The Miracle Mushroom *Hericium erinaceus* and its Relation to Nerve Growth Factor: A Perspective from Across the Atlantic

Luke Thomas Neal

Clinic Director, North Down Chiropractic Clinic, 43 Grays Hill, Bangor, BT20 3BB, United Kingdom; LukeThomasNeal@hotmail.com

Introduction

Hericium erinaceus is a medico-culinary mushroom that has been used for thousands of years. Recent research endeavors have highlighted the benefits of supplementation for a diverse number of neurological conditions. *Hericium erinaceus*'s miraculous effects are thought to revolve around the stimulation of neurotrophic peptides such as nerve growth factor (NGF). NGF has a diverse and interesting role in a number of processes spanning from central nervous system (CNS), to peripheral nervous system (PNS), immune to endocrine. The alteration of NGF's equilibrium in a number of pathologies has been highlighted but utilization of the peptide as a treatment has been severely hampered due to its inability to cross the blood brain barrier. It is this paper's role to highlight and review *Hericium erinaceus*'s theoretical benefits and clinical usage, with a particular focus on its centrally acting neuroprotective effects.

The Lion's Mane mushroom, Hericium erinaceus

The aptly named Lion's Mane mushroom has a long medico-culinary history in China where it has been utilized historically in traditional Chinese medicine (TCM) for a number of aliments. It was only in the 1990s that precise scientific studies began on the isolation of biochemical compounds, and since then *Hericium erinaceus* has been shown to be a venerable treasure trove of bioactive compounds that have such broad affects as immunomodulation (Wang, 2001; Lui, 2000; Xu, 1994), anticancer (Wang, 2001; Xu, 1994; Chen, 1987), antioxidative (Rahman, 2014), and antidiabetic (Yi, 2015) as well as the neuroprotective effects that this review will focus on.

Although the mushroom is relatively distinctive in appearance—and quite common in North America—it is in fact a rare mushroom in the United Kingdom. Here in the UK it is given the highest level of legal protection and is one of only four species of fungi listed as Schedule 8 on the Wildlife and Countryside Act of 1981 (https://www.woodlandtrust.org.uk/trees-woods-and-wildlife/fungi-and-lichens/bearded-tooth/). This means that theft of the mushroom can be punishable by six months imprisonment or a large fine. As with a number of our critically endangered species, the assumed reason for its decline is the progressive destruction of its habitat, which is known to be beech woods and large standing trees. Although rare in nature, it is an easily cultivated mushroom, with growers cultivating directly from spores.

When harvesting these mushrooms, there are two separate areas to be aware of: the fruiting body and the mycelium. The main bioactive substances of interest from the fruiting body are hericenones, of which there are 11 (hericenones A–K). Four of these are of particular interest to us (C, D, E, F) due to their ability to stimulate NGF (Ma, 2010; Kawagishi, 1991). More on this later.

The next area of interest is the mycelium. The bioactive chemical of interest here is called erinacines, however it should be noted the erinacines are not exclusively found in the mycelium, they have also been found in the fruiting body (Aoita, 2005). Out of the 15 erinacines, nine have been found to be potent stimulators of NGF (I-Chen, 2018), as well as having a number of other positive health benefits that are beyond the scope of this paper. Next we will explore what NGF is and why it is of importance for neurological health.

NGF: an overview of its role in CNS and PNS

NGF or nerve growth factor is a neurotrophic peptide that was first discovered in the 1940s by Rita Levi-Montalcini (Cohen, 1954). Originally, its known role was primarily in the sensory and autonomic nervous system. Research has shown its role also to involve the central nervous system, the endocrine system, and the immune system. NGF plays a critical role in the development and maintenance of the central nervous system (CNS) (Misko, 1987). NGF is part of a family of structurally related neurotrophic peptides alongside BDNF and NT3-7 (Barde, 1982). For this review, we will focus on the peptide NGF and its close relative BDNF (brain derived neurotrophic factor).

Of NGFs many roles, the one of particular interest for us in is the protection and maintenance of the central nervous system and its potential therapeutic application for a number of neurodegenerative diseases. NGF exerts its actions through two classes of neuronal receptor: the shared p75 and Trk (Wiesmann, 2001). These receptors can be found on the surface of predominantly sensory but also other types of neurons. The binding of NGF to the Trk receptors signals the cell to grow, mature and differentiate, as well as inhibiting cell death (apoptosis). The role of the sister receptor to Trk, called p75, is less clear.

