Don't Ergo the Ergots (or don't overlook the benefits of the rye fungi) by Robert Mason PhD

Ergoloid mesylates, co-dergocrine, dihydroergotoxine, are all a number of ergot derivatives that share a common ancestry, because they all derive from a type of fungi that can be found on rye.

This article evaluates 3 of the most proven and commercially used ergots and seeing how they differ from one another. In alphabetical order, they are bromocriptine (pronounced brome-o-cript-teen), hydergine ® and nicergoline.

Bromocriptine- the most potent ergot

This semisynthetic derivative of the ergo group of ergot alkaloids is a dopamine receptor agonist (for those who like precise detail it is a potent D2 agonist but also displays partial action on D1 receptors) and a prolactin inhibitor, (see figure one).

Its first major anti-aging use is the enhancement of dopamine, (a key brain neurotransmitter that undergoes an age-related decline). Past the age of 40 it is estimated that "on-average" the healthy person undergoes a dopamine decline of approximately 13% per decade (Ward, Fowkes & Morgenthaler) & [Ed.- see chart in the deprenyl article of this issue]. Accordingly, some neurologists have stated that "if we all live long enough we shall all become senile." This is due to the fact that abnormally low levels of dopamine (70% to 80% loss) are then diagnosed as Parkinson's disease, hence protection and enhancement of the dopamine producing neurons is a key strategy for anti-aging medicine. Not surprisingly then, bromocriptine is used in conjunction with other drugs (such as deprenyl and L-dopa) in the management of Parkinson's disease, but anti-aging medicine considers its preventative properties too.

Its second major anti-aging use is the inhibition of prolactin, this hormone is one of the few that actually appears to increase with age (see figure 2). Prolactin is produced by the pituitary gland and its release is inhibited by bromocriptine.

Prolactin has been described as a "fat synthesis hormone" because one of its primary functions is to trigger lactation (milk production) and weight gain in pregnancy. In women, bromocriptine has been used to help restore ovulation (the process by which this action occurs is too complex to explain for this small article) but it also helps to reduce serum prolactin levels in men (although the precise role of prolactin in men is

unclear).

A further possible need to control age-related prolactin levels is offered by some researchers who believe that prolactin is an immune system suppressant.

Bromocriptine also affects the most famous of all pituitary hormones- growth hormone (GH). Bromocriptine increases growth hormone secretion in individuals with normal growth hormone concentrations, but paradoxically suppresses GH secretion in some patients with acromegaly (a condition of excessive-production of GH). Studies indicate that bromocriptine does not affect the release of any other anterior pituitary hormones.

Due to its dopamine enhancement bromocriptine has even been cited as an aphrodisiac, although little effort has been made to study and confirm this action. There have been several reports of "better controlled" orgasms and "almost orgasms" before the real orgasm occurs. If any countries allow for more medical categories such as "weak orgasm syndrome" or perhaps "clinical sex-drive loss" then dopamine agonists such as bromocriptine are going to receive a lot of attention from the pharmaceutical manufacturers, especially in the wake of Viagra ® sales.

Another interesting clinical study administered a component of tobacco called DMBA to rats at a level where it is known to be very effective in producing breast cancer. However, rats that had been pretreated with bromocriptine completely avoided any cancer development. Bromocriptine therefore appears to also offer itself as a very potent free radical quencher.

One of the most recent studies indicates that bromocriptine may be a candidate for the treatment of Type-2 diabetes. This is because bromocriptine has been shown to suppress lipogenesis and improve glucose tolerance and insulin resistance.

One animal study suggested that a further action of bromocriptine is to alter CNS (central nervous system) regulating metabolism and as such has another important use in helping to prevent weight gain (this would be in addition to its improvement of diabetic conditions).

Dosages, Side Effects and Contraindications

Bromocriptine is a very potent substance and it mustn't be used by pregnant or lactating women unless under the guidance of a physician. Side effects include nausea, dizziness, lowering of blood pressure, hypotension and confusion. The first three are relatively

common, especially when undertaking initial use. It is also known to increase fertility, and thus "extra care" and contraception is advised where necessary.

It does contraindicate with psychoactive and hypotensive drugs and other dopamine enhancing drugs (such as deprenyl and L-dopa etc) should only be administered concurrently under a physician's guidance. Its effects can also be exaggerated when combined with other ergots including hydergine ® and nicergoline.

Overall, there is little need to exceed a dosage in excess of 1.25mg or 2.5mg daily for most people unless treating a serious medical disorder (and therefore only under a physician's guidance). Bromocriptine has a wide and diverse range of clinically applications, it should be considered to only be an anti-aging medicine for the serious longevist.

