

MONOAMINERGIC CHANGES IN LOCUS COERULEUS AND DORSAL RAPHE NUCLEUS FOLLOWING NORADRENALINE DEPLETION

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The noradrenergic system is involved in the mediation of several important central nervous system (CNS) processes including the stress response, the regulation of attentional processes and memory consolidation. Alterations in noradrenergic function also play an important role in the pathogenesis of psychiatric disorders including depression, anxiety, drug addiction and withdrawal. Noradrenergic depletion by the *in vivo* administration of the selective neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride (DSP-4) is an important experimental tool that is widely used to investigate the involvement of noradrenaline (NA) in different animal models of neuropsychiatric disorders.

Following its systemic administration, DSP-4 causes a selective destruction of the ascending noradrenergic projections that originate in the locus coeruleus (LC), which provides the main source of NA in the brain. So far, no studies have fully investigated in mice the neurochemical alterations and adaptive changes occurring in the LC and the dorsal raphe nucleus (DRN) (a major source of serotonin (5-HT) that has extensive reciprocal connections with the LC), after the systemic administration of DSP-4.

Here we demonstrate that DSP-4 (25 and 50 mg/kg, i.p.) causes a significant dose-dependent depletion of NA in both the LC and DRN, seven days after a single administration in mice. This depletion is also observed in two major projection areas of the LC, the prefrontal cortex and hippocampus. However, an increase of both 5-HT and its major metabolite, 5-hydroxyindolacetic acid (5-HIAA) was observed at the noradrenergic cell body level.

Considering the reciprocal interaction between NA and dopamine (DA), we focused our attention also on dopaminergic tissue levels, after DSP-4 administration in mice. A significant decrease of DA was detected in both the hippocampus and DRN but a decrease in DA major metabolite, homovanillic acid, was detected in the DRN.

These results highlight for the first time that the neurotoxic action of DSP-4 is not restricted to distal axons and LC terminal level, but it is also evident at the noradrenergic cell body area, where a number of adaptive changes involves both serotonergic and dopaminergic transmissions. These complex interactions may be particularly important to better understand the physiopathology of psychiatric disturbances where a noradrenergic depletion is involved.