In the CNS, the greatest amount of NGF is synthesized in the cortex, the hippocampus, and the pituitary gland, although quantities have been found in the basal ganglia, thalamus, and spinal cord. In the peripheral nervous system (PNS), NGF can be found in every tissue or organ that is innervated by sensory or sympathetic efferent (Wiesmann, 2001). In the peripheral nervous system, NGF has a similar role of neurotrophic activity related to maintenance and repair.

NGFs role as an important neuroprotective agent is well understood in the literature, in the CNS we find a beneficial effect of NGF on conditions such as Alzheimer's disease. This has been proven in vivo and vitro through NGF's effect on two pathological hallmarks of Alzheimer's disease; beta-amyloid toxicity and tau hyperphosphorylation (Aloe, 2012). It seems from L. Aloe's conclusions that NGF's effect on these two processes takes place as both as a direct anti-amyloidogenic factor regulating amyloid gene expression, protein processing and reducing tau hyperphosphorylation. Although the plaques and tangles are not the causative pathological process in Alzheimer's, they are still deleterious biological ramifications of it. Their presence in the brain is therefore deemed detrimental and when treatment is aimed at reducing them it seems to have beneficial effects.

There is some evidence for the role of the beneficial effect of NGF in the traumatic brain injury of animals and children; it was found that levels of NGF in the cerebrospinal fluid of mTBI (mild traumatic brain injury) patients had a prognostic effect on the outcome (Chiaretti, 2003). Of particular note are two studies where NGF was used to treat children after a hypoxic brain injury. The IV infusion seems to have a positive effect on recovery, however sample sizes are small and the effect of the IV was not

noted (Chiaretti, 2008; Chiaretti, 2005). Further discussion on these studies will be made towards the end of this article.

In the PNS, we find that reduced levels of NGF can cause symptoms of peripheral neuropathy, both animal and human models of disease induced peripheral neuropathy have found deregulation and reduced utilization by PNS neurons (Riaz, 1996). This has led to the hypothesis that NGF could be a causative factor in the peripheral neuropathies associated with diabetes, HIV, and cancer. Experimental studies on diabetic neuropathy have found deficits in NGF transport (Hellweg, 1990) and downregulation of signaling (Purves, 2001), which in animal models have improved with replenishment of NGF (Apfel, 1999; Apfel, 1994). From this information, we can conclude that NGF has an important role—not just in the CNS, but also in the optimal function of the PNS. With particular practical relation to the small diameter sensory fibers where the clinical manifestations of peripheral neuropathy are common, this author believes this to be an exciting area for future studies on compression neuropathies.

NGF: its role in neuroplasticity, neurogenesis and memory

Neuroplasticity can be defined as the ability of the nervous system to respond to either intrinsic or extrinsic stimuli by reorganizing its structure function and connections (Steven, 2011). In short, neuroplasticity is intricately involved in learning, adaptation, and the successful ability to change based on present environmental or psychological events. A concise example of this was demonstrated by a study on rats in which unsuccessful intermale aggressive behavior was monitored. It was found the subordinate rats had high levels of NGF in the subventricular zone and the hippocampus, two areas associated with neuroplasticity and memory. The increased NGF was hypothesized to catalyze neuroplastic adaptation and thus behavior change. Through this mechanism, the rat would remember the preceding events that led up to the unsuccessful interaction. The result being avoidance of further stress associated with loss, so as to protect the CNS from the barrage of glucocorticoids that this would entail (Alleva, 1993; Sapolsky, 1985). This led the authors to the conclusion that the high levels NGF in the subordinate rat caused the idiosyncratic neuroplastic changes, such as formation of dendritic spines and collateral sprouting that are indicative of learning (Alleva, 2001; Alleva, 1989). These changes give us a physical manifestation of the effects of NGF.

Theoretically, NGF is released in high amounts in novel stressful situations in order to allow the dramatic and lasting adaptation of the brain to the previously uncatalogued environmental/psychological stimulus; thus NGF would be integral to learning and adaptation. This can be seen in the study of soldiers performing their first parachute jump and who were found to have high levels of NGF in their blood (Aloe, 1994). It would be interesting to assess the levels of NGF in seasoned soldiers to see if the repetitive exposure to the same stimuli would reduce the need for NGF as the stimulus is no longer novel. It should be noted that the finding of NGF in the blood is not as specific as finding it directly in the brain, as NGF does not cross the blood brain barrier—as we will later see.

Following on from this it leads us to the topic of NGF in psychiatric conditions, and how neuroplasticity, or a lack thereof, may play an important role in the etiology and perhaps further treatment.

