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CNS safety pharmacology: A focus on cognitive functions.

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Abstract

INTRODUCTION: The guidelines from different agencies do not include studies on cognitive functions as part of safety pharmacology. This is unfortunate as it seems important to verify that drugs entering into the central nervous system (CNS) are devoid of detrimental effects on cognition. Our aim is to show examples on how an evaluation of unwanted effects of drugs on cognitive functions may be included in preclinical studies. Rather than a review of the scientific context, the present text is an appeal for a wider consideration of cognition as a safety pharmacology endpoint.

METHODS: The following procedures provide an index of the ability of substances to induce cognitive deficits in rodents. In the passive avoidance (PA) test, rats receiving an electric shock show on a later occasion an avoidance of the shock-associated environment. In the social recognition (SR) test, rats recognize familiar congeners. In the Morris water maze (MWM) test, rats placed into a tank containing water learn to find an invisible escape platform using extra-maze visual cues. In the delayed alternation (DA) test, rats placed in a Skinner box learn to alternate their pressing behaviour between two levers in order to obtain food rewards. In the operant reversal (OR) test, rats adapt their behaviour following a change of the reinforcement rule.

RESULTS: Standard reference agents were used to confirm that the different assays were able to detect pharmacologically induced cognitive impairments. Diazepam decreased associative memory performances in the PA test. MK-801-induced memory deficits in SR. Haloperidol increased escape latencies in the MWM test. Scopolamine decreased the number of correct responses in the DA test, and nicotine decreased the number of correct responses in the OR test. The relationship between the doses administered and the effects observed was also evaluated.

DISCUSSION: Cognitive assays may provide utility in determining potential undesirable effects or discharging perceived risks with novel CNS drugs under development.