

Cartas aos editores

Plus-maze following the microinjection of muscimol into the dorsal periaqueductal gray of the rat

Performance no labirinto em cruz elevado após microinjeção de muscimol na substância cinzenta periaquedutal dorsal do rato

Dear Editor,

Some experimental findings have indicated that the rat dorsal periaqueductal gray (DPAG) is part of a longitudinally organized neural system responsible for behavioral and vegetative manifestations of anxiety-like and aversive/defensive behaviors as well as active and passive emotional coping strategies towards threatening stimuli.¹ DPAG-evoked defense reactions might also provide some insights about panic attacks in humans. Systemically injected diazepam or intra-DPAG injection of midazolam promoted anxiolytic effects when animals were tested in the elevated plus-maze (EPM),² a behaviorally and pharmacologically validated animal model for

the study of anxiety.³ The inhibitory neurotransmitter γ -aminobutyric acid (GABA) and both GABA_A and GABA_B receptors are found in the DPAG. Here we report discrepant results found when we looked for the behavioral effects of microinjections of different doses of muscimol, a GABA_A receptor agonist, into the DPAG of rats tested in the EPM compared to the reported anxiolytic effects of midazolam.

We studied 3-month old male Wistar rats locally bred under standard laboratory conditions and according to international laws for ethical care. The EPM and its use were identical to previous descriptions.² Rats were submitted to unilateral stereotaxic surgery (Figure 1) and were microinjected into the DPAG with saline (0.3 μ l, n = 10), muscimol at the doses of 20 pg (n = 8), 50 pg (n = 12) and 150 pg (n = 8) or midazolam at the doses of 0.1 μ g (n = 5) or 35.3 μ g (n = 7). Other experimental groups served for testing the experimental procedure itself and we studied rats injected i.p. with saline and midazolam and tested in the EPM (n = 5-8, respectively) and a 'non-target' group (n = 15), i.e., rats that received saline or muscimol microinjections in the vicinity of the DPAG.