Chronic stress, and an inability to create new and more advantageous behavioral patterns, has long been shown to produce patterns of depression and anxiety like behavior which affects the distribution of NGF in animal and human studies (Connor, 1998; Aleva, 1989). Although neurotrophic peptides do not alter mood themselves, they have an important role in learning and adaptation as we have previously mentioned. This ability to adapt to novel situations, respond appropriately, and remember the outcome for future modification or integration into new more advantageous patterns, is the main staple of modern psychotherapeutic techniques such as cognitive behavioral therapy (CBT) as proposed by Dr Beck. This is an interesting area for further research could be levels of NGF in failed and successful CBT candidates.

The hippocampus is one of the most well studied areas of the brain. Anatomically, it is located on the edge of the temporal lobe and considered part of the limbic lobe. Although subcortical in location, it is not considered a subcortical structure (Gilbert, 2009). The hippocampus has been intricately linked with memory ever since the 1970s when an unfortunate patient known as HM with epilepsy had the hippocampus completely removed, and from then on HM was unable to form new episodic memories, essentially locking his existence into perpetual Groundhog Day (Preilowski, 2009). Interestingly, the hippocampus has also been shown to cause retro- and antero-grade amnesia when damaged (Markowitsch, 1985).

One notable characteristic of the hippocampus is its propensity for atrophy under numerous circumstances. This characteristic has been well researched and hippocampal atrophy has been found in depression and anxiety (Boldrini, 2013; Cole, 2011; Kempton, 2011; Frodl, 2007; Bremner, 2000). Atrophy is also used as a marker for deterioration in Alzheimer's disease, with values such as 15–30% reduction in volume corresponding to mild cognitive impairment (MCI) and moderate Alzheimer's up to 50% reduction in volume of the hippocampus (Dhikav, 2011; Frisoni, 2010). Although we are unsure why the hippocampus is so sensitive to atrophy, one particular theory proposes that the production of glucocorticoids under chronic stress may have a direct effect on the cells of the HC (Gilbert, 2009). This is further supported by the reduced size of HC in Cushing's patients who pathologically produce glucocorticoids (Patil, 2021). This glucocorticoid theory would be corroborative of the protective therapeutic use of NGF against chronic stress (facilitating advantageous behavioral change), and thus deleterious effects of glucocorticoids, as previously mentioned. It should also be noted that neurogenesis in the hippocampus has been found to continue far into adult life, supporting the utility of this particular hypothesis (Bonfanti, 2011).

Contemporary attempts to utilize the potential benefits of NGF have been severely hampered due to the neurotrophic peptides structure. Unfortunately, when systemically administered NGF is unable to cross the blood brain barrier (BBB), this has caused major issues with furthering

treatment protocols (Pan, 1998). There have been a number of attempts to bypass the BBB with varying degrees of success. One of the most promising was the application of NGF directly into the ventricles of patients with Alzheimer's disease. Improvements in verbal episodic memory were noted, however cognitive testing did not improve. Most worryingly, there were adverse effects of this method, including weight loss, back pain, and reduced efficacy; this was thought to be in relation to the method of application (Johnagen, 1998; Olsen, 1997). Contemporary work is the being pursued with gene therapy using genetically engineered fibroblasts that secrete NGF which, under clinical testing, have been shown to reduce cognitive decline with negligible long term adverse effects (Tuszynski, 2005; Tuszynski, 2004). Lastly, some novel methods of application are under investigation including intraocular and intranasal applications of NGF.

Presenting Lion's Mane as a potent stimulator of NGF across the blood brain barrier

We will now begin to explore the theoretical and clinical utilization of Lion's Mane as it transmits its effects safely across the blood brain barrier to stimulate NGF production in a number of diverse studies. *Hericium erinaceus* is supplied in a number of safe and non-invasive ways, most commonly as a dried extract capsule or as a tincture. The dosage varies from study to study and from condition to condition.

Firstly, we previously mentioned that four of the 11 hericenones from the fruiting body are of note, hericenones C,D, E, and H. These particular compounds have been shown to increase NGF synthesis in mouse astroglial cells in significant amounts, with hericenone D having similar NGF stimulation profile as the potent molecule used as a control: epinephrine. In the same study, they examined the ability of erinacines to stimulate NGF in a similar way, and interestingly they found that erinacine E and F had an even more potent stimulatory effect on NGF than epinephrine (Kawagishi, 1991). The potency of erinacines to stimulate NGF has been corroborated by the application of erinacine A in rats, which increased the levels of NGF in the hippocampus and locus corrolus significantly (Shimbo, 2005). The importance of these two areas with regard to NGF and neurogenesis has already been explained. Mori et al. (2009) did a further study on four mushrooms including *H. erinaceus*, this time confirming the stimulatory effects of that mushroom on human astrocytoma cell line 1321N1. It is therefore suggested that to reap the full benefits of NGF stimulation, any intervention should contain both the fruiting body and the mycelium. There is some dispute involving the potency of the hericenones compared to erinacines; this was highlighted by Mori (2008) who found that application of hericenones (C, D, and E, but interestingly not H) did not increase NGF mRNA expression.

