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Response to 'Nitric Oxide Synthase Mediation of Darbepoetin's Cognitive Benefits: A Paradoxical Effect?'

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We have recently reported that systemic administration of darbepoetin alfa improves the performance of STOP null mice (putative mouse model for schizophrenia) in the novel object recognition task (NORT) by increasing the production of nitric oxide (NO) in central neurons, suggesting that this erythropoietin may be useful in the treatment of cognitive deficits associated with schizophrenia (Kajitani *et al*, 2010). In contrast, Dr Venkatasubramanian (2012) cites several lines of evidence suggesting that therapeutics that enhance NO signalling may be detrimental rather than beneficial in the treatment of this disorder. Emphasis is placed on two lines of data from animal experimentation, implicating elevated NO production in the prefrontal cortex as a major contributing factor to impaired information processing produced by phencyclidine and reversal of these deficits by the NO synthase inhibitor (N(G)-nitro-L-arginine methyl ester (L-NAME)). With respect to the former findings, we would like to point out that administration of darbepoetin alfa at doses that improved the NORT performance of STOP null mice failed to increase NO production in the cortex (Kajitani *et al*, 2010). Instead the ability of this erythropoietin to improve NORT performance was associated with increased NO activity in the ventral hippocampus and amygdala (Kajitani *et al*, 2010), brain regions implicated in the positive effects of erythropoietin on mood and cognition in depressed patients (Miskowiak *et al*, 2008). In terms of the latter results cited by Dr Venkatasubramanian, the role of NO as a key intercellular messenger necessary for the synaptic events that mediate memory consolidation are well established (Arancio *et al*, 1996), whereas their importance for the enhancement of long-term potentiation by erythropoietin have only recently been demonstrated (Adamcio *et al*, 2008). As for Dr Venkatasubramanian's proposal that minocycline may improve cognitive deficits in patients with schizophrenia by blocking NO synthase, it should be kept in mind that this tetracycline antibiotic interacts with a wide variety of proteins and modulates a broad array of signalling events implicated in inflammation and neurodegeneration—processes highly relevant to cognitive decline (Yong *et al*, 2004). Lastly, schizophrenia is a complex disorder for which many susceptibility genes have been described, including neuronal NO synthase (Reif *et al*, 2006); however, nearly all of these genes encode proteins that regulate some aspect of neurotransmission, suggesting that schizophrenia is a disorder of the synapse and, if used carefully, therapeutics such as darbepoetin alfa which improve synaptic strength may have a unique role in the treatment of this devastating disorder.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

Adamcio B, Sargin D, Stradomska A, Medrihan L, Gertler C, Theis F *et al* (2008). Erythropoietin enhances hippocampal long-term potentiation and memory. *BMC Biol* **6**: 37.

Arancio O, Kiebler M, Lee CJ, Lev-Ram V, Tsien RY, Kandel ER *et al* (1996). Nitric oxide acts directly in the presynaptic neuron to produce long-term potentiation in and the hippocampus. *Proc Natl Acad Sci USA* **101**: 14515–14520.

Kajitani K, Thorne M, Samson M, Robertson GS (2010). Nitric oxide synthase mediates the ability of darbepoetin alpha to improve the cognitive performance of STOP null mice. *Neuropsychopharmacology* **35**: 1718–1728.

Miskowiak K, Inkster B, Selvaraj S, Wise R, Goodwin GM, Harmer CJ (2008). Erythropoietin improves mood and modulates the cognitive and neural processing of emotion 3 days post administration. *Neuropsychopharmacology* **33**: 611–618.

Reif A, Herterich S, Strobel A, Ehlis AC, Saur D, Jacob CP *et al* (2006). A neuronal nitric oxide synthase (NOS-I) haplotype associated with schizophrenia modifies prefrontal cortex function. *Mol Psychiatry* **11**: 286–300.

Venkatasubramanian G (2012). Nitric oxide synthase mediation of darbepoetin's cognitive benefits: a paradoxical effect? *Neuropsychopharmacology* **37**: 1074.

Yong VW, Wells J, Giuliani F, Casha S, Power C, Metz LM (2004). The promise of minocycline in neurology. *Lancet Neurol* **3**: 744–751.