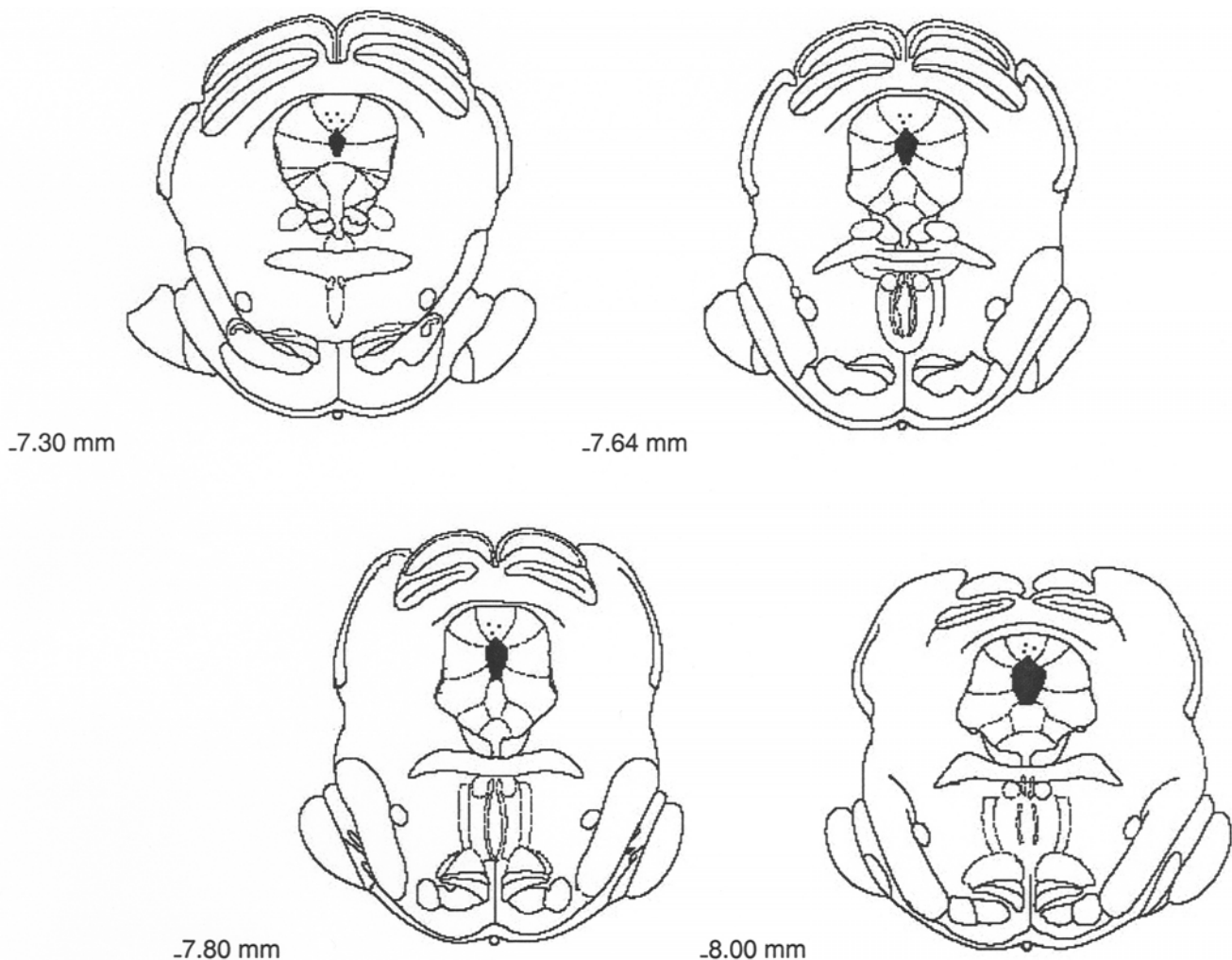


Figure 1 - Schematic drawings of coronal slices of the rat brain located 7.3 (top), 7.64, 7.8, and 8.0 (bottom) mm posterior to the bregma, according to the Paxinos and Watson atlas. Representative microinjection sites for saline or muscimol are depicted (points) within the medial or lateral DPAG. There are few points than the number of animals studied in all groups due to overlappings.

Moreover, in another experiment, muscimol decreased maternal aggressive behavior when microinjected into the paraventricular hypothalamic nucleus (data not shown).

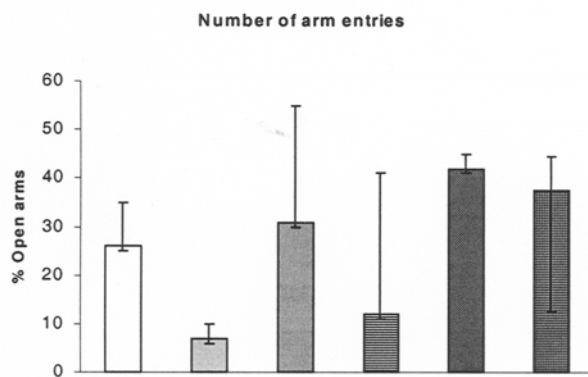
Interestingly, results showed that DPAG microinjections of muscimol or midazolam had no effects on EPM performance. Neither the percentage of open arm entries nor the time spent in open arms, which are considered two indexes of anxiety,³ were affected by muscimol when we compared both the saline and the 'non-target' groups. Intra-DPAG muscimol did not promote an overall sedative action as evaluated by the total number of arm entries and the entries in closed arms (Figure 2). On the other hand, systemically injected midazolam promoted its expected anxiolytic actions compared to saline.

Therefore, DPAG GABA_A receptors appear not to affect rat EPM performance. Caution is recommended when interpreting previously reported intra-DPAG midazolam anxiolytic actions² due to its intrinsic chemical characteristics (i.e., its solubility

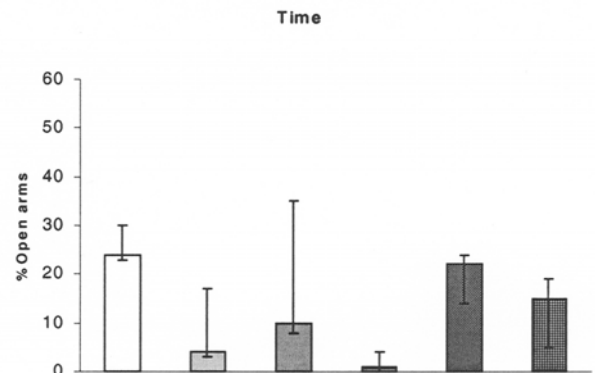
occurs in low pH solutions) and possible diffusion to other areas that can also affect this behavior, such as the nearby dorsal raphe.^{2,4} It is noteworthy that midazolam effects cannot be completely antagonized by bicuculline, a GABA receptor antagonist. Indeed, benzodiazepines can interact with other neurotransmitters within the DPAG and, compared to muscimol, can exert different actions on heterogeneous GABA_A receptor subtypes.⁵ The well-known complexity of the neurochemical basis of anxiety is supported by the findings reported above.

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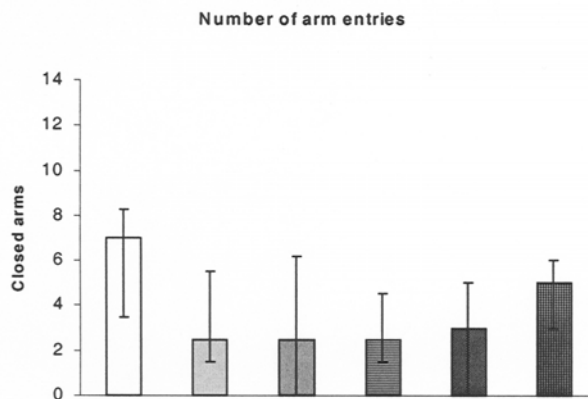
A