Considering the protective function of NGF on the CNS, and the ability of *H. erinaceus* to stimulate NGF particularly with regard to the hippocampus, the next studies will be cognitive decline with relation to memory. Alzheimer's disease is a neurodegenerative disease characterized by progressive and often debilitating symptoms of confusion memory loss and profound behavioral changes most commonly occurring in the over 65s age group and having a severe impact on quality of life. Idiosyncratic and progressive biochemical sequalae occur including deficiency of neurotransmitters, reduction in function/death of neural cells and reduction of adult neurogenesis in the hippocampus (Crews, 2010). Two of the most prominent and obvious changes are the tangles of tau and beta amyloid plaques, from the previous statement we know there are in vitro studies that have shown NGF to have a protective effect against the formation of these two processes, this leads us to the work of Tzeng (2016). Tzeng used 5 month-old female APPswe/PS1dE9 transgenic mice and gave them an oral solution of Erinacine A enriched *Hericium erinaceus* 300mg/kg for 30 days. The author found that the solution was able to eliminate amyloid plaque burden, preventing recruitment and activation of plaque associated microglia and astrocytes. It improved the NGF/Pro NGF ratio as well as increased the proliferation of neuron progenitors and newly born neurons in the dentate gyrus.

Nagai (2006) has investigated the correlation between ER stress, neuronal cell death, and the formation of amyloid ß peptide. He found that a substance Dilinoleoyl-phosphatidylethanolamine (DLPE) isolated from *H. erinaceus* was able to reduce ER stress and ß amyloid toxicity. Further study is needed to draw conclusions about this pathway in humans and its relevance to the biochemical pathways in Alzheimer's.

Two studies of interest have investigated the use of *H. erinaceus* on mild cognitive impairment. Mild cognitive impairment is experienced by 15–20% of over 65s and is defined as cognitive changes that are noticeable but not severe enough to have an impact on the individual's ability to live autonomously. The prolific researcher on this subject, Mori (2009) found Lion's Mane had a significantly positive effect on mild cognitive impairment in a double-blind placebo control study on 50- to 80-year-olds. These findings were corroborated by Saitsu et al. (2019) who performed a randomized, double-blind, placebo-controlled RCT on 34 otherwise healthy participants over 50 years old. They used a number of metrics including the mini mental state exam (MMSE), the Benton visual retention test, and the standard verbal paired-associate learning test to measure cognitive function. Saitsu et al. found a significant improvement in the MMSE as well as a prevention in the deterioration of short term memory and this led him to conclude that *H. erinaceus* may help with the regeneration of neural networks in the adult brain. This study parallels our previous assumptions about the effects of NGF on the adult hippocampus.

Depression is a large amorphous clinical condition with multiple etiologies, both physiological and psychological. The exploration of the pathological and clinical intricacies related to depression is far beyond the scope of this paper, however a quick glance through the relevant research will further corroborate our neurogenic and pro-neuroplastic hypothesis of *H. erinaceus*. One neuroanatomic feature of depression which mirrors Alzheimer's is a reduced hippocampal volume (Czéh, 2007). As this has been a target which has functionally improved with treatment targeted at NGF production in other clinical entities, would it be hypothetically possible to have a similar

effect on depressive symptoms? This is exactly what three of the clinical studies have set out to explore. Firstly, Nagano (2010) conducted a randomized, double-blind, placebo-controlled trial across four weeks with 30 females in their 40s. The treatment group took a total 2g of Lion's Mane (fruiting body only) in a series of four cookies. It is interesting that no mycelium was used in this study to utilize more of the potent erinacines. Nagano (2010) used four psychometric tests to measure menopausal, depressive, sleep related and ambiguous symptoms. In this small-scale study, using only female participants of a certain age range, it was found that *H. erinaceus* had a positive effect—not just on anxiety and depression, but also palpitations, which led the author to suggest a possible interaction with the autonomic nervous system.

Following this, a study by Vigna (2019) conducted a study on 77 obese participants, who were assigned a low-calorie diet, with or without *H. erinaceus*. The hypothesis was based around the neurological and biochemical effects of a high fat, high calorie diet and its known effects of systemic inflammation and concomitant low circulating BDNF levels. BDNF is a neurotropic peptide similar in nature to NGF, which has an proposed analogous role in neuroplasticity. Vigna (2019) found that Lion's Mane supplementation improved depressive-anxious type behavior as well as sleep quality. This benefit was maintained eight weeks after cessation of *H. erinaceus*, leading the author to speculate on the neuroplastic effects of Lion's Mane and how they can be maintained long term. This neuroplastic effect and how it can create a lasting change in behavior has been discussed at length in previous paragraphs and strongly corroborates the authors viewpoint.

