Title : MORPHINE TOLERANCE, DEPENDENCE, ANALGESIA AND HYPERALGESIA: AN ELECTROPHYSIOLOGICAL APPROACH

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Introduction. The caudate nucleus (CN) and the periaqueductal gray (PAG) are two brain sites known to contain high concentration of opiate receptors. While the CN was suggested to mediate processes which lead to hyperalgesia (1), the PAG has been suggested to have a role in the mediation of morphine-induced analgesia (2). The present study compares the direct actions of morphine and naloxone on the neuronal activity of the CN and PAG in both morphine-naive (MNR) and morphine-dependent (MDR) rats. Such a comparison is especially important in the wake of increasing number of reports demonstrating the presence of multiple opiate receptors in brain tissue.

Methods. Experiments were performed on male Sprague-Dawley rats. Each rat in the MDR group was subcutaneously implanted with one pellet of morphine base (75 mg) and was used in the experimental procedure 72 to 96 hours after the implantation. Animals were anasthetized with urethane (1.2 g/kg) and placed in a stereotaxic apparatus. Recordings of CN and PAG neuronal activity and microiontophoresis of morphine and naloxone were made using 5-barreled micropipettes. Data were collected and recorded on an analog magnetic tape and later were retrieved for analysis with a microcomputer via a window discriminator to produce frequency histograms and accumulating integrated activity (Fig. 1)

Results. Four different patterns of neuronal response to increasing microiontophoretic doses of morphine could be detected in both the CN and the PAG of either MNR or MDR. However, differences in the response to morphine were found between the two areas in MDR. While the CN neurons of these animals exhibited supersensitivity to microiontophoretically applied morphine, the PAG neurons of MDR displayed tolerance to the drug and in some, morphine dependence was evident when naloxone microiontophoresis was used. The distribution of the spontaneously active neurons within the two brain regions in MDR was found to be generally corresponds to the known distribution of opiate binding sites in the striatum and the central gray matter.

Discussion. The results of the present study support the notion that the distinction between the CN and the PAG responses to direct application of morphine is the outcome of differences in the nature of the opiate receptors of these two brain nuclei. Moreover, phenomena like morphine acute and chronic tolerance, and morphine dependence were characterized electrophysiologically, and have been shown to be related to different brain sites where analgesia and tolerance to morphine (PAG) and hyperalgesia and supersensitivity (CN) are originating.

References.

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2. Jacquet YF, Lajtha A: The periaqueductal gray: site of morphine analgesia and tolerance as shown by 2-way cross tolerance between the systemic and the intracerebral injections. Brain Res. 103: 501-514, 1976

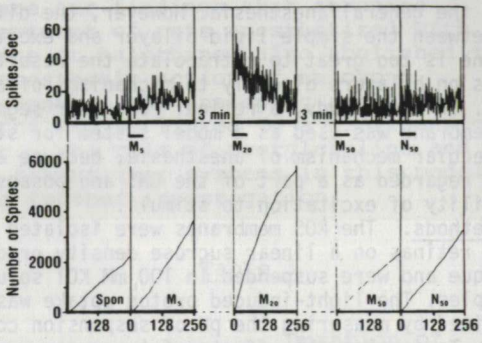

Fig. 1. Frequency histogram and integrated accumulating counts of a PAG neuron in naive rat and the effect of increasing iontophoretic currents (nA) of morphine (M) and one dose of naloxone (N). A recovery period of 3 min was allowed between each morphine treatment.

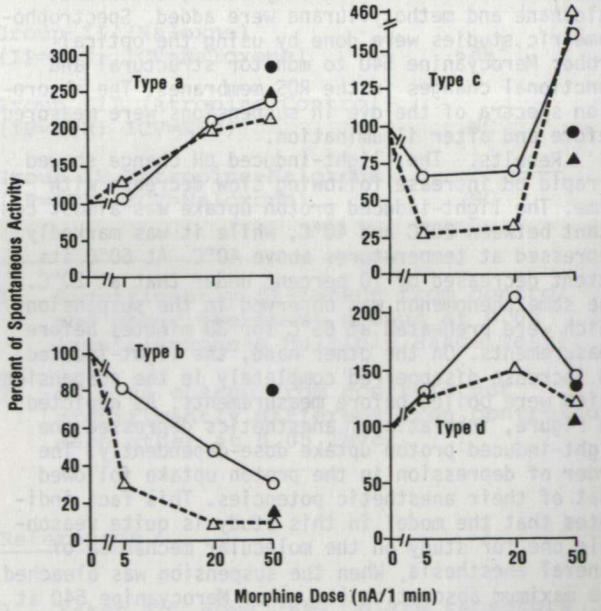

Fig. 2. Representative effects of increasing doses of microiontophoretically applied morphine on 4 CN (o—o) and 4 PAG (△--△) neurons firing rate in naive rats as compared to control (spontaneous activity), and the effect of one dose (50 nA/1 min) of naloxone (●,▲)given after the last injection of morphine. Four different patterns of response (a, b, c, and d) are shown.