targeting central stress mechanisms are fundamental for the development of successful treatment strategies. Ocimum sanctum (OS) is an Indian medicinal plant traditionally used for the treatment of various stress-related conditions. Previously, we have isolated and characterized three OS compounds; Ocimarin, Ocimumoside A and Ocimumoside B. However, their role in modulating chronic stress-induced central changes is unexplored. Thus, in the present study the efficacy of these OS compounds have been evaluated on the chronic unpredictable stress (CUS)-induced alterations in the monoaminergic and antioxidant systems in the frontal cortex, striatum and hippocampus, along with the changes in the plasma corticosterone levels. CUS (two different types of stressors daily for seven days) resulted in a significant elevation of plasma corticosterone level, which was reversed to control levels by pretreatment with Ocimumoside A and B (40 mg/kg p.o.), while Ocimarin showed no effect. The levels of NA, DA and 5-HT were significantly decreased in all the three brain regions by CUS, with a selective increase of DA metabolites. A significant decrease in the glutathione (GSH) content, the activities of superoxide dismutase and catalase with a significant increase in the glutathione peroxidase activity and lipid peroxidation was observed in all the three regions of the brain by CUS. The OS compounds alone did not cause any significant change in the baseline values of these parameters. However, Ocimumoside A and B (40 mg/kg body p.o.) attenuated these CUS-induced alterations with an efficacy similar to that of standard anti-stress (Panax quinquefolium; 100 mg/kg p.o.) and antioxidant (Melatonin; 20 mg/kg i.p.) drugs. While, Ocimarin failed to modulate these CUS-induced alterations. Therefore, this is the first report which identified the anti-stress activity of novel Ocimumoside A and B at the level of central monoamines and antioxidant properties, implicating their therapeutic importance in the prevention of stress-related disorders. (C) 2012 Elsevier GmbH. All rights reserved.
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<th><strong>Research Areas</strong></th>
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<td><strong>Center Name</strong></td>
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16. Optimization of Saanen sperm genes amplification: evaluation of standardized protocols in genetically uncharacterized rural goats reared under a subtropical environment

Barbour EK (Barbour, Elie K.); Saade MF (Saade, Maya F.); Sleiman FT (Sleiman, Fawwak T.); Hamadeh SK (Hamadeh, Shady K.); Mouneimne Y (Mouneimne, Youssef); Kassaifi Z (Kassaifi, Zeina); Kayali G (Kayali, Ghazi); Harakeh S (Harakeh, Steve); Jaber LS (Jaber, Lina S.); Shaib HA (Shaib, Houssam A.)

Abstract

The purpose of this research is to optimize quantitatively the amplification of specific sperm genes in reference genomically characterized Saanen goat and to evaluate the standardized protocols applicability on sperms of uncharacterized genome of rural goats reared under subtropical environment for inclusion in future selection programs. The optimization of the protocols in Saanen sperms included three production genes (growth hormone (GH) exons 2, 3, and 4, alpha S1-casein (CSN1S1), and alpha-lactalbumin) and two health genes (MHC class II DRB and prion (PrP)). The optimization was based on varying the primers concentrations and the inclusion of a PCR cosolvent (Triton X). The impact of the studied variables on statistically significant increase in the yield of amplicons was noticed in four out of five (80%) optimized protocols, namely in those related to GH, CSN1S1, alpha-lactalbumin, and PrP genes (P < 0.05). There was no significant difference in the yield of amplicons related to MHC class II DRB gene, regardless of the variables used (P > 0.05). The applicability of the optimized protocols of Saanen sperm genes on amplification of uncharacterized rural goat sperms revealed a 100% success in tested individuals for amplification of GH, CSN1S1, alpha-lactalbumin, and MHC class II DRB genes and a 75% success for the PrP gene. The significant success in applicability of the Saanen quantitatively optimized protocols to other uncharacterized genome of rural goats allows for their inclusion in future selection, targeting the sustainability of this farming system in a subtropical environment and the improvement of the farmers livelihood.

