DYNAMICS OF CHOLINERGIC SYNAPTIC MECHANISMS AFFECTED BY MANGANESE

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✺ Evidence in the literature implies that cholinergic activity plays a role in the pathophysiology of manganese neurotoxicity. However, the data on manganese-induced changes in CNS cholinergic systems are considerably less extensive than those concerning other neurotransmitter systems.

✺ Cholinergic synaptic mechanisms are the targets for manganese activity: presynaptic choline uptake (1), quantal release of acetylcholine into the synaptic cleft (3), binding of acetylcholine to postsynaptic receptors (5) and its synaptic degradation by acetylcholinesterase (4).

✺ Furthermore, manganese significantly influences choline transport systems (6) and acetylcholine binding proteins in the astrocytes (7). Thus, manganese influences the highly dynamic reciprocal relationship between astrocytes and cholinergic neurons.

MANGANISM:

Manganism is a well-defined nosologic entity, given the specific clinical pattern, overall picture of pathologic disruption in the globus pallidus with sparing of the dopaminergic nigrostriatal pathway.

✺ A central nervous system disease following exposure to high concentrations of manganese oxides was first described in the 19th century.

✺ Until 1960's, most manganism cases were occupational and diagnosed in miners.

✺ Later on, cases have been described in workers engaged in the ferromanganese-alloy industry and the manufacturing of dry-cell batteries.

✺ During the last three decades, welding has come gradually into focus as a possible high risk occupational factor for developing manganism.

early clinical stage:

The medical term locura manganica has been coined to characterize this initial neuropsychiatric syndrome in miners of manganese ores in Chile, Australia and Taiwan.

locura manganica is a neuropsychiatric syndrome, the most frequent symptoms and signs of which are: emotional lability, memory loss, visual hallucinations and flight of ideas.

Psychomotor slowing and cognitive decline evolve later.

extrapyramidal stage:

The organic mental syndrome is usually followed by disturbances of gait and excessive salivation, as the first manifestations of a movement disorder - an extrapyramidal syndrome which clinically resembles Parkinson's disease.
later clinical stage:

The organic psychosis frequently disappears when parkinsonian signs supervene.

Manganism may be reversible if diagnosed and treated in the early stages. Development of extrapyramidal syndrome denotes permanent damage to the CNS.

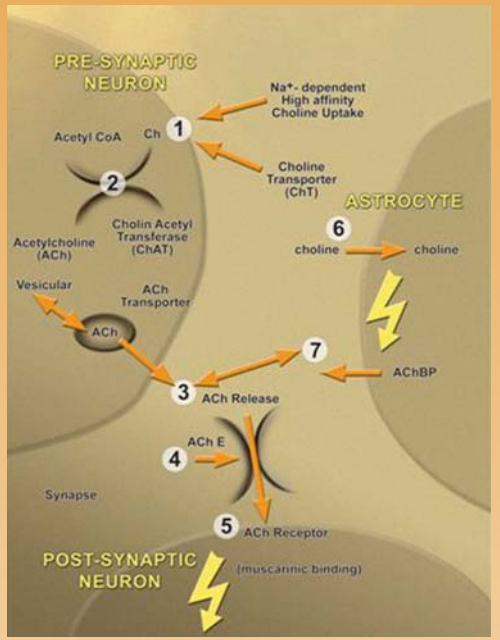

Fig. 1: The effect of Manganese on cholinergic neurotransmission

Manganese exerts is effects along the chain of synaptic cholinergic activity: (1) high-affinity sodium-dependent choline uptake into the presynaptic cell; (2) acetylcholine (ACh) synthesis from choline and acetyl-coenzyme A (AcCoA), mediated by cholinacetyltransferase (ChAT); (3) ACh release into the synaptic gap; (4) ACh hydrolysis by acetylcholinesterase (AChE); (5) postsynaptic binding of ACh to muscarinic receptors; (6) high-affinity sodium-dependent choline uptake into the glial cell; (7) glia-derived soluble acetylcholine-binding protein (AChBP) release into the synaptic cleft.