Hydergine ®- the most popular ergot

Now we move onto one of the most popular and widely used smart-drugs that has been in use for over 40-years- Hydergine ® (pronounced hi-der-gene). See figure 3.

Hydergine ® has received only "mild" reviews whilst being used to treat senile dementias, (although it is widely regarded to have been used in dosages that were far too small for those purposes). However, hydergine ® presents itself as a remarkable anti-aging medicine and a adjunct for the treatment of age-related mental decline.

Hydergine ® is known to have all the following effects:

1. Increase blood supply to the brain.
2. Increase oxygen delivered to the brain.
3. Enhance metabolism of brain cells.
4. Protect the brain from insufficient oxygen supply.
5. Slow the deposit of the age pigment lipofuscin in the brain.
6. Prevent free radical damage to brain cells.
7. Increase intelligence, memory, learning and recall.

Oxygen is unique in that it is both a free radical generator and a free radical scavenger. At optimum concentrations, oxygen neutralizes more free radicals than it produces. Either too much or too little can upset the balance and generate the production of free radicals, which in turn can lead to aging. One of the major ways in which oxygen

generates free radicals is its reaction with unsaturated fats, a process called peroxidation.

Unfortunately, our brain cells contain more unsaturated fats than any other part of the body, therefore it is our brains that are most susceptible to peroxidation. Here are some conditions that can cause major peroxidation and the formation of massive amounts of potent free radicals:

1. Heart attack.
2. Stroke.
3. Pollution (Carbon monoxide greatly reduces the oxygen carrying ability of the blood).
4. Smoking cigarettes (Nicotine constricts blood vessels and decreases oxygen supply to the brain. It is estimated that those who smoke more than 20 cigarettes a day lose at least 7% of the normal blood flow to the brain).

Some European countries use hydergine ® for emergencies and accidents that involve shock, hemorrhage, strokes, heart attacks, drowning, electrocution and drug over-dose. Hospitals give hydergine ® to patients before an operation in order to gain time in case of any ensuing crises. This is because hydergine ® helps to stabilize brain oxygen levels, if they are too high hydergine ® lowers them, if they are too low then hydergine ® improves them. This was graphically illustrated in a cat experiment.

Two groups of cats were anaesthetized and their brains electronically monitored. The scientists reduced the brain's blood supply (and therefore oxygen supply). The cats in the control group (i.e. no hydergine ®) had brain damage within 5-minutes and died within 15-minutes. However, the cats in the pre-hydergine ® treated group had strong brain wave patterns up to 45-minutes later. This experiment proved two things, firstly that a decrease in the normal oxygen balance results in tremendous free radical damage and secondly that hydergine ® protects against this free radical damage when the oxygen level is upset.

Hydergine ® has also been shown to increase the level of neurotransmitters in the brain, whilst this may not be significant enough for the treatment of senile dementia, such action has implications and benefits for the treatment and prevention of age-related mental decline.

There is also evidence that Hydergine ® stimulates the growth of dendrite nerve fibers.

Dendrites can normally be expected to decline with aging and some scientists have associated the number and density of dendrites with intelligence (see figure 4).

This decrease in brain cell connection has been hypothesized to be due to an impairment in the energy supply at synaptic regions. Because of hydergine ®'s known ability to improve nerve cell metabolism, a group of Italian scientists studied the ultra-cellular features of synaptic mitochondria to see if long-term hydergine ® treatment could delay or prevent the loss of synaptic connections.

The mitochondria are the "intracellular powerhouses" where the universal energy molecule- ATP (adenosine triphosphate) is produced (see figure 5). The scientists found that the number of mitochondria are greatest at about 12-months of age in rats (equivilant to a 25-year old in human terms) and then progressively decreases. However, the size of the mitochondria increased progressively after 12 months. Thus in young adult rats, the energy required at synaptic regions is provided by a large number of small, highly efficient mitochondria, whereas in old rats, energy is produced by a smaller number of larger, less efficient mitochondria.

But, astonishingly after treatment with hydergine ®, it can be seen that the total mitochondrial volume of old rats was nearly the same as the young rats. Furthermore, the mitochondrial size was altered to a more youthful direction (these results can be seen in the figures 6 and 7).

Like its ergot relatives, hydergine ® has also shown itself to be a mild vasodilator (it enhances brain blood flow) and improves the uptake of the brain energy molecule-glucose. Hydergine ® also reduces the accumulation of the age-related toxin, lipofuscin.

Time and again, clinical trials indicate that hydergine ® can improve cognitive functions, mental alertness, clarity and mood.