With relation to studies on mood disorders, Okamura (2015) conducted a small study on eight female students and found an increase in salivatory MHPG post-wakening, as well as a reported reduction in anxious feelings. From this small study it is hard to draw any conclusions, but certainly worth mentioning for future research. Although there is a general paucity of research with *H. erinaceus* and depression, it is an area with legitimate biochemical interest. Hopefully, in the future this interesting mushroom may well have utility with regard to neuroplastic change, neurogenesis and sleep quality.

Lastly, it is prudent to suggest some areas of interest that have not been looked at with regard to Lion's Mane supplementation for future investigation. First and foremost, with NGF's role as a neuroprotective peptide, I would like to draw your attention towards two studies previously mentioned on TBI in children/infants. In these studies, NGF was given directly into the ventricles of children with hypoxic brain injury. The treatment was given in one study 30 days post-TBI, and in a second study, four months post-TBI. These dates, considering the rapid changes in the brain post injury, seem relatively delayed, as well as the aggressive intervention of injecting the NGF in the ventricles. Both studies, however, found a benefit in the measured biochemical markers, and concluded a possible protective effect of NGF supplementation on hypoxic brain injury (Chiaretti, 2008; Chiaetti, 2005). Although the ethics of conducting a study on *H. erinaceus* and TBI in children may be troublesome and costly, an area such as recovery from sport-related concussion could be a fruitful area to conduct future research. Participants would be easy to come by with university sports teams, but one difficulty could be the variable nature of concussions symptoms and its variable recovery pattern. However, psychometric outcome measures such as the SCAT5 coupled with vestibulo-occular testing and balance assessments would be a good place to start to gather quantitative data. Another viable research area could be the use of Lion's Mane on post ischemic stroke patients. *Hericium erinaceus* could be used in order to promote neuroplasticity through NGF and BDNF stimulation causing advantageous rerouting of neurological pathways and increased ability to adapt to the pathological loss of function. This has already been tested on rats by Lee et al. in 2014, who found that the application of erinacine A to post-ischemic stroke rats had a reduction on infarcted area by 22–44%, depending on dosage, proving the neuroprotective effects of erinacines on cell death.

Conclusions

Hericium erinaceus has a number of uses in the CNS which seem to run in close parallel but not in limitation to the effects of NGF. In this author's opinion, Lion's Mane mushroom should be used with both the mycelium and the fruiting body in order to make use of the potency of the erinacines and their strong stimulatory effects. The hypothesis of *H. erinaceus* acting as a centrally acting pro-NGF mediator leading to increased neuroplastic ability as well as reducing neuronal apoptosis through neuroprotective means, seems to be corroborated by a number of different and separate thought processes and clinical studies. Although numerous studies have been undertaken, the number of participants and the population bias means that large scale extrapolation is not advisable as of yet. However, Lion's Mane's diverse effects are exciting for future research.

Acknowledgments

The author wishes to thank the anonymous reviewer for helpful comments.

References Cited

Aloe, L., M. Rocco, P. Bianchi, and L. Manni. 2012. Nerve growth factor: from the early discoveries to the potential clinical use. *Journal of Translational Medicine* 10: 239 doi: 10.1186/1479-5876-10-239.

Alleva, E., and D. Santucci. 2001. Psychosocial vs. "physical" stress situations in rodents and humans: role of neurotrophins. *Physiology and Behavior* 73(3): 313–320.

Alleva, E., and L. Aloe.1989. Physiological roles of NGF in adult rodents: a biobehavioral perspective. *International Journal of Comparative Psychology* 2: 213–230.

Alleva, E., L. Aloe, and S. Bigi. 1993. An updated role for nerve growth factor in neurobehavioral regulation of adult vertebrates. *Reviews in the Neurosciences* 4(1): 41–62.

