



Physiology and Anatomy

Elixir Physio. & Anatomy 75C (2014) 27649-27652

Elixir
ISSN: 2229-712X

Neurodegenerative disease and herbs-research review

Ravishankar MV and Sandhya D

Jawaharlal Nehru Medical College, Department of Anatomy, KLE University, Belgaum, Karnataka State, India.

ARTICLE INFO

Article history:

Received: 2 July 2014;

Received in revised form:

25 September 2014;

Accepted: 11 October 2014;

Keywords

Alzheimer's disease,

Cerebral cortex,

Hippocampus,

Juvenile diabetes.

ABSTRACT

The incidence of neurodegenerative diseases are increasing in the present generation. Based on their diversified causes it is targeting almost all the age groups including young (juvenile) and old (senile) population without discrimination. There are some metabolic diseases which are targeting the brain functions in young. The juvenile diabetes is one among them, where the excess of unutilized glucose is following wide range of deranged paths resulting into encephalopathy. The early detection of such diseases needs to be identified and tackled at the earliest. The existing modern treatment is having much limitation; hence it is inviting the contribution from the field of alternate herbal medicine.

© 2014 Elixir All rights reserved.

Introduction

The neurodegenerative diseases are more prevalent ailments seen in the present population. There are more than 600 disorders which are targeting the nervous system¹. Their clinical presentation may vary from subtle to gross form. It is becoming an important global issue. Generally these diseases can be recognized at its different stages in an individual's life. They can be recognized during the childhood as well as in late adult hood; hence they are recognized under the name of juvenile and senile neurodegenerative diseases. The neurodegenerative diseases of childhood encompass large number of heterogeneous disease due to genetic, biochemical, environmental causes. The progressive dysfunction of central or peripheral nervous system is a hall mark in the neurodegenerative disorders.² Increasing senile population and the increasing human life span causing a great burden on the global health care. Much of the adult population aged above 70 years are likely to suffer from progressive neurological defects from subtle to gross form, which is gradually crippling their routine, normal and social life. Such diseases are inevitably forcing them to depend on helping hands. Among number of adult neurodegenerative diseases Alzheimer's, Parkinson's disease, Huntington's diseases are the leading ones. These disease conditions are often associated with gradual changes in the peripheral and central nervous system. Clinically these defects range from simple reduced cutaneous sensation to severe atrophy of brain. Clinically it was found that the deposition of amyloid material and formation of neurofibrillary tangles in the brain is a common associated finding³. The exact pathogenesis of these diseases is still remains inconclusive. But subsequent research in this direction may open many opportunities to test novel hypothesis. Alzheimer's disease is one of the leading disorders affecting the adult population resulting in senile dementia. It involves the gradual synaptic loss, reduced secretion of neurotransmitters, and atrophy of brain and progressive death of neurons ultimately lead to dementia and death.

Why we need to tackle the disease early?

Among number of neurodegenerative diseases, the childhood neurodegenerative diseases are dragging attention much early. There is a rapid growth and modification of brain

during infancy and childhood, which is directly influencing the cognitive functions⁴. Any factor interrupting the healthy growth of brain may lead to learning and memory defects. Such early age related adverse changes are almost permanent and irreversible. One such childhood (juvenile) disease seen in the present generation is "juvenile diabetes mellitus". It starts to show its adverse effects on the multiple systems. But its adverse effect on the brain is likely to interfere with growth and development of child during its potential early period of life. To recognize its early adverse changes in the brain the radiological investigations stand as an important non-invasive clinical tool which can detect the changes in brain. Among number of neurological diseases the juvenile diabetes is a highly indexed common pediatric problem. The constant hyperglycemia can cause degenerative changes in young developing and modifying brain by hampering the normal growth and development during their potential period. Early diabetes makes an individual to become insulin dependent for their survival. Onset of early diabetes can affect normal metabolism leading to gradual and subtle derangements. Such changes may fail to drag the attention during its early stages. But later on it may be recognized in association with extensive or permanent disabilities related to learning, memory function, motor activities, reduced intelligent quotient (IQ) etc. These changes could be due to encephalopathy associated with cognitive dysfunctions⁵. The regressive and progressive adverse changes in the brain are affecting the speech, vision, hearing, locomotion etc. Often these changes may be associated with epileptic seizures as well⁵. Early recognition of neurodegenerative diseases and initiation of an effective treatment is still an outstanding challenge for the researchers. It opens the ways to quest for an effective, natural, cheap and rational alternate treatment strategy.

