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The 10,000 Fold Effect of Retrograde Neurotransmission: A New Concept for Cerebral Palsy Revival by the Use of Nitric Oxide Donars

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Abstract : Background: Nitric Oxide Donars (NODs) (intrathecal sodium nitroprusside (ITSNP) and oral tadalafil 20mg post ITSNP) has been studied in this context in cerebral palsy patients for fast recovery. This work proposes two mechanisms for acute cases and one mechanism for chronic cases, which are interrelated, for physiological recovery. a) Retrograde Neurotransmission (acute cases): 1) Normal excitatory impulse: at the synaptic level, glutamate activates NMDA receptors, with nitric oxide synthetase (NOS) on the postsynaptic membrane, for further propagation by the calcium-calmodulin complex. Nitric oxide (NO, produced by NOS) travels backward across the chemical synapse and binds the axon-terminal NO receptor/sGC of a presynaptic neuron, regulating anterograde neurotransmission (ANT) via retrograde neurotransmission (RNT). Heme is the ligand-binding site of the NO receptor/sGC. Heme exhibits > 10,000-fold higher affinity for NO than for oxygen (the 10,000-fold effect) and is completed in 20 msec. 2) Pathological conditions: normal synaptic activity, including both ANT and RNT, is absent. A NO donor (SNP) releases NO from NOS in the postsynaptic region. NO travels backward across a chemical synapse to bind to the heme of a NO receptor in the axon terminal of a presynaptic neuron, generating an impulse, as under normal conditions. b) Vasopasm: (acute cases) Perforators show vasospastic activity. NO vasodilates the perforators via the NO-cAMP pathway. c) Long-Term Potentiation (LTP): (chronic cases) The NO–cGMP-pathway plays a role in LTP at many synapses throughout the CNS and at the neuromuscular junction. LTP has been reviewed both generally and with respect to brain regions specific for memory/learning. Aims/Study Design: The principles of “generation of impulses from the presynaptic region to the postsynaptic region by very potent RNT (10,000-fold effect)” and “vasodilation of arteriolar perforators” are the basis of the authors’ hypothesis to treat cerebral palsy cases. Case-control prospective study. Materials and Methods: The experimental population included 82 cerebral palsy patients (10 patients were given control treatments without NOD or with 5% dextrose superfusion, and 72 patients comprised the NOD group). The mean time for superfusion was 5 months post-cerebral palsy. Pre- and post-NOD status was monitored by Gross Motor Function Classification System for Cerebral Palsy (GMFCS), MRI, and TCD studies. Results: After 7 days in the NOD group, the mean change in the GMFCS score was an increase of 1.2 points mean; after 3 months, there was an increase of 3.4 points mean, compared to the control-group increase of 0.1 points at 3 months. MRI and TCD documented the improvements. Conclusions: NOD (ITSNP boosts up the recovery and oral tadalafil maintains the recovery to a well-desired level) acts swiftly in the treatment of CP, acting within 7 days on 5 months post-cerebral palsy either of the three mechanisms.

Keywords : cerebral palsy, intrathecal sodium nitroprusside, oral tadalafil, perforators, vasodilations, retrograde transmission, the 10,000-fold effect, long-term potantiation
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