How to Increase Intelligence by Increasing Cerebral blood flow: can a pill do it?

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Introduction:
• Function of organs increase as blood flow increases.
• Hyper-perfusion of the stomach and liver induces increase in gastric secretion and motility and liver production of bile and clearance of BSP.
• Areas of the brain in use increase blood flow demonstrated by PET. Vision illuminates posterior lobe.

PET AND BRAIN PERFUSION

Disclosures
• PATENTS IN BOLTON AND ST GEORGE

Introduction:
• Perfusion of the brain increases during learning, as the student becomes an expert, number of neurons needed decrease and perfusion drops.
• Hyperperfusion, as can be detected by TCD, PET, Perfusion CT scan and MRI can produce edema and even bleeding. (Hyper-perfusion Syndrome) when auto-regulation is not functioning properly (carotid stenosis for instance)
• Three substances have been identified to increase perfusion without producing edema simvastatin, persantin and cylostazol. Substances action is through nitric oxide (NO)-dependent vascular effects by increasing CBF.
Kim, Hyung-Hwan; Sawada, Naoki; Soydan, Guray; Lee, Ho-Seong; Zhou, Zhipeng; Hwang, Seo-Kyoung; Waeber, Christian; Moskowitz, Michael A.; Liao, James, K., 2008: Additive effects of statin and dipyridamole on cerebral blood flow and stroke protection. Journal of Cerebral Blood Flow and Metabolism 28(7): 1285-1293

Recent studies suggest that dipyridamole (DP) may exert stroke protective effects beyond platelet inhibition. The purpose of this study is to determine whether statin and DP could enhance stroke protection through nitric oxide (NO)-dependent vascular effects. Mice were pretreated with DP (10 to 60 mg/kg, q 12h, 3 days) alone or in combination with a statin (simvastatin; 0.1 to 20 mg/kg per day, 14 days) before transient intraluminal middle cerebral artery occlusion. Although simvastatin (1 mg/kg per day, 14 days) increased endothelial NO synthase (eNOS) activity by 25% and DP (30 mg/kg, q12 h, 3 days) increased aortic cGMP levels by 55%, neither statin nor DP alone, at these subtherapeutic doses, increased absolute cerebral blood flow (CBF) or conferred stroke protection. However, the combination of subtherapeutic doses of simvastatin and DP increased CBF by 50%, and improved neurologic motor deficits, all of which were absent in eNOS-deficient mice. These findings indicate that statin and DP exert additive NO-dependent vascular effects and suggest that the combination of CILOSTAZOL

It is well-established that hypertension leads to endothelial dysfunction in the cerebral artery.

Recently, cilostazol has been used for the secondary prevention of ischemic stroke. Among antiplatelet drugs,

phosphodiesterase inhibitors including cilostazol have been shown to have protective effects on endothelial cells

To assess the contribution of eNOS in maintaining cerebral blood flow, the authors monitored cerebral blood flow by laser-Doppler flowmetry after L-NS-(1-iminoethyl)ornithine infusion. Additionally, they evaluated residual microperfusion using fluorescence-labeled serum protein and infarct size after transient focal brain ischemia. (Stroke. 2011;42:2571-2577)

CILOSTAZOL

The aim of the study was to investigate the effects of cilostazol on endothelial nitric oxide synthase (eNOS) phosphorylation in the cerebral cortex, endothelial function, and infarct size after brain ischemia in spontaneously hypertensive rats (SHR).

Methods—Five-week-old male SHR received a 5-week regimen of chow containing 0.1% cilostazol, 0.3% cilostazol, or the vehicle control.

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Protective effects of statins have been well documented for stroke therapy.

Here, we used a systematic review and meta-analysis to assess these evidences. We identified 190 studies using statin treatment in stroke animal models by electronic searching. From those, only studies describing ischemic occlusive stroke and reporting data on infarct volume and/or neurological outcome were included in the analysis (41 publications, 1882 animals). Statins reduced infarct volume by 25.12% (20.66%–29.58%, P < 0.001) and consistently, induced an improvement on neurological outcome (20.36% (14.17%–26.56%), P < 0.001). Stratified analysis showed that simvastatin had the greatest effect on infarct volume reduction (23.54%), whereas bigger infarct reduction was observed giving the statin as a pre-treatment (33.3%) compared with post-treatment (16.02%).

In conclusion, this meta-analysis provides further evidences of the efficacy of statins, supporting their potential use for human stroke therapy.
Treating with cilostazol, but not aspirin, significantly improved cerebral blood flow response to L-N5-(1-iminoethyl)ornithine. Cilostazol also increased residual perfusion of the microcirculation and reduced brain damage after ischemia compared to vehicle control and aspirin. Conclusions—These findings indicate that cilostazol, but not aspirin, can attenuate ischemic brain injury by maintaining endothelial function in the cerebral cortex of SHR.

Hypothesis:

• Increase of brain perfusion can increase brain function, including cognitive function.
• In order to prove the hypothesis an experimental study in rats has been performed repeating a previous experience, but in addition learning skills were assessed using the labyrinth method and the maze testing after giving the medication to the animals for three weeks.
• Preliminary humans studies were initiated.

Hypothesis:

• Study in rats: included 30 rats (15 control) in which we used the combination of subtherapeutic concentrations of DP (30 mg/kg per day, 3 days orally) and simvastatin (1 mg/kg per day, 21 days, injected subcutaneously)
• In a previous study in rats, after 21 days, treatment increased absolute CBF by 50%±6% (n=8, P = 0.02).

Preliminary Studies

• 30 young rats were studied, 15 had injections of Simvastatin and oral administration of Persantin, 15 rats received placebo.
• Previous studies showed an increase in CBF of 50 % as an average.
• Labyrinth and Maze test showed that treated animals learnt 1.7 (ST.D: 0.3) times faster that control rats

Humans studies

• After Ethical Committee aproval and informed consent, 9 normal subjects were included in the study until now.
• Cerebral blood flow was calculated using TCD monitoring.
• Cognitive studies were conducted before starting the treatment.
Cerebral blood flow measurement

- Pulse pressure
- Pulsatility Index
- Cerebral flow velocity (MCA)
- Area of the MCA section perpendicular to the main axis.

Cognitive Tests used in the Study

- Learning Test of Rey
- Subtest of Repetition of digits (WAIS).
- Trail Making Test (A y B)
- Addenbroke’s Cognitive Examination (ACE)
- INECO frontal Screening

Preliminary Studies

- Human studies of volunteers was planned to complete 30 individuals using Simvastatin (oral 80 mg daily) and Persantin (oral dose of 100 mg) during the last three days of a three weeks experiments.
- 30 individuals (15 treated and 15 with Placebo were included).
- Before and after treatment cerebral perfusion was studied using TCD monitoring or CT Perfusion and complete cognitive studies.

Preliminary Studies

- Studies are being conducted at this moment. Preliminary results are very encouraging.
- Two patients with severe stable cognitive deficit after strokes were treated with significant improvement using Simvastatin, Persantin and Cylostazol.

Pefusion CT before and after Simvastatin-Persantin Treatment

Preliminary studies in individual after 10 minutes vertical position during Yoga exercises.

- Five individuals were studied performed mini-mental tests and measuring cerebral blood flow by TCD before and a minute and 1 hrs after performing the vertical position exercise.
- CBF increased 42% as average and the mini-mental tests showed significant changes in all.
Conclusions:

- Increase of cerebral blood flow seems to have a significant impact in cognitive function.
- Complete studies are warranted.