Factors influencing the neurodegeneration

Generally the environmental causes, altered food habits, exposure to pollutants, use of fertilizers, advancing age etc. are some of the important factors which are influencing our biological system directly or indirectly. But many of them are not showing their direct evidence to prove their role, hence it invites research in this direction⁶. The factors which are causing

the neuro degenerative diseases are mainly including genetic polymorphism, advancing age, underlying diseases, stress, habits like smoking, alcohol, drugs etc. Finding direct evidence on such factors in neurodegenerative disease is often difficult. But the post mortem studies can give more insight into the disease and its impact on the structural (anatomy) changes in the vital organs like brain. One of the important factors which precipitate the neurodegenerative disease is free radicals, which are the byproducts of aerobic cellular metabolism. The body is having a strong reactive oxygen species (ROS) scavenging enzymes, which can prevent the stagnation of cellular metabolic waste materials^{7,8}. Despite having an effective scavenging system, our body may fail to do so normally, due to accumulated load of excess cellular waste. The toxicity due to free radicals accumulation may affect the mitochondrial function leading to gradual DNA damage which ultimately driving the cell to follow several deranged paths; subsequently the cell may enter into a stage of apoptosis. Such adverse activity of brain cells may be a substantial cause for number of neuro-degenerative ailments.

Nootropic and antidiabetic herbs

Antioxidant effect of medicinal herbs is a most widely exploited property by the researchers, which is copiously available through the natural resources. Vegetables and herbs are the major source of antioxidants; they differ with medicinal herbs with respect to their potency. These herbs are dragging the attention of commercial sectors by showing more promising results in number of experiments worldwide. The role of antioxidants is to tackle the free radicals in the neurodegenerative diseases is supported through the number of experimental models on preventive and curative diseases. Such observations in the existing literature are a base for novel research. Our experiment was intended to test antidiabetic and nootropic effect of the drug *clitoria ternatea* (Linn.) and *salacia chinensis* (Linn.) individually and in combination.

The modern researchers are using the large quantum of efforts by spending huge amount of time, money, manpower etc., to understand and also to find an effective drug to treat number of neuro-degenerative diseases. But the outcome of its practical benefit is still in the state of infancy. The present situation is demanding an aggressive applied research in this direction to find a remedy to console untamed growth of brain related disorders to serve the intellectual population at large. In the present situation new research findings in alternate medicine is drawing more attention around the globe. Ancient medical sciences are including ayurveda, siddha, unani etc. have contributed lot to understand the action of herbal drugs in the neurodegenerative diseases. The reference of herbs in traditional chinese medicine is also an important in supporting the utility of herbs in neurological diseases⁹. Most of these medical sciences make use of drugs which are of herbo-mineral origin. Such holistic alternate medicines clearly mentions that the health is not just an individual's disease free state, but it is a complete state of physical, mental and spiritual wellbeing. Ayurvedic therapies are not just used to treat disease conditions but it equally stress the importance of health maintenance to achieve a disease free life in a holistic manner.

The peculiarity of herbal therapy is that they are showing multifaceted and diversified action on biological systems¹⁰. Different phytochemicals present in the multi-drug combination may show influence by altering the metabolic reactions in the molecular level, often which is difficult to trace such actual molecular events. One of the most common properties of herbal therapy is that they can act as antioxidants. These antioxidants are showing activities as anti-inflammatory, anti-atherosclerotic,

anti-mutagenic, anti-cancerous, antibacterial, antiviral etc. The principles of ayurvedic medicine have mentioned the use of single and poly herbal therapies to prevent or to treat number of diseases including neuro-degeneration. Single drug can be used to treat multiple diseases¹¹. Often many young researchers try to make use of such poly herbal combinations in their experiments probably with the intention of obtaining significant changes in their research findings. Often such experimental ideas may bias their findings, which may not be the actual one due to involvement of confounding factors. Trial with administration of combined (polyherbal) drug administration in experiments may show overlapping effects by altering the action of large number of phytochemicals in the pool of biological system. Which may likely to threaten the experimental animals with dire consequence. The experimental findings with single drug applications are more likely to direct a basic researcher in much better way to support the advanced studies in future.

Experimental background

Our experiment was involving well grown root part of two plants, *clitoria ternatea* (Linn) and *salacia chinensis* (Linn.). The study protocol was including the young wistar rats aged around three weeks. The alcoholic root extract of these drugs were administered orally at a dose of 100mg/kg body weight. The diabetes was induced by the administration of single dose of 60 mg of streptozotocin given intraperitoneal. Trial drugs were administered immediately (as preventive therapy) and late (as curative therapy) after the confirmation of diabetes in different experimental groups. The herb *clitoria ternatea* (Linn.) is a well-known nootropic agent belongs to family *celestraceae* and generally it is commonly known as shankapushpi. There are number of herbs mentioned as nootropic agents, like jatamamsi, vacha, jyothishmati, yestimadhu, bhrami etc., and shankapushpi is one among them. In ayurveda they are mentioned under the category of madhya rasayanas (brain tonics). It is a group of drugs showing nootropic and anxiolytic activities, hence they were recommended in neuropsychological diseases.