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17. Relationship between Inflammatory Mediators, A beta Levels and ApoE Genotype in Alzheimer Disease

Reale M (Reale, M.); Kamal MA (Kamal, M. A.); Velluto L (Velluto, L.); Gambi D (Gambi, D.); Di Nicola M (Di Nicola, M.); Greig NH (Greig, N. H.)

Abstract

Activation of inflammatory processes is observed within the brain as well as periphery of subjects with Alzheimer’s disease (AD). Whether or not inflammation represents a possible cause of AD or occurs as a consequence of the disease process, or, alternatively, whether the inflammatory response might be beneficial to slow the disease progression remains to be elucidated. The cytokine IL-18 shares with IL-1 the same pro-inflammatory features. Consequent to these similarities, IL-18 and its endogenous inhibitor, IL-18BP, were investigated in the plasma of AD patients versus healthy controls (HC). An imbalance of IL-18 and IL-18BP was observed in AD, with an elevated IL-18/IL-18BP ratio that might be involved in disease pathogenesis. As part of the inflammatory response, altered levels of RANTES, MCP-1 and ICAM-1, molecules involved in cell recruitment to inflammatory sites, were observed in AD. Hence, correlations between IL-18 and other inflammatory plasma markers were analyzed. A negative correlation was observed between IL-18 and IL-18BP in both AD and HC groups. A positive correlation was observed between IL-18 and ICAM-1 in AD patients, whereas a negative correlation was evident in the HC group. IL-18 positively correlated with A beta in both groups, and no significant correlations were observed between IL-18, RANTES and MCP-1. An important piece of evidence supporting a pathophysiologic role for inflammation in AD is the number of inflammatory mediators that have been found to be differentially regulated in AD patients, and specific ones may provide utility as part of a biomarker panel to not only aid early AD diagnosis, but follow its progression.
18. Studies on BVD involving establishment of sentinel calves and assessment of herd immunity in a large dairy farm in Saudi Arabia

Abu Elzein E (Abu Elzein, Eltayb); AlKhalyifa M (AlKhalyifa, Mofeed)

Abstract

Little information is, Published, so far, regarding bovine viral diarrhea (BVD) in Saudi Arabia and the Gulf region. This study is the first of its kind in the country. Its aim was to explore the BVD situation in a large dairy farm, which has been experiencing reproduction problems suggestive of BVD virus infection, albeit the practice of routine vaccination. The study took two pathways; the first involved establishment of a cohort of sentinel calves so as: (a) to note the BVD virus activity in the farm by following the time lapse and pattern for waning of the maternally derived antibodies and detection of any subsequent seroconversion and (b) to look for any clinical signs suggestive of BVD virus infection in these calves. The second pathway was to assess the level of herd immunity in the different age groups of lactating cows and maiden heifers. The obtained results were discussed, and control strategies were outlined.
19. Subereamolline A as a Potent Breast Cancer Migration, Invasion and Proliferation Inhibitor and Bioactive Dibrominated Alkaloids from the Red Sea Sponge Pseudoceratina arabica

Shaala LA (Shaala, Lamiaa A.); Youssef DTA (Youssef, Diaa T. A.); Sulaiman M (Sulaiman, Mansour); Behery FA (Behery, Fathy A.); Foudah AI (Foudah, Ahmed I.); El Sayed KA (El Sayed, Khalid A.)

Abstract

A new collection of several Red Sea sponges was investigated for the discovery of potential breast cancer migration inhibitors. Extracts of the Verongid sponges Pseudoceratina arabica and Suberea mollis were selected. Bioassay-directed fractionation of both sponges, using the wound-healing assay, resulted into the isolation of several new and known brominated alkaloids. Active fractions of the sponge Pseudoceratina arabica afforded five new alkaloids, ceratinines A-E (2-6), together with the known alkaloids moloka‘iamine (1), hydroxymoloka‘iamine (7) and moloka‘akitamide (8). The active fraction of the sponge Suberea mollis afforded the three known alkaloids subereamolline A (9), aerothionin (10) and homoaerothionin (11). Ceratinine B (3) possesses an unprecedented 5,7-dibrominated dihydroindole moiety with an epoxy ring on the side chain of a fully substituted aromatic moiety. Ceratinines D (5) and E (6) possess a terminal formamide moiety at the ethylamine side chain. Subereamolline A (9) potently inhibited the migration and invasion of the highly metastatic human breast cancer cells MDA-MB-231 at the nanomolar doses. Subereamolline A and related brominated alkaloids are novel scaffolds appropriate for further future use for the control of metastatic breast cancer.

