Age-dependent antinociception and behavioral inhibition by morphine

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ABSTRACT

In current clinical practice, morphine is dosed in older patients based on patient-weight, with different calculations for adjustment. However, at present, neither clinical experience nor the literature offers a clear evidence base for the relationship between antinociception, behavioral effects and morphine administration in older patients. In this study, we compared the nociceptive response of 8 and 24 week old rats after subcutaneous administration of morphine per body weight and analyzed their behavior using an advanced multi-conditioning system. Residual morphine in all major tissues was determined. We observed prolonged morphine-induced antinociception in older rats compared to younger rats. Moreover, morphine significantly stimulated locomotor and rearing behavior 180 min after injection, which was significantly higher in the 8 week compared to 24 week old rats. Tissue analysis from animals extracted 240 min post-injection revealed a significantly higher concentration of residual morphine in the brains of older versus younger animals when standardized on tissue weight. However, this effect was not observed when residual morphine was standardized on protein content. Collectively, our data suggest that in older rats morphine exhibits higher antinociception and increased behavioral inhibition compared to younger animals. This effect is likely due to a significantly higher accumulation of morphine in the brain of older animals.

1. Introduction

The proportion and number of older people is increasing globally with an expected 20% of the total population above 60 years of age by 2050 (WHO, 2015). These individuals experience pain comparatively more than younger people, which affects their daily activities and total quality of life. Noticeably, due to the high prevalence of pain, individuals over 60 years of age are the highest users of analgesics and with an expected 20% of the total population above 60 years of age by 2050 (WHO, 2015). These individuals experience pain comparatively more than younger people, which affects their daily activities and total quality of life. Noticeably, due to the high prevalence of pain, individuals over 60 years of age are the highest users of analgesics and

Therefore, there is an urgent need to identify a possible correlation between the antinociceptive and behavioral effects of morphine in aged individuals. At present, a limited number of studies suggest a physiological and/or molecular basis for the differences observed in opioid pharmacology when comparing aged and younger individuals (Tucker et al., 1989; Simon et al., 2015). However, the evident lack of

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The behavioral testing used six different activity parameters (total distance travelled, rearing time, ratio of presence in periphery versus center, clockwise rotation, anti-clockwise rotation and moving time). Behavior was tested in an open-field arena in a Multi-Conditioning System (MCS) (TSE GmbH, Homburg, Germany) 2 min after nociception-testing at 0 min (pre), 30 and 180 min after administration of morphine over a period of 5 min. Measurements in open field arena over a period of 5 min are commonly used (Rex et al., 1998; Prut and Belzung, 2003; Sestakova et al., 2013; Hollais et al., 2014) and allowed the concurrent measurements of antinociception in the same group of animals in this study. The MCS platform included an internal noise/light/temperature insulation system and a 3D infrared-beam frame that provided fast and accurate animal movement detection (100 Hz), combined with a high-resolution video monitoring and automated movement tracking system. Quantification and visualization of the MCS data were processed by integrated system software (TSE ActiMot). The open-field arena was thoroughly cleaned between each animal using paper towels soaked in diluted F10 solution. Background white noise (20 dB) was used during all experiments to cancel out environmental sounds.

2.5. Tissue collection

Immediately after testing antinociception at 240 min post-administration of morphine, animals were anesthetized with 5% (w/v) isoflurane in oxygen at a flow rate of 1 l/min, until loss of consciousness was observed (usually 5–7 min) and the animals were decapitated. Blood was collected from the decapitated body by gravity flow using 15 ml centrifuge tubes (Corning Centristar) and immediately
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