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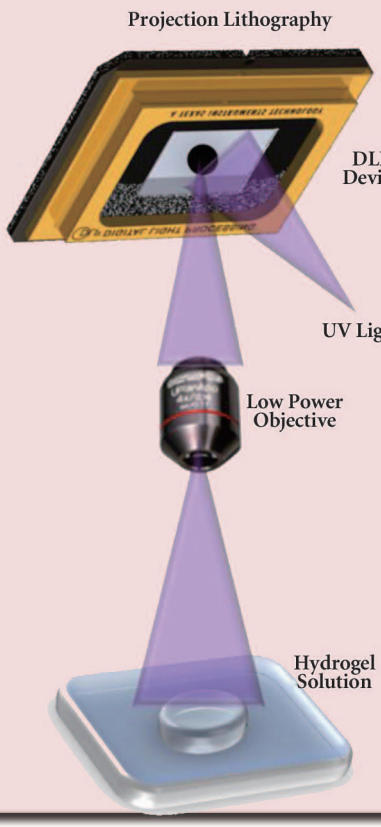
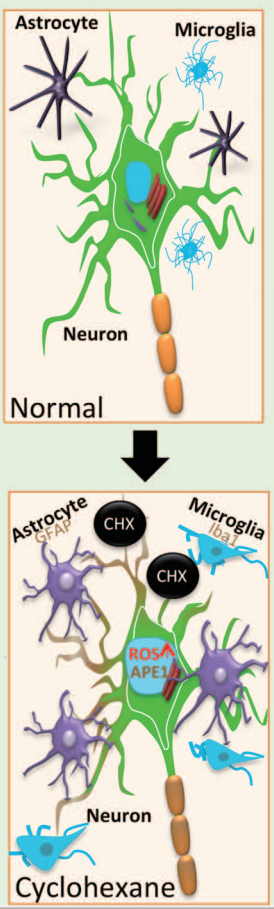
Microscale tissue-engineered models: overcoming barriers to adoption for neural regeneration research

Michael J. Moore



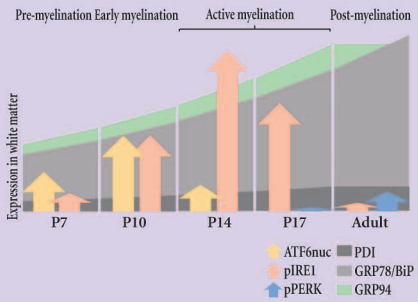
Glial plasticity after hexahydrobenzene exposure

Tania Campos-Ordonez, Oscar Gonzalez-Perez



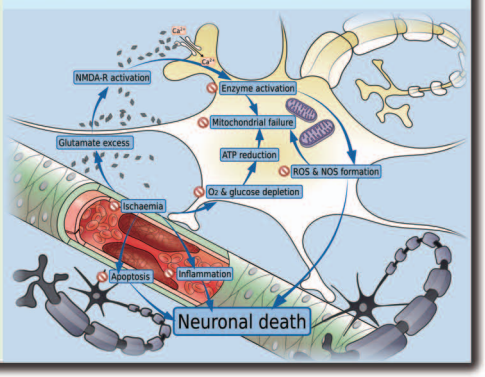
The role of the unfolded protein response in myelination

Michelle C. Naughton, Jill M. McMahon, Una F. FitzGerald



Intranasal insulin neuroprotection in ischemic stroke

Vasileios-Arsenios Lioutas, Vera Novak



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PERSPECTIVE

An open-label pilot study with high-dose thiamine in Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder clinically characterized by motor symptoms (bradykinesia, tremor, rigidity, postural instability) and non-motor symptoms (hyposmia, sleep disorders, autonomic and sphincteric dysfunctions, fatigue, pain, depression, and cognitive disorders) (Sprenger and Poewe, 2013). The neuropathological hallmark of PD is the degeneration of the pigmented dopaminergic neurons in the *substantia nigra*; other nuclei involved in neurodegeneration are *locus coeruleus*, reticular nuclei of brain stem, dorsal motor nucleus of vagus, basal nucleus of Meynert, amygdala, CA2 area of hippocampus, and frontal cortex. At the onset of parkinsonian symptoms, the neuronal loss is quite 70% in the lateral ventral part and 50% in the caudal part of the *substantia nigra* (Kordower et al., 2013). For this reason, and for the long time between the cellular onset and the clinical onset of the disease, it is mandatory to develop new therapies with disease-modifying and neuroprotective actions. The gold standard therapy for PD is always levodopa, while other currently validated treatments are dopamine agonists, cathecol-O-methyltransferase inhibitors, monoamine-oxidase-B inhibitors, and amantadine (Poewe et al., 2010; Sprenger and Poewe, 2013).