Aloe, L., L. Bracci-Laudiero, E. Alleva, A. Lambiase, A. Micera, and P. Tirassa. 1994. Emotional stress induced by parachute jumping enhances blood nerve growth factor levels and the distribution of nerve growth factor receptors in lymphocytes. *Proceedings of the National Academy of Science*

USA 91 (22): 10440–10444.
Aoita, Y., K. Danbara, and M. Kikuchi. 2005. Two new aromatic compounds from *Hericium erinaceum* (Bull.: Fr.) PERS. *Chemical and Pharmaceutical Bulletin* 53: 1202–1203.
Apfel, S.C. 1996. Neurotrophic factors in the therapy of diabetic neuropathy. *American Journal of Medicine* 107: 34S–42S.
Apfel, S.C., J. Arezzo, M. Brownlee, H. Federoff, and J. Kessler. 1994. Nerve growth factor administration protects against experimental diabetic sensory neuropathy. *Brain Research* 634: 7–12.
Barde, Y.A., D. Edgar, and H. Thoenen. 1983. New neurotrophic factors. *Annual Review Physiology* 45: 601–612.
Barde, Y.A., D. Edgar, and H. Thoenen. 1982. Purification of a new neurotrophic factor from mammalian brain. *EMBO Journal* 1(5): 549–553.
Boldrini, M., A. Santiago, R, Hen, A. Dwork, G. Rosoklija, H. Tamir, V. Arango, and M. John. 2013. Hippocampal granule neuron number and dentate gyrus volume in antidepressant-treated and untreated major depression. *Neuropsychopharmacology* 38(6): 1068–1077.
Bonfanti, L., and P. Peretto. 2011. Adult neurogenesis in mammals—a theme with many variations. *European Journal of Neuroscience* 34: 930–950.
Bremner, J.D., M. Narayan, E. Anderson, L. Staib, H. Miller, and D. Charney. 2000. Hippocampal volume reduction in major depression. *American Journal of Psychiatry* 157(1): 115–118.
Chiaretti, A., A. Antonelli, O. Genovese, E. Fernandez, D. Giuda, P. Mariotti, and R. Riccardi. 2008. Intraventricular nerve growth factor infusion improves cerebral blood flow and stimulates doublecortin expression in two infants with hypoxic-ischemic brain injury. *Neurological Research* 30: 223–228.
Chiaretti, A., M. Piastra, G. Polidori, C. Di Rocco, E. Caresta, A. Antonelli, T. Amendola, and L. Aloe. 2003. Correlation between neurotrophic factor expression and outcome of children with severe traumatic brain injury. *Intensive Care Medicine* 29: 1329–1338.
Chiaretti, A., O. Genovese, R. Riccardi, C. Di Rocco, D. Di Giuda, P. Mariotti, S. Pulitano, M. Piastra, G. Polidori, G. Colafati, and L. Aloe. 2005. Intraventricular nerve growth factor infusion: a possible treatment for neurological deficits following hypoxic-ischemic brain injury in infants. *Neurological Research* 27: 741–746.
Chen, Z.Y., R. Yan, G. Qin, and L. Qin. 1987.Effect of six edible plants on the development of AFB1-induced gamma-glutamyltranspeptidase-positive hepatocyte foci in rats. *Zhonghua ZhongLiu ZaZhi* 9(2): 109–111.
Cohen, S., R. Levi-Montalcini, and V.A. Hamburger. 1954. Nerve growth-stimulating factor isolated from sarcomas 37 and 180. *Proceedings of the National Academy Science USA* 40(10): 1014–1018.
Cole, J., S. Costafreda, P. McGuffin, and C. Fu. 2011. Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. *Journal of Affective Disorders* 134(1–3): 483–487.
Connor, B., and M. Dragunow. 1998. The role of neuronal growth factors in neurodegenerative disorders of the human brain. *Brain Research Reviews* 27(1): 1–39.
Cramer, S.C., M. Sur, B. Dobkin, C. O'Brien, T. Sanger, J. Trojanowski, J. Rumsey, R. Hicks, J. Cameron, D. Chen, W. Chen, L. Cohen, C. deCharms, C. Duffy, G. Eden, E. Fetz, R. Filart, M. Freund, S. Grant, S. Haber, P. Kalivas, B. Kolb, A. Kramer, M. Lynch, H. Mayberg, P. McQuillen, R. Nitkin, A. Pascual-Leone, P. Reuter-Lorenz, N. Schiff, A. Sharma, L. Shekim, M. Stryker, E. Sullivan, and S. Vinogradov. 2011. Harnessing neuroplasticity for clinical applications. *Brain* 134(6): 1591–1609.
Crews, L., and E. Masliah. 2010. Molecular mechanisms of neurodegeneration in Alzheimer's disease. *Human Molecular Genetics* 19: 12–20.
Czéh, B., and P. Lucassen. 2007. What causes the hippocampal volume decrease in depression? *European Archive Psychiatry Clinical Neuroscience* 257: 250–260.
Dhikav, V., and K. Anand. 2011. Potential predictors of hippocampal atrophy in Alzheimer's disease. *Drugs and Aging* 28: 1–11.
Frisoni, G.B., N. Fox, C. Jack, P. Scheltens, and P. Thompson. 2010. The clinical use of structural MRI in Alzheimer disease. *National Review of Neurology* 6: 67–77.
Frodl, T., C. Schüle, G. Schmitt, C. Born, T. Baghai, P. Zill, R. Bottlender, R. Rupprecht, B. Bondy, M. Reiser, H. Möller, and E. Meisenzahl. 2007. Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Archives of General Psychiatry* 64(4): 410–416.
Gilbert, P.E., and A. Brushfield. 2009. The role of the CA3 hippocampal subregion in spatial memory: a process oriented behavioral assessment. *Progress in Neuro-psychopharmacology and Biology Psychiatry* 2009(33): 774–781.
Hellweg, R., and H. Hartung. 1990. Endogenous levels of nerve growth factor (NGF) are altered in experimental diabetes mellitus: a possible role for NGF in the pathogenesis of diabetic neuropathy. *Journal of Neuroscience Research* 26: 258–267.
https://www.woodlandtrust.org.uk/trees-woods-and-wildlife/fungi-and-lichens/bearded-tooth/ accessed March 1, 2021.
I-Chen, Li., L. Li-Ya, T. Tsai-Teng, C. Wan-Ping, C. Yen-Po, S. Young-Ju, and C. Chin-Chu. 2018. Neurohealth properties of *Hericium erinaceus* mycelia enriched with erinacines. *Behavioral Neurology* doi.org/10.1155/2018/580263.
Jonhagen, E.M., A. Nordberg, K. Amberla, L. Backman, T. Ebendal, B. Meyerson, L. Seiger, M. Shigeta, E.Theodorsson, M. Viitanen, B. Winblad, and L. Wahlund. 1998. Intracerebroventricular infusion of nerve growth factor in three patients with Alzheimer's disease. *Dementia and Geriatrics Cognitive Disorders* (5): 246–257.
Kawagishi, H., M. Ando, H. Sakamoto, S. Yoshida, F. Ojima, Y. Ishiguro, N. Ukai, and S. Furukawa. 1991. Hericenones C, D and E, stimulators of nerve growth factor (NGF)-synthesis, from the mushroom *Hericium erinaceus*. *Tetrahedron Letters* 32: 4561–4564.
Kempton, M.J., Z. Salvador, M. Munafo, J. Geddes, A. Simmons, S. Frangou, and S. Williams. 2011. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Archives of General Psychiatry* 68: 675–690.
Lee, K.F., J. Chen, C. Teng, C. Shen, M. Hsieh, C. Lu, K. Lee, L. Lee, W. Chen, C. Chen, W. Huang, and H. Kua.

