Hemoglobin-Independent Organ Protection by EPO in Humans: Amelioration of Cognitive Loss in Chronic Schizophrenia

Improvement of Cognitive Functions in Chronic Schizophrenic Patients by Recombinant Human Erythropoietin. Mol Psychiatry October 10, 2006 [epub ahead of print]


In the distant past nephrology had an encounter with schizophrenia after Wagemaker and Cade (1) had reported impressive improvement of the symptoms of schizophrenia by hemodialysis and had speculated about potential removal of low molecular weight water soluble effector substances. Their finding did not hold up in subsequent studies (2,3).

In contrast, the above study of Ehrenreich, an investigator with an impressive track record concerning erythropoietin (EPO) actions on neuronal structures (4–12), and her colleagues point to a mechanistically plausible link between the renal hormone EPO and schizophrenia. In a past pilot study, the investigator had already shown that administration of EPO reduces the infarct size and improves the functional deficit of patients with acute ischemic stroke from occlusion of cerebri media artery (10). This new study points to a broader indication in nonischemic neurodegenerative disease.

It may come as a surprise that EPO should play a role in brain disease, so some background information may be useful. EPO is expressed in the brain of the embryo and plays an important role in brain organogenesis (13), but the EPO system is largely silent in the normal adult brain. However, in neuronal and glial cells (5), EPO receptors are upregulated when the brain is subjected to metabolic distress, e.g., hypoxia and ischemia (14,15). Of particular interest is the finding that EPO receptors are densely expressed in the hippocampus and cortex of schizophrenic but not of normal subjects (16). EPO is transported from the blood compartment across the blood-brain barrier into the brain both in mice and in humans (16,17), particularly in the presence of metabolic brain distress.

Apart from penetration of circulating EPO into the brain, local synthesis of EPO driven by hypoxia and hypoxia-inducible factor 1α (HIF1α) occurs in the brain as well (18,19). In humans with brain lesions, blood and cerebrospinal fluid EPO concentrations differ, suggesting local synthesis (20,21).

A beneficial effect of the administration of EPO and its potential congeners (22) has been shown in a great number of diverse models of injury of neonatal or adult brain (23), spinal cord, and retina, e.g., models of multiple sclerosis (8), retinal degeneration (24), β-amyloid toxicity (25), ischemia-reperfusion (26), fimbria fornix transsection (27), spinal cord compression (28), etc. The uniform efficacy of EPO despite the diversity of primary causes of neuronal damage can best be explained by the hypothesis that EPO interferes with a final common pathway. The neuroprotective action of EPO is not completely surprising given its potential to antagonize in neuronal cells apoptosis (11), excitotoxicity of glutamate (29), oxidative damage (30), and inflammatory pathways (31). EPO also promotes stem cell differentiation in the brain (32).

Why does it make sense to study the effect of EPO in schizophrenia? Schizophrenia affects 1% of the population across cultures and causes loss of previously acquired cognitive capacity, a finding for which E. Kraepelin (33), in his original description of schizophrenia, coined the expression “dementia praecox,” i.e., the progressive loss of acquired intellectual competence. Modern antipsychotic agents control so-called positive symptoms such as delusion, hallucination, etc., while the negative symptoms persist, e.g., loss of affective interaction, progressive loss of cognitive competence... of equal, if not greater, importance for the life plans and social integration of these patients. There are good arguments that the morphologic equivalent of intellectual loss is subtle progressive gray matter loss, starting in the parietal association cortex.
as documented by magnetic resonance imaging (34) and later spreading to other brain regions, culminating in ventricular enlargement (35)—consistent with the idea of a neurodegenerative process involving both neurodevelopmental and neurodegenerative abnormalities. It is further relevant that EPO prevents brain atrophy in a murine model of progressive neurodegeneration after a focal unilateral cryolesion of the parietal brain; this model had reproduced some behavioral features of schizophrenia and was characterized by progressive brain atrophy (4).

Before this study was begun by Ehrenreich et al., some further small studies were conducted to test several assumptions underlying the intervention trial (16). After injection of 40,000 IU of radio-indium–labeled EPO, EPO penetrated into the brain parenchyma as measured by the single-photon emission computed tomography technique; such uptake of radiolabeled EPO was higher in schizophrenic patients. Furthermore, it was found that the expression of EPO receptors by neuronal and glial cells was higher in schizophrenic as compared with control patients (16).

To test the working hypothesis that EPO, as a neuroprotective add-on strategy in addition to stable antipsychotic medication, improved cognitive function in chronic schizophrenic patients, 39 chronic schizophrenic men were recruited for a double-blind, placebo-controlled, randomized, multicenter, proof-of-principle study. Twenty patients were randomized to receive short intravenous infusions of 40,000 IU EPO beta weekly for a period of 12 weeks, while 19 patients received saline. The patients were 25 to 55 years old, had schizophrenia for >10 mo, had no recent acute psychotic episode, and had a stable cognitive deficit. Patients were subjected to a battery of tests. The main end point was schizophrenia-relevant cognitive function at 12 weeks assessed by the RBANS score (Repeatable Battery for the Assessment of Neuropsychological Status) and the WCST-64 (Wisconsin Card Sorting Test). Compared with the baseline, the schizophrenia relevant cognitive function score improved in both groups, presumably reflecting the nonspecific stimulatory effect of the participation in a study of patients living in a monotonous environment. But with appropriate statistical analysis the improvement was significantly greater in the EPO than in the placebo group. Importantly, cognitive tests other than those that were selected as the “schizophrenia test set” did not differ between the groups and during follow-up.

The concentration of S100B, a marker of glial damage, declined in the EPO group. The hemoglobin values were kept stable by a surprisingly low number of venesections, suggesting a remarkably low hematopoietic EPO response despite no increase in conventional inflammatory markers. No change in blood pressure was observed.

EPO is the first substance shown to improve the cognitive deficit in schizophrenia. Although EPO is certainly not a primary causal treatment, the data are exciting because they open new therapeutic strategies.

It should be mentioned that explorative data in an uncontrolled study on patients with multiple sclerosis are very encouraging as well (Ehrenreich, personal communication, 2006), and, in view of the assumed pathophysiological principles, neurologic diseases such as Alzheimer’s or Parkinson’s diseases are also plausible candidates for such an intervention (16).

The implications of this study go beyond psychiatry. This is the first study in humans using EPO as an agent for hemoglobin-independent organ protection, an approach that had been used successfully in experimental studies not only for neuroprotection but also for organ protection such as cardioprotection (36) or renoprotection (37), as well as for ischemic preconditioning (38). Further applications of EPO with the aim of hemoglobin-independent organ protection may be around the corner.

References
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