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20. Successful propagation of Alkhumra (misnamed as Alkhurma) virus in C6/36 mosquito cells

Madani TA (Madani, Tariq A.); Kao M (Kao, Moujahed); Azhar EI (Azhar, Esam I.); Abuelzein ETME (Abuelzein, El-Tayeb M. E.); Al-Bar HMS (Al-Bar, Hussein M. S.); Abu-Araki H (Abu-Araki, Huda); Ksiazek TG (Ksiazek, Thomas G.)

Abstract

Epidemiological data suggest that Alkhumra (misnamed as Alkhurma) virus (ALKV) is transmitted from livestock animals to humans by direct contact with animals or by the mosquito bites, but not by ticks. To assess the ability of the virus to replicate in mosquito cells, serum and plasma of seven acutely febrile patients with clinically suspected ALKV infection reported in Najran, Saudi Arabia in 2009 were inoculated onto Aedes albopictus mosquito cells (C6/36) and directly examined with ALKV-RNA-specific real time RT-PCR as well as indirect immunofluorescence assay (IFA) using ALKV-specific polyclonal antibodies. The isolated virus was titrated in the mammalian rhesus monkey kidney cells (LLC-MK2). Five of the seven specimens were RT-PCR- and culture-positive demonstrating cytopathic effects in the form of cell rounding and aggregation appearing on day 3 post inoculation with syncytia eventually appearing on day 8 post inoculation. Identification of ALKV-RNA in the cell culture was confirmed with RT-PCR and IFA. The virus titre was 3.2 x 10(6) tissue culture infective dose 50 (TCID50) per mL. Three more viral passages were successfully made in the C6/36 cells. This is the first description of propagation of ALIN in mosquito cells. (C) 2011 Royal Society of Tropical Medicine and Hygiene., Published by Elsevier Ltd. All rights reserved.
Superiority of the buffy coat over serum or plasma for the detection of Alkhumra virus RNA using real time RT-PCR

Madani TA (Madani, Tariq A.); Abuelzein ETME (Abuelzein, El-Tayeb M. E.); Azhar EI (Azhar, Esam I.); Kao M (Kao, Moujahed); Al-Bar HMS (Al-Bar, Hussein M. S.); Abu-Araki H (Abu-Araki, Huda); Ksiazek TG (Ksiazek, Thomas G.)

Abstract

RT-PCR to detect Alkhumra virus (ALKV) RNA in plasma or serum has been the standard practice to confirm this infection in the first seven days of illness. In this study, RT-PCR detection of viral RNA from the plasma, serum, and buffy coat (BC) was compared to virus isolation. Plasma, serum, and BC were obtained from seven patients with clinically suspected ALKV infection in Najran, Saudi Arabia. Baby hamster kidney (BHK-21) and rhesus monkey kidney (LLC-MK2) cell culture monolayers were used for virus isolation. Real-time RT-PCR was used to confirm ALKV infection and to detect viral RNA directly from plasma, serum, and BC. ALKV was isolated from five of the seven patients. The virus was isolated from all three specimen types (plasma, serum, and BC) of the five confirmed patients. ALKV RNA was detected directly by RT-PCR in BC in all five (100%) culture-positive patients and in plasma or serum in only four (80%) of the five patients. Three of the five patients for whom ALKV RNA was detected in BC also had detectable viral RNA in plasma and serum. In the remaining two patients with detectable ALKV RNA in the BC, the plasma was positive but the serum was negative in one patient, whereas the serum was positive and the plasma was negative in the other patient. The use of real-time RT-PCR to detect ALKV RNA in the BC was superior to using plasma and serum and equivalent to virus isolation.
Targeting Parkinson's - Tyrosine Hydroxylase and Oxidative Stress as Points of Interventions

Khan MS (Khan, Mohd Shahnawaz); Tabrez S (Tabrez, Shams); Priyadarshini M (Priyadarshini, Medha); Priyamvada S (Priyamvada, Shubha); Khan MM (Khan, Mohd M.)