2014. Protective effects of *Hericium erinaceus* mycelium and its isolated erinacine against ischemia-injury-induced neuronal cell death via the inhibition of iNOS/p38 MAPK and nitrotyrosine. *International Journal Molecular Science* 15: 15073–15089.

Liu, C., P. Gao, J. Qian, and W. Yan. 2000. Immunological study on the antitumor effects of fungus polysaccharides compounds. *WeiSheng YanJiu* 29(3): 178–180.

Ma, B.J., J.W Shen, H.Y. Yu, Y. Ruan, T.T. Wu, and X. Zhao. 2010. Hericenones and erinacines: stimulators of nerve growth factor (NGF) biosynthesis in *Hericium erinaceus*. *Mycology* 1(2): 92–98.

Markowitsch, H.J., and M. Pritzel. 1985. The neuropathology of amnesia. *Progressive Neurobiology* 25: 189–287.

Misko, T.P., M.J. Radeke, and E.M. Shooter. 1987. Nerve growth factor in neuronal development and maintenance. *Journal of Experimental Biology* 132: 177–190.

Mori, K., Y. Obara, M. Hirota, Y. Azumi, S. Kinnugasa, S. Inatomi, N. Nakahata. 2008. Nerve growth factor-inducing activity of *Hericium erinaceus* in 1321N1 human astrocytoma cells. *Biological and Pharmaceutical Bulletin* 9: 1727–1732.

Nagai, K., A. Chiba, T. Nishino, T. Kubota, and H. Kawagishi. 2006. Dilinoleoyl-phosphatidylethanolamine from *Hericium erinaceus* protects against ER stress-dependent Neuronal cell death via protein kinase C pathway. *Journal Nutritional Biochemistry* 17: 525–530.

Nagano, M., K. Shimizu, R. Kondo, C. Hayashi, D. Sato, K. Kitagawa, and K. Ohnuki. 2010. Reduction of depression and anxiety by 4 weeks *Hericium erinaceus* intake. *Biomedical Research* 31(4): 231–237.