There are number of antidiabetic agents like acacia arabica, aegle marmelos, alche millamollis, allium cepa, vaccinium myrtillus L.etc¹². The shrub *salacia chinensis* (Linn) is one of the reputed antidiabetic drug in use since centuries, belongs to family *hippocretaceae*. Numbers of experiments have supported their use by observing their antidiabetic properties. Its antidiabetic effect could be due to their anti hyperglycemic or hypoglycemic action.

In our experiments we have chosen the drug *clitoria ternatea* (Linn.) which is a known nootropic agent and *salacia chinensis* (Linn.) is a known antidiabetic agent. The combination of these drugs was chosen not only with the intention to tame the diabetic condition, but it is also to test their nootropic effect on the brain cells. Where the treatment was given individually and in combination as preventive (early) and curative (late) therapy in diabetic condition. The present trials simultaneously would like to test nootropic and antidiabetic effects on young developing and modifying brain under the influence of diabetes. Hence is essential to recognize the juvenile diabetes at the early so a rational therapy can be initiated without further delay.

Experimental findings in treatment groups

In our experiment the group treated early with *salacia chinensis* has shown some unusual and favorable findings. Here the frontal cortical neurons were seen relatively smaller in size with less neurodegenerative changes in that region. But it was interesting to note that this particular early treatment group has shown large number of small dendritic spines in the frontal

cerebral cortical neurons. But the arborization in these cerebral cortical neurons was not relatively fair when compared with other control groups. Such typical dendritic spines were not noticed in any other treatment groups¹³. The extensive dendritic spine growth in the group treated with early *salacia chinensis* may support the overall brain cell function by enhancing the recovery of fatigue neurons or it may enhance the number of synaptic contacts or it may influence the neurotransmitter activity. But observations in case of curative treatment group where the treatment was started with a gap of one month time duration was found without such positive findings. Probably these findings are showing the limitation of action of root extract of *salacia chinensis* (Linn) on relatively stable and advanced diabetic neuro degeneration.

Especially in diabetic studies, during the administration of antidiabetic drugs it is required to consider the routine dietary intake and physical activity of the subject to get an idea about the net energy consumption by an individual. It is important to consider the life style and the diurnal fluctuation of blood glucose before making a decision on quantity of drug administration, especially while using the combination of drugs like *salacia chinensis* and *clitoria ternatea*. Such combination can cause severe hypoglycemia in the experimental subjects¹⁴. The administration of such combination for a longer duration may likely to bring permanent adverse changes on the structure (anatomy) of vital organs like brain; often such effect could be fatal one. They younger experimental animals are more sensitive to show adverse drug effects quickly. The repeated transient hypoglycemic episodes may gradually lead to poor cognitive performance in the subjects. It is better to avoid administering such antidiabetic drugs especially during the night hours; to prevent severe hypoglycemia, often such episodes may not be recognized by the subject or by his attendants leading to irreversible brain damage.

Experimental group treated early with the drug *clitoria ternatea* has witnessed with copious growth of cerebral cortical dendrites. Where large number of viable neurons were found in the cerebral frontal cortical region. The size of neurons was increased, showing less degenerative changes^{15, 16}. Though these neurons were not shown any dendritic spine patterns unlike the group treated with *salacia chinensis* but they have shown their support to enhance the copious growth in length of dendrites, and such discriminating findings may need advanced research focus. But the curative treatment given with the drug *clitoria ternatea* has shown comparatively limited growth pattern of dendrites.

It was observed that the herb *clitoria ternatea* has shown some hypoglycemic effects, but it was within the physiological limits¹⁷. These observations may alert the young researchers before they start experiments by using combination of such herbs. So it can guide the researchers to focus on the action of single drug administration at a time to avoid much bias on anticipated effects. The combined herbal drug effects can be evaluated only in advanced and sophisticated studies.

In the experiments with combined drug administration we have come across that the cerebral frontal cortical neurons were showing the cell loss, cell shrinkage and chromatolysis associated with short dendritic growth patterns in all the treatment groups. These observations were compared with other experimental control groups where the animals received the drugs individually has shown some positive findings. Probably it is showing the susceptibility of cerebral cortical neurons due to the effect of combined drugs leading to hypoglycemia. It is mimicking the administration of excess dose or combined

administration of antidiabetic drugs both in children and adult can leading to hypoglycemic coma. Such hypoglycemic episodes are considered to be more dangerous than the hyperglycemia. It seems to be more ideal to administer such drugs in a separate schedule to avoid drastic hypoglycemia induced adverse effects on the subject.