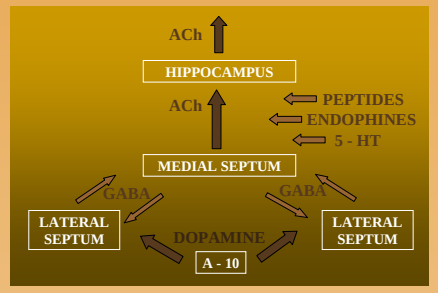

Fig.2: The main neurotransmitter systems in the septo-hippocampus

✺ The dopaminergic (DA) pathway from the midbrain (A-10) to the lateral nuclei of the septum.

✺ GABAergic interneurons connecting the dopaminergic (DA) lateral nuclei to the cholinergic (ACh) medial nucleus of the septum.

✺ The cholinergic (ACh) pathway from the medial nucleus of the septum to the hippocampus.

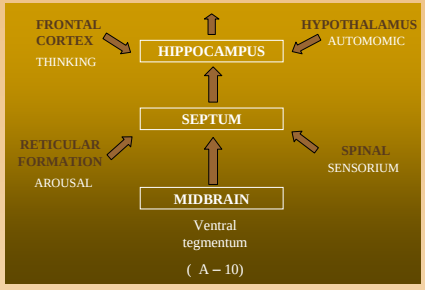

Fig.3: The afferent connections of the septo-hippocampus

All the afferent stimuli are conveyed to the cholinergic hippocampal system via indirect anatomical pathways.

CONCLUSIONS:

The natural history of manganese intoxication could be a clinical reflection of the preferential involvement of the cholinergic systems, initially in the septo-hippocampus and its limbic connections and later in the basal ganglia and motor systems.

Cholinergic afferents are of extreme importance in the physiology of locomotion, cognition, emotion and behavioral response.

Manganese exerts its effect as a chemical stressor in cholinergic neurons in a region-specific manner causing disruption of the cellular homeostatic mechanisms.

The anatomical selectivity of most manganese-induced cholinergic effects is compatible with the clinical correlates of manganism, involving impairment of emotional response, decline in higher cortical functions and a movement disorder.

These observations move into the foreground the importance of analyzing the role of the CNS cholinergic systems in manganese-induced neurotoxicity.

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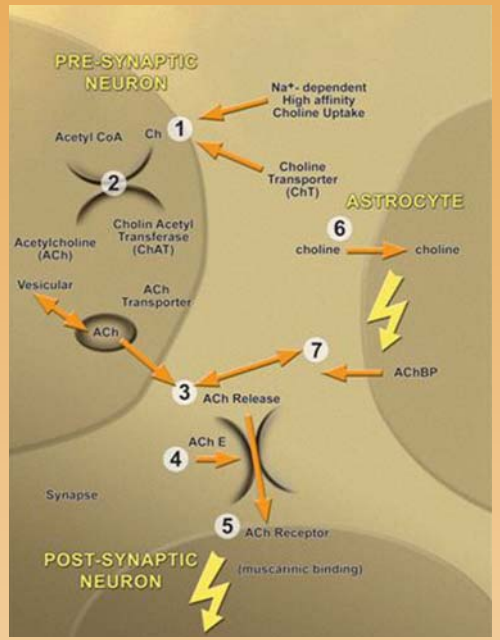

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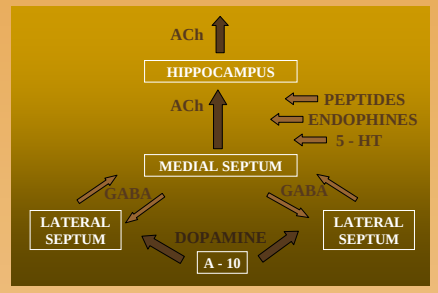

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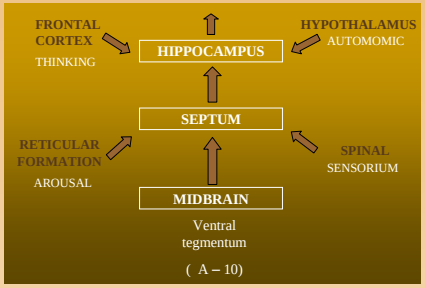

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