B



C



D

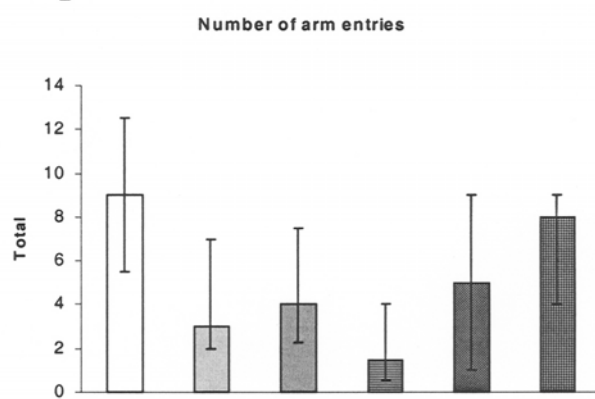


Figure 2 - Bars represent median values and the distribution of data as interquartile ranges for the percentage of open arm entries (A), percentage of total time spent on the open arms (B), number of closed arm entries (C), and total number of arm entries (D) of rats tested in the elevated plus-maze. Animals were microinjected into the DPAG with saline (0.3 µl), muscimol (20, 50 or 150 pg/0.3 µl) or midazolam (0.1 or 35.3 µg/0.3 µl). No statistically significant effect was found in any of the studied parameters among groups (after the Kruskal-Wallis test, significant level set as $p < 0.05$).

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Bipolar disorder: building the path of return to the ideas of Kraepelin

Transtorno bipolar: a construção do caminho de retorno às idéias de Kraepelin

Dear Editor,

Kraepelin (1921) described a wide spectrum of cases of mania and hypomania ranging from euphoric episodes up to predominantly dysphoric or mixed presentations with symptoms of depression.¹ However, in the middle of the 20th century, influential psychoanalytical writings focused on the euphoric cases of these episodes. Post-hoc interpretations of Kraepelin's ideas led to the adoption of the term 'bipolar' which implies that mania and hypomania are opposite poles of depression.² Many authors suggest that a return to the concepts developed by Kraepelin would be advantageous.² However, there are some criticisms to the widening of the concept of BD.³ Recent advances (to some extent referring to the original descriptions of Kraepelin)¹ expanded bipolarity to a broader spectrum.⁴

From a pragmatic standpoint, we believe that the adoption of the concept of a bipolar spectrum may be rather premature. Even using the standard DSM-IV nomenclature, the lag between the initial symptoms of the disorders and the diagnosis of bipolar illness is usually of about one decade, across different countries.⁵⁻⁶ A worrying scenario would be "an overenthusiastic" adoption of the bipolar spectrum in the international nomenclature, not matched by the necessary re-education of health care professionals. The descriptions made by Kraepelin derived from careful observation, which was systematic and longitudinal. Would such sophisticated psychopathology be feasible within the managed care era? We believe that there is a lot to be done in order to bridge the advances made in the psychopathological appraisal of bipolar patients and the adoption of operational criteria to classify patients suffering from the 'soft spectrum' of the Bipolar Disorders.

Should we return to Kraepelin? This seems the right thing to do. However, it's important to pave this returning path with sound evidence, and continuing medical education programs.

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Mogens Schou e o uso do lítio em psiquiatria

Mogens Schou and the use of lithium in psychiatry

Sr. Editor,

Muitos artigos na literatura científica fornecem dados históricos sobre a descoberta do lítio e seu desenvolvimento na psiquiatria, desde sua descoberta na Austrália, seu desenvolvimento primeiramente na Europa e então nos Estados Unidos.¹ O grande marco na história do lítio ocorreu em 1954, quando o pesquisador dinamarquês Mogens Schou e colegas publicaram seu primeiro estudo duplo-cego do lítio na mania, iniciando um trabalho de toda a vida de Schou na pesquisa do lítio e ensino.² O uso do lítio no transtorno bipolar (TB) causou uma revolução na psicofarmacologia, pois forçou os psiquiatras a pensarem em termos de diagnóstico, pois a utilidade do lítio nos quadros de mania clássica foi consagrada por diversos estudos científicos²⁻⁴ e pela prática clínica.

Durante muitos anos, o lítio foi o único estabilizador do humor. Mais recentemente, outras medicações começaram a ser utilizadas para esse fim, principalmente os anticonvulsivantes e antipsicóticos atípicos. Estas medicações, com características farmacológicas, posológicas e clínicas diferentes, colocaram em cheque o "reinado" do lítio e o seu papel atual no arsenal terapêutico do TB. O que se observa na prática clínica é um declínio do uso desta medicação. Diversos motivos podem ser alegados para isso: dificuldades posológicas, efeitos adversos graves (raros) e o investimento da indústria farmacêutica no desenvolvimento de novas medicações.

Contudo, o carbonato de lítio, após 50 anos, continua sendo um tratamento de primeira linha para a maioria dos pacientes bipolares. Os estudos e a prática clínica ainda consagram o lítio como o estabilizador de humor por excelência. Diretrizes elaboradas através de uma abordagem baseada em evidências