Conclusion

The nature consists of large number of medicinal herbs; among them some of herbs can be used in more than one disease. Some of our observations are supporting and encouraging the use of single herb to target dual action as nootropic and antidiabetic agent. Diabetes is one such disease need to be recognized at the early and the treatment should be initiated without further delay. In long run the diabetes is likely to bring degenerative changes in multiple organs and systems. The early recognition of diabetes in young is much vital when compare the same with the adults. Our overall research observations at one particular angle is coinciding to show multi action potential of a single drug to treat encephalopathy caused due to early childhood diabetics. In this direction we need to diversify our modern research to identify such multi action natural phytochemicals or compounds for the human benefit. The research in the field of natural medicine may bring hopes in millions of sufferers worldwide to gift an invaluable hidden panacea from this diversified nature.

Acknowledgement-The author would like to thank KLE University and Jawaharlal Nehru medical college, dept. of anatomy where this whole research has been carried out, and also acknowledge their complete cooperation and support for this work.

Competing interest

Here the authors declare that they don't have any competing interest.

References

1. Wong V, Neurodegenerative diseases in children. Hong Kong Med J. 1997;3(1):89-95.
2. Amor S, Puentes F, Baker D, Valk PVV, Inflammation in neurodegenerative diseases. Immunology 2010;129(2):154-159.
3. Xiaoning Bi, Alzheimer Disease: Update on Basic Mechanisms, JAOA, 110(9).
4. Lenroot RK, Giedd JN. Brain development in children and adolescents; Insights from anatomical magnetic resonance imaging. Neuroscience behavioral review. 2006; 30:718-729.
5. Kodl CT and Seaquist ER. Cognitive Dysfunction and Diabetes Mellitus. Endocrine reviews. 2008; 29(4):494-511.
6. Brown RC, Lockwood AH, Sonawane BR, Neurodegenerative Diseases: An Overview of Environmental Risk Factors, Environmental Health Perspects, 2005; 113(9): 1250-1256.
7. Uttara B, Singh AV, Zamboni P, Mahajan R.T, Oxidative Stress and Neurodegenerative Diseases: A Review of Upstream and Downstream Antioxidant Therapeutic Options, Current Neuropharmacology, 2009; 7(1):65-74..
8. Khalaf NA, Shakya A K, Al-Othman A, El-Agbar Z, Farah H. Antioxidant Activity of Some Common Plants. Turkish journal of biology, 2008;32:51-55.
9. Melanie- Howes J R, Peter J, Houghton. Plants used in Chinese and Indian traditional medicine for improvement of memory and cognitive function-Review Article, Pharmacology Biochemistry and Behavior, 2003;75(3): 513-517..
10. Kulkarni R, Girish KJ, Kumar A. Nootropic herbs (Madhya Rasayana) in Ayurveda: An update. Pharmacogenomics Review, 2012; 6(12) 147-153,

11. YadavP, UplanchiwarV,Gahane A, ModiA, Telrandhe U, Bheemachari. Nootropic activity of 1-33 – a polyherbal formulation. Pharmacologyonline, 2010;2:818-827.
12. Joseph B and Jini D. Insight into the Hypoglycemic Effects of traditional Indian Herbs used I the treatment of Diabetes. Research journal of medicinal plant. 2011; 5(4)352-375.
13. Ravishankar MV, Arborization effect of root extract of *Salacia chinensis* (Linn) on dendritic arborization of frontal cortical neuron in early diabetic young rat experimental model- A preliminary investigation. Elixir, 2013;(65): 19840-19843
14. Ravishankar MV, Jevoor PS. Combined Effect of individual and combination of herbal extracts on glucose tolerance, in euglycemic rats. International journal of life sciences biotechnology and pharma research.2013; 2(1):217-224.
15. Mathada RV, Jevoor PS, Rajashree, Effect of *Clitoria ternatea* Linn plant root extract on the hippocampal area CA 3 and pancreas of juvenile diabetic rats- A preliminary investigation. Spatula Drug Discovery, 2012;2(1): 9-16.
16. Ravishankar MV. Effect of *Clitoria ternatea* (Linn) plant root extract on the neurons of frontal cortex and dentate gyrus of young diabetic rats-A preliminary investigation. Experiment, 2013; 16(4):1138-1144.
17. Daisy P, Rajathi M. Hypoglycemic effects of *Clitoria ternatea* Linn.(Fabaceae) in alloxan induced diabetes in rats.Tropical journal of Pharmaceutical research.2009;8(5); 393-398.