Hydergine ®, Dosages, Side Effects and Contraindications

With literally thousands of published clinical research papers and hydergine ®'s decades of use around the world, it has proven itself to be nontoxic and relatively safe. Its potential side effects include mild nausea, gastric disturbances and bradycardia. It should be avoided by people who suffer from psychosis, or those with low blood pressure or abnormally slow heartbeat. Seek a health professional's advice if combining hydergine ® (at dosages in excess of 9mg per day) with other ergot derivatives or

vasodilators.

Most people do well at dosages of around 2.25mg to 4.5mg per day with occasional breaks. The most common side effect of stomach upset can be avoided with the use of specially coated tablets (known as FAS) or sublingual liquid versions.

With its beneficial affects, mild side effects and few contraindications, hydergine ® is ranked as one of the most important anti-aging medicines available today.

Nicergoline- the latest ergot derivative

Nicergoline (pronounced nice-er-go-lean) is perhaps the latest commercially available variation of all the ergot preparations. It has become most popular in Japan and indeed many of its clinical trials have been performed there.

Nicergoline appears to be a potent vasodilator (improving brain blood flow). On the cerebral level it prompts a lowering of vascular resistance, an increase in arterial flow and stimulates the use of oxygen and glucose. However, clinical trials confirm that nicergoline also improves blood circulation in the lungs and limbs and that blood platelet aggregation is inhibited.

Studies also indicate that nicergoline does not affect arterial tension and that in cases of patients suffering from hypertension, it may induce a gradual lowering of the tension.

Its approved uses to date have therefore included all of the following:

1. Migraines (of vascular origin).
2. Platelet aggregability and arterial hypertension.
3. Eye disorders (retinal thromboses, diabetic retinopathy and macular degeneration).
4. Problems of a vascular nature (dizziness, auditory problems, hypoacusis).
5. Treatment of senile dementias.

One interesting Japanese clinical study on rats showed that nicergoline increases nerve growth factor in the brains of aged animals, but it shows no statistical affect upon the brains of young animals!

Further studies indicate that nicergoline can enhance glutamate re-uptake and protect the brain against ischaemia (lack of blood flow). This appears to be the main action of

nicergoline and it presents itself as a mild stimulant and enhancer with long-term protection against brain disorders that may be due to blood, glucose or oxygen deprivation.

Nicergoline- dosages, side effects and contraindications

Side effects are usually limited to nausea, hot flushes, mild gastric upset, hypotension and dizziness. At high dosages bradycardia, increased appetite, agitation, diarrhea and perspiration have been known to present themselves.

Persons suffering from acute bleeding, myocardial infarction or bradycardia should avoid nicergoline use. Persons using alpha or beta receptor agonists (such as propranolol/ Inderal ®) should not take nicergoline concurrently as nicergoline is known to enhance the cardiac depressive effects. Nicergoline is also known to heighten the effects of pharmaceutical products that produce hypotension, such as other ergot preparations in high doses (i.e. hydergine ® and bromocriptine).

Although not stated by the manufacturer, other potent vasodilatation agents such as vinpocetine, xanthinol nicotinate or picamilone should only be used concurrently under the guidance of a physician.

Dosages for known conditions are usually administered at 5-10mg three times a day, however anti-aging preventative purposes may want to consider 5mg once or twice a day more adequate.

Conclusion

These three ergot preparations are all related and yet we can see their differences in the results of their various clinical studies. Each have differing strengths of reaction and indeed different effects.

Fungi's from rye were used by our ancestors for many different reasons, some of them as rites of passage into adulthood, most were considered to be "mind-expanding." Now we know many of the pharmacological actions and roles they play in mental and memory enhancement and in the slowing of age-related brain disorders.

Today, we understand that brain protection and enhancement is a most important factor- if not the most important factor for anti-aging medicine and successful longevity.

References

Bromocriptine:

1. "DMBA induced tumors in rats treated with Bromocryptine" Trends in Pharmacological Sciences March 1981.
2. Carter C, "Hormones and Sexual Behavior" Dowden Hutchinson & Ross 1974.
3. Debono, "Bromocryptine and Dopamine Receptor Stimulation" British Clinical Pharmacol 3: 977- 982 1976.
4. DeMartino M, "Sex and the intelligent women" Springer Publishing Co 1974.
5. Parlodel drug insert, November 2000, Novartis.
6. Luo S, Hodge J, Castro S, Cincotta A, "The Anti-Diabetic Effects of Bromocriptine Effectively Mediated via Intracerebroventricular Administration" Ergo Science, Boston, MA, USA.
7. Yanagisawa N, Kanazawa I, Goto I, et al, "Seven year follow-up study of bromocriptine therapy for Parkinson's disease" European Neurology 1994: 34 (suppl. 3): 29-35.
8. Medscape Drug Info, "Bromocriptine mesylate oral pharmacology and chemistry" Dec. 2000.

