AGONIST ACTIVITY OF N-DESMETHYLCLOZAPINE, A MAJOR CLOZAPINE METABOLITE, AT DELTA OPIOID RECEPTORS

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In the present study we report that N-desmethylclozapine (NDMC), a pharmacologically active metabolite of the atypical antipsychotic clozapine (CLOZ), acts as a selective and efficacious agonist at δ-opioid receptors. In Chinese hamster ovary (CHO) cells stably expressing the human δ-opioid receptor (CHO/DOR), NDMC behaves as a full agonist in stimulating [^{35}S]GTPγS binding and in inhibiting cyclic AMP formation. In radioligand binding assays, NDMC inhibits [^{3}H]naltrindole binding to CHO/DOR membranes with competition curves that are modulated by guanine nucleotides in an agonist-like manner. Estimation of intrinsic efficacies indicates that NDMC has an efficacy value equal to ~ 80 % of that of the full δ-opioid receptor agonist DPDPE, whereas CLOZ and the other CLOZ metabolite clozapine N-oxide display a much lower efficacy. NDMC exhibits poor agonist activity at the κ-opioid receptor and is inactive at the μ-opioid and NOP receptors. In NG108-15 cells, NDMC inhibits cyclic AMP formation and stimulates ERK1/2 phosphorylation by acting on δ-opioid receptors. Moreover, long-term exposure to NDMC causes desensitization of δ agonist-induced responses. In membranes of different rat brain regions, NDMC stimulates [^{35}S]GTPγS binding and regulates adenylyl cyclase activity and these effects are potently antagonized by naltrindole. These data suggest that the unique property of NDMC to activate δ-opioid receptors may contribute to the clinical actions of the atypical antipsychotic CLOZ.