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ANTINOCICEPTIVE PROPERTIES OF SPHINGOSINE CYCLOANALOGUES

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INTRODUCTION

The effective treatment of severe pain continues to be one of the major challenges in healthcare. Sphingosine (SPH) is a natural unsaturated C-18 linear aminodiol, biosynthetically formed from its saturated precursor dihydrosphingosine (DSPH), and integrates sphingolipids, ceramides and other lipidic metabolites. Aiming to discover new antinociceptive agents, we have evaluated several SPH / DSPH cyclic analogues, with defined relative stereochemistries of the double bond and the amino and hydroxyl groups.

MATERIAL AND METHODS

The starting chemical substrates were certain racemic 3-alkylidenecyclohexane epoxides, which were either hydrolyzed to diols, or transformed into alkylaminocyclo-alkanols, through epoxide opening with primary amines, and some of them into cyclic diamines, through several steps from aminoalcohols. Swiss Webster male mice were pre-treated with the compounds (1.0 mg/kg, *ip*), administered prior to the injection of aqueous acetic acid (0.6%). Positive control animals were pre-treated with acetylsalicylic acid (ASA) (10 mg/kg, *ip)* as the reference drug. The number of abdominal constrictions was cumulatively counted over a period of 20 min. The antinociceptive activity was expressed as the difference in the number of abdominal contractions between control and pre-treated animals. The experiments were approved by CEUA (113/2005-03)

RESULTS

The sphingosine cycloanalogues here studied, were designed from previous lipidic linear ethylenediamine and amino-alcohol derivatives, which had displayed promising analgesic effects. All the compounds evaluated resulted much more potent than ASA, used as standard drug, because the sphingosine cycloanalogues were tested at 1 mg/kg and, at such dose, attained levels of 55.3 - 85.6 % of contractions inhibition, whereas ASA, tested at 10 mg/kg, only attained a 35% of inhibition in the same test. Together with the epoxide precursor, that presented a 78.1% of inhibition, the most potent compounds were the aminocyclohexanols with the C14 side-chain and with different alkyl substituents on the amine. Those with ethyl, *n*-butyl, and *n*-decyl groups attained the highest inhibition levels of 85.6, 79.8 and 82.2 %, respectively.

CONCLUSIONS

All the compounds tested showed relevant analgesic activity, with the ß-aminoalcohol derivatives as the most promising. Compared to the reference drug ASA, these compounds resulted similarly potent at doses around eighteen times lower. In conclusion, cyclosphingosine analogues seem to merit further studies oriented to the development of new analgesic agents.

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