REVIEW OF CLINICAL PHARMACOLOGY AND
PHARMACOKINETICS INTERNATIONAL
EDITION 24: 176-177 (2010)

Behavioural and Neurochemical Changes of Etoricoxib: A Possible Implication of Serotonin Receptors 5-$HT_{1A/2A}$

Martha Nikolaidou, Katerina Antoniou, Periklis Pappas, Marios Marselos

Department of Pharmacology, Medical School, University of Ioannina, GR-45110 Ioannina, Greece

S u m m a r y. Etoricoxib, a selective inhibitor of cyclooxygenase-2 (COX-2) has been found to provoke behavioural changes in the rat. In the present study, we examined the possible involvement of serotonin receptors (5-HT_{1A} and 5-HT_{2A}) on etoricoxib-induced effects on behaviour. Male Wistar rats were used in all experiments. Selective agonists and antagonists of 5-HT_{1A} and 5-HT_{2A} receptors were injected separately, or in combination with etoricoxib. Spontaneous activity was recorded for one hour and was found to be increased when etoricoxib was given alone. The levels of brain serotonin were also determined by HPLC and were found significantly increased after etoricoxib administration. The increased behavioural activity produced by etoricoxib was inhibited by either a selective 5-HT_{1A} antagonist or a 5-HT_{2A} agonist. Our results indicate that behavioural changes after etoricoxib treatment are mediated by central seroto-ninergic mechanisms.

INTRODUCTION

Cyclooxygenase is the key enzyme that converts arachidonic acid (AA) to prostaglandins (PGs) and exists in two isoforms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Although COX-2 is induced by inflammation and cell proliferation, it is constitutively expressed in the rat brain predominantly, in discrete population of neurons (1).

So far, several studies have demonstrated an implication of serotonin receptors (5-HT_{1A}, 5-HT_{2A}) in fever, analgesia and inflammation (2-4). Mackowiak et al., (2002) also reported a co-localization of 5-HT_{2A} receptors and expression of cyclooxygenase-2 in cortical regions of the brain (5). In a previous work we demonstrated that etoricoxib (a cyclooxygenase-2 inhibitor) induced neurochemical changes and alterations on behavioural activity even at doses similar with those used in humans (6). Therefore, it was of interest to examine further a possible implication of specific serotonin receptors (5-HT_{1A}, 5-HT_{2A}) in the actions of etoricoxib.

MATERIALS AND METHODS

Male Wistar rats (3-months old) were included in all experimental protocols. A 5-HT_{1A} selective agonist (8-OH-DPAT) and antagonist (WAY-100135) were injected separately, at doses of 0.3 mg/kg and 1 mg/kg respectively, or in combination with etoricoxib (1 and 10 mg/kg). In another experimental protocol, a 5-HT_{2A} selective agonist (DOI) and antagonist (ketanserin) were injected separately, at doses of 0.3 mg/kg and 3 mg/kg respectively, or in combination with etoricoxib (1 and 10 mg/kg).

Spontaneous behaviour was recorded for one hour, using a computerized activity monitoring system (ENV515, Activity Monitor, version 5, Med. Associates, USA). At the end of experiment several brain tissues were removed for the evaluation of serotonin (5-HT) and dopamine (DA) levels in discrete brain regions. A High Pressure Liquid Chromatography (HPLC) method was used to determine the levels of brain neurotransmitters (7, 8).

RESULTS

Even though 8-OH-DPAT had no impact on the increased mobility observed after etoricoxib administration, the 5-HT_{1A} agonist completely inhibited the increased levels of serotonin after administration of etoricoxib, in all brain regions studied. On the other hand, WAY-100135 abolished the action of etoricoxib only on the vertical mobile activity while abolished the action of etoricoxib on

serotoninergic function in specific rat brain regions.

With regard to 5-HT_{2A} receptors, it appears that DOI inhibited the effects of etoricoxib on rat mobility as well as on the serotoninergic function in the brain regions included in the study. On the contrary, ketanserin had no effect on etoricoxib-induced changes on the rat mobility while inhibited partially the etoricoxib action on serotoninergic function.

CONCLUSIONS

Etoricoxib induced changes on the behaviour of the rat as well as on neurochemical parameters of the brain, mainly referring to the serotoninergic transmission. Further investigation on the action of etoricoxib revealed an involvement of the serotoninergic receptors 5-HT_{1A} and 5-HT_{2A}, of which the 5-HT_{2A} seems to have a more important role. The involvement of 5-HT_{2A} in the expression of cyclooxygenase-2 in the brain (5) is also supported by our results. The effects of etoricoxib on the serotoninergic system in the rat brain indicate a possible interaction of this drug with central prostaglandins and other inflam-mation factors. This phenomenon needs to be further investigated.

*This research project is co-financed by E.U.-European Social Fund (75%) and the Greek Ministry of Development-GSRT (25%).

REFERENCES

1. Yamagata K., Andreasson K.I., Kaufmann W.E., Barnes C.A., Warley P.F.: Expression of a mitogen-inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. *Neuron 11*: 371-386 (1993)
2. Blessing W.W.: 5-Hydroxytryptamine 1A receptor activation reduces cutaneous vasoconstriction and fever associated with the acute inflammatory response in rabbits. *Neuroscience 123*: 1-4 (2004)
3. Sufka K.J., Schomburg F.M., Giordano J.: Receptor mediation of 5-HT-induced inflammation and nociception in rats. *Pharmacol. Biochem. Behan. 41*: 53-56 (1992)
4. Sadrini M.L., Vitale G., Pini L.A.: Effect of rofecoxib on nociception and serotonin system in the rat brain. *Inflamm. Res. 51*: 154-159 (2002)
5. Mackowiak M., Chocyk A., Sanak M., Czyrak A., Fizal K., Wedzony K.: DOI, an agonist of 5-$HT_{2A/2C}$ serotonin receptor, alterss the expression of cyclooxygenace-2 in the rat parietal cortex. *J. Physiol. Pharmacol. 53*: 395-407 (2002)
6. Nikolaidou M., Pappas P., Antoniou K., Marselos M.: Effects of a selective cyclooxygenase inhibitor on behavioural and neurochemical parameters. *Rev. Clin. Pharmacol. Pharmacokinet. 22*: 263 (2008)
7. Sharp T., Zetterström T., Series H.G., Carlsson A.,A., Grahame-Smith D.G., Ungerstedt U.: HPLC-EC analysis of catechols and indoles in rat brain dialysates. *Life Sci. 41*: 869-872 (1987)
8. Dalla C., Antoniou K., Kokras N., Drossopoulou G., Papathanasiou G., Bekris S., Daskas S., Papadopoulou-Daifoti Z.: Sex differences in the effects of two stress paradigms on dopaminergic neurotransmission. *Physiol Behav. 93*: 595-605 (2008)