Olson, L., A. Nordberg, H. von Holst, L. Backman, T. Ebendal, I. Alafuzoff, K. Amberla, P. Hartvig, A. Herlitz, and A. Lilja. 1992. Nerve growth factor affects 11C-nicotine binding, blood flow, EEG, and verbal episodic memory in an Alzheimer patient (case report). *Journal of Neural Transmisson, Parkinson and Dementia section* 4(1): 79–95.

Patil, C.G., S. Lad, L. Katznelson, and E. Laws. 2007. Brain atrophy and cognitive deficits in Cushing's disease. *Neurosurgical Focus* 23(3): E11 doi:10.3171/foc.2007.23.3.13.

Pan, W., W. Banks, and A. Kastin. 1998. Permeability of the blood–brain barrier to neurotrophins. *Brain Research* 788: 87–94.

Preilowski, B. 2009. Remembering an amnesic patient (and half a century of memory research). *Fortschritte Neurologie Psychiatrie* 77: 568–576.

Purves, T., A. Middlemas, S. Agthong, E. Jude, A. Boulton, P. Fernyhough, and D. Tomlinson. 2001. A role for mitogen-activated protein kinases in the etiology of diabetic neuropathy. *FASEB Journal* 15: 2508–2514.

Riaz, S.S., and D. Tomlinson. 1996. Neurotrophic factors in peripheral neuropathies: pharmacological strategies. *Progress in Neurobiology* 49: 125–143.

Saitsu, Y., A. Nishide, K. Kikushima, K. Shimizu, and K. Ohnuki. 2019. Improvement of cognitive functions by oral intake of *Hericium erinaceus*. *Biomedical Research* 40(4): 125–131.

Sapolsky, R.M., L. Krey, and B. McEwen. 1985. Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. *Journal of Neuroscience* 5(5): 1222–1227.

Shimbo, M., H. Kawagishi, and H. Yokogoshi. 2005. Erinacine A increases catecholamine and nerve growth factor content in the central nervous system of rats. *Nutrition Research* 25: 617–623.

Tuszynski, M.H., L. Thal, M. Pay, D. Salmon, H. Sang, R. Bakay, P. Patel, A. Blesch, H. Vahlsing, G. Ho, G. Tong, S. Potkin, J. Fallon, L. Hansen, E. Mufson, J. Kordower, C. Gall, and J.Conner. 2005. A phase 1 clinical trial of nerve growth factor gene therapy for Alzheimer's disease. *Nature Medicine* 11(5): 551–555.

Tuszynski, M.H., and A. Blesch. 2004. Nerve growth factor: from animal models of cholinergic neuronal degeneration to gene therapy in Alzheimer's disease. *Progress in Brain Research* 146: 441–449.

Tsai-Teng, T., C. Chin-Chu , L. Li-Ya, C. Wan-Ping, L. Chung-Kuang, S. Chien-Chang, H. Chi-Ying, C. Chien-Chih, and Y. Shiao. 2016. Erinacine A-enriched Hericium erinaceus mycelium ameliorates Alzheimer's disease-related pathologies in APPswe/PS1dE9 transgenic mice. *Journal of Biomedical Science*. 23(1): 49.

Vigna, L., F. Morelli, G. Agnelli, F. Napolitano, D. Ratto, A. Occhinegro, and P. Rossi. 2019. *Hericium erinaceus* improves mood and sleep disorders in patients affected by overweight or obesity: could circulating pro-BDNF and BDNF be potential biomarkers? Evidence-Based Complementary and Alternative Medicine 2019: 1–12.

Wang, J.C., S. Hu, W. Lee, and L. Tsai. 2001. Antimutagenicity of extracts of Hericium erinaceus. *Kaohsiung Journal of Medical Sciences* 17(5): 230–238.

Wiesmann, C., and A. de Vos. 2001. Nerve growth factor: structure and function. *Cellular and Molecular Life Science* 58: 748–759.

Xu, H.M., Z. Xie, and W. Zhang. 1994. Immunomodulatory function of polysaccharide of *Hericium erinaceus*. *Chinese Journal of Integrated Traditional and Western Medicine* 14(7): 427–428.

Yi, Z., Y. Shao-Long, W. Ai-Hong, S. Zhi-Chun, Z. Ya-Fen, X. Ye-Ting, and H. Yu-Ling. 2015. Protective effect of ethanol extracts of *Hericium erinaceus* on alloxan-induced diabetic neuropathic pain in rats. *Evidence-based Complementary and Alternative Medicine* 215(2): 1–5.