REPEATED RESTRAINT STRESS AND ANXIOLYTIC DRUGS DIFFERENTIALLY MODULATE LATENT INHIBITION IN C57BL6 MICE

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Latent inhibition (LI) is observed when a stimulus is repeatedly presented without other consequences and is subsequently used as the conditioned stimulus (CS) in a standard Pavlovian conditioning paradigm. This pre-exposed CS develops a weaker association with the unconditioned stimulus, as measured by the strength of the ensuing conditioned response, than does a non pre-exposed CS. The LI phenomenon can also be observed in humans, and is viewed as the capacity of an individual to exclude non-relevant information by shifting the stream of incoming stimuli. LI is commonly used to model attention deficits in schizophrenia. In animals LI is seen as a failure to switch to a new behaviour in response to a given stimulus. Chronic stress might lead to excessive LI by inducing a state of "emotional perseveration" or cognitive inflexibility that impedes animals to switch from one learned response to another.
Stress and anxiety are some of the most important factors found to determine the levels of LI. Although anxiety is not the defining feature of schizophrenia, it is a major component of the disease in terms of its association with negative symptoms, as well as in relation with the action of typical vs. atypical antipsychotic drugs on the symptoms of anxiety. Considering that benzodiazepines anxiolytic drugs might decrease the effects of stress through their effects on attention, learning and memory, the aims of this study were first, to compare the effect of typical and atypical antipsychotics with that of various doses of the anxiolytic drug diazepam and, second, to study the effect of repeated stress and diazepam on LI in C57Bl6 mice. LI was assessed using conditioned tone lick-suppression and conditioned freezing paradigms. It was found that, in the conditioned lick-suppression, diazepam (1, 3, 10 mg/kg, i.p.) decreases LI when administered before the pre-exposure phase, in experimental conditions favouring LI in control animals. This was similar to the effect observed with clozapine (5 mg/kg i.p.) and olanzapine (2.5 mg/kg i.p.). Haloperidol was inactive when administered during pre-exposure. Using the conditioned freezing model, the exposure of mice to repeated stress facilitated LI in experimental conditions in which significant LI is not observed. However, the administration of diazepam before the pre-exposure phase prevented the facilitation of LI in stressed animals.
Our results suggest that anxiolytic drugs such as diazepam could attenuate learning associated with irrelevant stimuli and reduce stress-induced emotional perseveration processes leading to inadequate contingency responses. These results might be relevant for modelling the negative symptoms of schizophrenia in mice.