Abstract

Parkinson's disease (PD) is characterized by the progressive loss of the dopaminergic neurons leading to decrease in striatal dopamine (DA) levels. In the present review, our focus was on recent advances in the treatment procedures of PD to achieve an increase in deficient tyrosine hydroxylase (TH) activity and/or expression. Stimulation of residual TH activity by the cofactors, 6R-L-erythro-tetrahydrobiopterin (BPH4) or NADH, or by brain transplant of natural TH-containing cells (fetal substantia nigra) or genetically engineered TH-containing cells, has been tried experimentally and clinically lately. As a promising approach to the gene therapy, intrastriatal expression of DA-synthesizing enzymes through transduction with separate adeno-associated virus (AAV) vectors/ marrow stromal cells (MSCs) or nonviral intravenous administration of rat transferrin receptor monoclonal antibody (TfRmAb)-targeted PEGylated immunoliposomes (PILs) has been found to be effective in animal models. Oxidative stress has been identified as one of the intermediary risk factors that could initiate and/or promote degeneration of DA neurons. TH itself is a prime target of oxidative/nitrosative injury. Certain superoxide dismutase and catalase mimetic prevented nitration of TH in cultured dopaminergic neurons. Therefore, development of therapeutic agents that can prevent formation of or specifically remove nitrating agents without interfering with normal neuronal function may protect protein from inactivation and provide means of limiting neuronal injury in PD. Non-pharmacological approaches such as diet therapy or use of active constituents of plants and phytomedicines have also emerged as a new - area of high interest. New treatment strategies for TH dysfunction rectification, a provision for neuroprotection in PD, seem to be on the horizon with many therapies under investigation.
Transcriptome analysis of amoeboid and ramified microglia isolated from the corpus callosum of rat brain

Parakalan R (Parakalan, Rangarajan); Jiang B (Jiang, Boran); Nimmi B (Nimmi, Baby); Janani M (Janani, Manivannan); Jayapal M (Jayapal, Manikandan); Lu J (Lu, Jia); Tay SSW (Tay, Samuel S. W.); Ling EA (Ling, Eng-Ang); Dheen ST (Dheen, S. Thameem)

Abstract

Background: Microglia, the resident immune cells of the central nervous system (CNS), have two distinct phenotypes in the developing brain: amoeboid form, known to be amoeboid microglial cells (AMC) and ramified form, known to be ramified microglial cells (RMC). The AMC are characterized by being proliferative, phagocytic and migratory whereas the RMC are quiescent and exhibit a slow turnover rate. The AMC transform into RMC with advancing age, and this transformation is indicative of the gradual shift in the microglial functions. Both AMC and RMC respond to CNS inflammation, and they become hypertrophic when activated by trauma, infection or neurodegenerative stimuli. The molecular mechanisms and functional significance of morphological transformation of microglia during normal development and in disease conditions is not clear. It is hypothesized that AMC and RMC are functionally regulated by a specific set of genes encoding various signaling molecules and transcription factors.

Results: To address this, we carried out cDNA microarray analysis using lectin-labeled AMC and RMC isolated from frozen tissue sections of the corpus callosum of 5-day and 4-week old rat brain respectively, by laser capture microdissection. The global gene expression profiles of both microglial phenotypes were compared and the differentially expressed genes in AMC and RMC were clustered based on their functional annotations. This genome wide comparative analysis identified genes that are specific to AMC and RMC. Conclusions: The novel and specific molecules identified from the transcriptome explains the quiescent state functioning of microglia in its two distinct morphological states.

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