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Effects of systemic administration of L-kynurenine sulfate on behavior and on c-Fos expression level in C57Bl/6 mice

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L-Kynurenine (L-KYN) is a central metabolite of tryptophan degradation through the kynurenine catabolic pathway (KP). In the kynurenine catabolic pathway several endogenous metabolite exert neuromodulatory properties, of which kynurenic acid (KYNA) has been in therapeutic focus for more than two decades. KYNA can act as a non-competitive antagonist on 7nACh receptor, can exert dual action on AMPA receptors, and it can also competitively antagonize the NMDA receptor. Concomitant decreases in the concentration of extracellular glutamate, acetylcholine, dopamine and GABA can be observed, during the elevated KYNA level. The systemic administration of L-KYN sulfate (L-KYNs) leads to a dose-dependent increase in several downstream KP metabolite level, though in short term the most prominent change occurs in the concentration of the KYNA. An elevated level of KYNA can exert multiple effects on the synaptic transmission, resulting in complex behavioral changes, such as hypoactivity or spatial working memory deficits. Furthermore, a shift in the brain concentration of KYNA has been described in several neurodegenerative disorders e. g. Parkinson's disease, Schizophrenia and Alzheimer's disease. The L-KYN itself has a direct role in neuroinflammatory processes. In several studies neuroprotection was achieved through kynurenergic manipulation. Our research group's previous findings proved that, administration of L-KYN, KYNA or its derivatives can be neuroprotective in cerebral ischemic events. The behavioral effects of acut or chronic administration of L-KYNs are partially described. However, most of these observations emerged from studies focused on rats. Description of the behavioral effects of kynurenergic manipulations in mice are virtually lacking so, it is fundamental to investigate a dose-dependent impacts of acut L-KYNs administration in intact mice.

For this reason our aim was to investigate whether the systemic administration of L-KYNs (25, 100, 300 mg/bwkg) would produce alterations in behavioral tasks connected to locomotion (open field), anxiety (open field) and memory formation (object recognition) in C57Bl/6 mice, compare to the control group (0.1M PB). Then, to evaluate the changes in neuronal activity after L-KYNs treatment, we estimated the c-Fos expression levels in the corresponding subcortical brain areas. For this, we used that dose, which was found to exert the most prominent alteration in the behavioral tasks (300 mg/bwkg).

The L-KYNs dose-dependently affected the general ambulatory activity and the moving velocity of the mice. The lower doses led to hypoactivity, decreased the moving speed and the moving time, whereas the high dose led to hyperactivity, increased the moving speed, while decreased the moving time. Thus, the administration of the high-dose (300 mg/bwkg) altered the moving pattern also. The treatment dose-dependently increased anxiety-like behaviors, as peripheral zone preference of the open field arena progressively emerged and the rearing activity was gradually attenuated. The object recognition performance was not affected by the lowest (25 mg/bwkg) dose, whereas the higher doses completely abolished the formation of object recognition memory. Significant decreases in the number of c-Fos-immunopositive-cells was found in the dorsal striatum and in the CA1 pyramidal cell layer of the hippocampus. These subcortical brain areas can be linked to the regulation of moving speed and memory formation processes, respectively.

We could conclude that a single exposure to L-KYNs leads to dose-dependent behavioral disturbances, which might be related to the altered basal c-Fos protein expression levels in C57Bl/6j mice. In the near future we are planning to characterize different conditional kynurenine mutant mouse lines. Our present results can form a good reference to evaluate the behavioral disturbances of a genetically modified mice.

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