Recent data showed that in some inherited and degenerative diseases of the nervous system the pathogenesis of the symptoms could be linked to a focal deficiency of thiamine (vitamin B1) due either to dysfunction of the intracellular thiamine transport or to structural enzymatic abnormalities. Thiamine is a cofactor of enzymes involved in fundamental pathways of the energetic cell metabolism, particularly critical in glucose metabolism. Thiamine deficiency (TD) is a complication of severe malnutrition associated with chronic alcoholism, HIV-AIDS, and gastrointestinal disease, frequently resulting in Wernicke-Korsakoff encephalopathy, a subacute neurologic disorder characterized by ophthalmoplegia, gait ataxia, confusion, and memory loss (Butterworth, 2003). TD pathophysiology involves several events and results in focal neuronal cell death. Such events, *e.g.*, the reduced activity of alpha-keto-glutarate dehydrogenase, the impaired oxidative metabolism, the increased oxidative stress, and the selective neuronal loss in specific brain regions, represent also some pathological mechanisms involved in the neurodegenerative diseases. TD reduces the activity of the thiamine-dependent enzymes with regional selectivity, being different cerebral areas affected with different severity (Butterworth, 2003). TD could then be an useful model in neurodegeneration (Jhala and Hazell, 2011). New studies suggest that thiamine has also non-coenzymatic roles, potentially relevant in neuroprotection (Mkrtchyan, 2015).

Several studies demonstrated a link between PD and thiamine (Lu'o'ng and Nguyên, 2011). A decreased activity of the thiamine-dependent enzymes and a selective loss of the mitochondrial complex I have been reported in the nigral neurons of patients with PD (Butterworth, 2003; Schapira, 2014). In the cerebrospinal fluid of patients with PD, free thiamine levels are lower than controls (Jiménez-Jiménez et al., 1999). Experimental findings showed an increased dopamine release in rat striatum after the intrastriatal thiamine administration. In the brain of patients with PD, a reduction in glucose metabolism and an increase of oxidative stress have been reported; in fact, the thiamine-dependent processes are critical in the glucose metabolism, and recent studies implicate thiamine in the oxidative stress, the protein processing, the peroxisomal function, and the gene expression (Brandis et al., 2006; Jhala and Hazell, 2011). Moreover, an interesting study about an alpha-synuclein fission yeast model found that thiamine lowers the alpha-synuclein expression in a dose-dependent manner and that A53T mutated alpha-synuclein aggregates at lower concentrations than wild-type alpha-synuclein: these data suggest that increasing intracellular thiamine could reduce the alpha-synuclein concentration and then the alpha-synuclein aggregation (Brandis et al., 2006). Furthermore, a dysfunction of the intracellular thiamine functions has been described in some genetic diseases characterized by mutations in genes coding for thiamine transporters or thiamine metabolism enzymes, while several inborn metabolic diseases clinically improved after the administration of pharmacological doses of thiamine, such as in Wernicke-like encephalopathy (Kono et al., 2009). However, the role played by thiamine in PD pathogenesis has not yet been extensively investigated.

Recent clinical studies showed a considerable and stable improvement of motor and non-motor symptoms in patients affected by PD treated with intramuscular high-dose thiamine (100 mg) administered twice a week (Costantini et al., 2015). Therefore, we decided to extend the treatment with high doses of thiamine to a series of patients with PD in order to clarify the potential effect of thiamine in this disease.

We evaluated ten consecutive patients with PD attending our Neurological Departments. The diagnosis of PD had been made according to UK Parkinson Disease Society Brain Bank Criteria by expert neurologists working in primary Italian neurological Institutes. All the participants signed an informed consent to the participation to the study. The study was approved by the Ethical Committees of our Hospitals. Eight patients were males and two were females. Mean age was 74.5 ± 7.0 years, while mean disease duration was 5.2 ± 3.4 years. Four subjects were drug-naïve patients, while the other six patients were in treatment with dopaminergic drugs (one with dopamine agonists only, five with levodopa associated with other antiparkinsonian drugs); mean daily levodopa dose was 180.0 ± 233.6 mg. Basal levels of plasma thiamine were normal in all the patients. All the patients were evaluated by expert neurologists in movement disorders in the morning, during the "on" phase, at baseline and two months after the beginning of treatment with thiamine, with Unified Parkinson Disease Rating Scale (UPDRS) (Movement Disorders Society, 2003), parts I to VI. After the baseline evaluation, the patients continued treatment with i.m. 100 mg of thiamine twice a week, without any change to the personal pharmacological therapy or the rehabilitation program. After the first month, nine patients, in order to further improve their clinical performances, increased the daily amount of thiamine and levodopa, or started the treatment with levodopa in association with thiamine. In agreement with other authors, we believe that the occurrence of the motor complications is related to the disease progression rather than to the duration of levodopa therapy (Cilia et al., 2014).

