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Sertraline and amitriptyline enhance histamine metabolism in guinea-pig tissues

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Background

Aside from their typical use to treat depression, many antidepressants are also used to treat anxiety disorders and chronic pain disorders. Moreover, it has been proved that they show anti-inflammatory effects. We believe that a part of this effect of antidepressants can arise as a consequence of histamine elimination from the site of inflammation. In mammals, histamine is mainly metabolised by diamine oxidase (DAO) and histamine-N-methyltransferase (HNMT). Therefore, we studied the effects of two antidepressants, amitriptyline and sertraline, on histamine metabolism in guinea-pigs.

Methods

Guinea-pigs were treated with amitriptyline (4 mg/kg, i.p.) and/or histamine (10 µg/kg, i.v.). Tissue and plasma histamine and methylhistamine concentrations were then measured using high performance liquid chromatography. In the animals treated only with amitriptyline (or saline), DAO and HNMT tissue mRNAs were detected by PCR. In the same tissues, specific enzymatic activities of DAO and HNMT were measured by radiometric assays. In addition, DAO and HNMT activity was measured after *in vitro* incubation with different concentrations of sertraline and amitriptyline.

Results

Five minutes after i.v. histamine application, plasma histamine concentration reached its maximum and thereafter slowly decreased. Meanwhile, histamine was distributed into several tissues, where concentrations of histamine and methylhistamine significantly increased. This distribution was faster in animals pre-treated with amitriptyline, reflecting also faster decreases in plasma histamine concentrations. In some tissues of the amitriptyline-treated animals the amount of DAO and HNMT mRNA as well as enzyme activity increased. In these tissues, we detected lower histamine concentrations and higher methylhistamine concentrations, indicating a faster histamine metabolism in the amitriptyline-treated animals. Our *in vitro* results showed that both antidepressants change DAO and HNMT activity also at the molecular level.

Conclusions

Our results clearly show that the metabolism of histamine is enhanced when antidepressants are present. Amitriptyline induced enzyme mRNA synthesis and increased enzyme activity, and consequently lowered tissue histamine concentration. At some concentrations, sertraline increased DAO activity, but had no effect on HNMT activity. Due to the fact that we managed to decrease the histamine concentration in the tissues, we expect the effects of histamine in antidepressant-treated animals to be less dramatic.