Hydergine ®:

1. Emmenhegger H, Meier Ruge W, " The actions of Hydergine ® on the brain" Pharmacology (1968) 1:65-78.
2. Boismare F, "Biochemical and behavioral effects of hypoxic hypoxia in rats, study of the protection afforded by Hydergine ®" Gerontology (1978) 24, No 1 6- 13.
3. Boula G, "Effects of Dihydroerogotoxine mesylate on aging neurons in vitro" Gerontology (1978) 24: 66- 70.
4. Cahn J, Borzeix M, "Aging and Hypertension as risk membranes." Aging (1983) 23: 413- 425.
5. Ditch M, "An ergot preparation in the treatment of Cerebrovascular disorders in the geriatric patient" Journal of the American Geriatrics society (1971) 19 No 3 208- 217.
6. Sandoz Inc., "Hydergine ®" Manufacturers product information sheet (1999)
7. Hughes J, "An ergot alkaloid preparation in the treatment of dementia" Journal of the American Geriatric society (1976) 24 490- 497.
8. Yoshilawa M, "A dose response study with dihydroergotoxine mesylate in

cerebrovascular disturbances" Journal of the American Geriatric Society (1983) 31 1 1-7.
9. Cranton M: Franckelton J: "Treatment of Free Radical Pathology in chronic degenerative diseases with EDT chelation therapy" Journal of Holistic Medicine (1984) 6-1.
10. Pearson D: Shaw S: "Life Extension" Warner books, New York (1982).
11. Copeland R: "Behavioural and Neuro chemical effects of Hydergine ® in rats" Archives of International Pharmacodynamics (1981) 252: 113- 123.
12. Rao B: Norris J: "A double blind investigation of Hydergine ® in the treatment of cerebrovascular insufficiency in the elderly." John Hopkins Medical Journal (1971) 130 317- 323.
13. Weil C, "Pharmacology and clinical pharmacology of Hydergine ®" Handbook of experimental Pharmacology (1978) Springer Verlag New York.
14. Fanchamps A, "Dihydroergotoxine in senile cerebral insufficiency" Aging (1983) 23 311- 322.
15. Hindmarch I, "The effects of an ergot alkaloid derivative on aspects of psychomotor performance" The journal of clinical pharmacology (1979) 726- 731.
16. Speigel R, "A controlled long term study with Hydergine ®, in healthy elderly volunteers" Journal of the American Geriatrics society (1983) 31, No 9 549- 555.
17. Yesavarage J, "Dihydroergotoxine 6mg v 3mg dosage in the treatment of senile dementia" Journal of the American Geriatric Society (1979) No 2 80-82.
18. Dean W, "Hydergine ®, potential anti-aging drug still highly recommended" Anti-Aging Bulletin, Volume 3 Issue 4, Spring 1998, International Anti-Aging Systems.
19. Bertoni-Freddari C, Fattoretti P, Casoli T, Spanga C, Meier-Ruge W, "Morphological alterations od synaptic mitochondria during aging- the effect of hydergine ® treatment in the pharmacology of the aging process- methods of assessment and potential interventions." New York Academy of Sciences, Volume 717 by Imre. Zs.-Nagy and Kenichi Kitani eds.) NYAS, NY 1994.
20. Cucinotta D, DeLeo D, Frattola L, Trabucchi M, Parnetti L, "Dihydroergokryptine vs. placebo in dementia of Alzheimer type: Interim study after a 1 year follow up." Archives of Gerontology and Geriatrics, 22, 169-180 (1996).

Nicergoline:

1. Bernd Saletu, et al, "Nicergoline in senile dementia of Alzheimer type and multi-infarct dementia: A double blind, placebo controlled, clinical and EEG/ ERP mapping study." Pharmacia & Upjohn

2. Nicergoline drug insert, Pharmacia & Upjohn, October 2000.
3. Asai S, Zhao H, Yamashita A, Jike T, Kunimatsu T, Nagata T, Kohno T, Ishikawa K, "Nicergoline enhances glutamate re-uptake and protects against brain damage in rat global brain ischaemia." European Journal Pharmacology 1999 Nov 3: 3;383(3):267-74.
4. Takeshi N, Nobuhiko S, Shoei F, Ichiro A, Yukitsuka K, "Repeated injections of nicergoline increase the nerve growth factor level in the aged rat brain." Japanese Journal Pharmacology, 76 (3), 321-323 (1998).
5. Iliff L, DuBoulay GH, Marshall J, et al, "Effect of nicergoline on cerebral blood flow." Journal Neurol. Neurosurg. Psychiatry, 1977, 40:746-7.