The treatment with thiamine led to a significant improvement of PD symptoms: UPDRS part II improved from 12.5 ± 4.0 to 7.7 ± 3.5 ($P < 0.001$, *t*-test for paired data), motor UPDRS part III improved from 21.6 ± 4.8 to 11.8 ± 6.0 ($P < 0.00001$, *t*-test for paired data). The Hoehn and Yahr score (UPDRS part V), a disease stage measure, significantly improved from 3.0 ± 0.8 to 2.5 ± 0.6 ($P < 0.001$, *t*-test for paired data); also the Schwab and England functional score (UPDRS part VI) significantly improved from 69.0 ± 18.5 to 80.0 ± 12.5 ($P < 0.05$, *t*-test for paired data). The clinical motor improvement was even higher during the second month of treatment, after the increase of the dosage of thiamine associated with the increase of levodopa for the patients already in treatment with this drug, or after the beginning of the treatment with levodopa for the patients naïve for this therapy. The mean daily levodopa dose after two months was 515.0 ± 228.6 mg. Some patients with a milder phenotype had a complete clinical recovery. No patient experienced adverse events or discontinued the treatment.

In comparison with other currently available therapies, the treatment with thiamine was associated with a similar improvement in the motor functions, as assessed by the reduction in UPDRS scores. In our patients treated with thiamine, we observed a mean

improvement in UPDRS part III of 59.61 ± 23.63%. This is a significant result, considering that the responsiveness to levodopa as diagnostic criterion for PD requires a reduction in the score of UPDRS part III higher than 30% (Poewe et al., 2010).

We suppose that the improvement of the energetic metabolism of the survivors neurons in the *substantia nigra*, due to the high doses of thiamine, could lead to an increase of synthesis and release of the endogenous dopamine, to an increase of activity of the thiamine-dependent enzymes, or to a better utilization of the exogenous levodopa (Jiménez-Jiménez et al., 1999; Lu'o'ng and Nguyên, 2012; Costantini et al. 2015). We suggest that the abnormalities in the thiamine-dependent processes could be overcome by a diffusion-mediated transport at supranormal thiamine concentrations.

Considering that there is no correlation between the positive effects of thiamine administration and the brain levels of thiamine diphosphate or thiamine diphosphate-dependent enzymatic activities, the potential contribution of the non-coenzyme action of thiamine should not be neglected in patients with neurodegenerative diseases (Mkrtchyan et al., 2015). The high dose of thiamine may elevate not only thiamine diphosphate, but also the non-coenzyme forms, which may thus be also responsible for the therapeutic effects of thiamine. The recently identified protein targets and mechanisms of the non-coenzyme action of thiamine could be important for the neuroprotection (Lu'o'ng and Nguyên, 2012; Mkrtchyan et al., 2015).

Based on preclinical and clinical data, the clinical efficacy of continuous treatment with high doses of thiamine in our patients with PD could indicate that PD symptomatology is the manifestation of neuronal TD. A dysfunction of thiamine-dependent metabolic pathways, either *via* coenzymatic or non-coenzymatic processes, could cause a selective neural damage in the centers typically affected by this disease and might be a fundamental molecular event provoking neurodegeneration (Butterworth, 2003; Jhala and Hazell, 2011; Mkrtchyan et al., 2015).

The long-lasting treatment with thiamine, as demonstrated by our study, is also safe; we did not observe any adverse events; also in literature there is no mention of thiamine-related adverse effects even at high doses and for very long periods of administration.

The most relevant limitation of our study is the absence of a placebo-controlled group. Although it has been described that in the pharmacological trials, the patients with PD assigned to the placebo group may have an immediate subjective improvement but not a significant objective motor change, in comparison with the patients assigned to the levodopa group, and although the clinical improvement of our patients is continuous and stable, the lack of a placebo group leads to consider these results as preliminary and to be interpreted carefully. However, we are confident that these results represent a significant contribution to the issue of PD treatment.

The administration of high doses of thiamine to patients with PD was effective in reversing the parkinsonian symptoms; we then suppose that the parenteral thiamine supplementation may play an important role in restoring the survivor neurons and in limiting the disease progression, and that the dysfunction of the thiamine-dependent processes could be a primary pathogenic pathway leading to the death of dopaminergic and non-dopaminergic neurons in PD.

The thiamine-dependent processes are impaired in the cerebral tissues of patients with several neurodegenerative diseases and the activity reduction of the thiamine-dependent enzymes can be readily linked to the symptomatology and the pathology of the disorders. Most neurodegenerative diseases share then similarities and could be responsive to high doses of thiamine (Butterworth, 2003; Jhala and Hazell, 2011; Lu'o'ng and Nguyên, 2012; Costantini et al., 2015; Mkrtchyan et al., 2015).

In conclusion, we found that the long-term treatment with the intramuscular administration of thiamine has led to a significant improvement of motor and non-motor symptoms of the patients with PD; this improvement was stable during time and without side effects. Our report represents an important contribution to PD therapy, although further experience is necessary to exclude the placebo effect and to confirm the present observation, with clinical, cellular, and molecular data. The aim of the future studies will be to investigate the clinical, restorative, and neuroprotective effects of the long-term treatment with thiamine in PD.

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