RTI Author Awards Series

Enantioselective Effects of Hydroxy Metabolites of Bupropion on Behavior and on Function of Monoamine Transporters and Nicotinic Receptors

Damaj, M.I., **Carroll, F.I.,** Eaton, J.B., **Navarro, H.A., Blough, B.E.**, Mirza, S., Lukas, R.J., Martin, B.R. (2004). Enantioselective effects of hydroxy metabolites of bupropion on behavior and on function of monoamine transporters and nicotinic receptors, *Molecular Pharmacology*, 66 (3):675-682.

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Bupropion is an atypical antidepressant with an unusual non-serotonergic mechanistic profile, compared to the more common serotonin reuptake inhibitor (SSRI) class of antidepressants. Although it was prescribed clinically as Wellbutrin®, scientists quickly discovered that bupropion also had smoking cessation properties. At the time of this article's publication, bupropion was the only therapeutic in the clinic for smoking cessation, other than nicotine replacement strategies (gum or patch). The underlying mechanisms for this clinical observation were unknown, but as with bupropion's antidepressant activity, the metabolite of bupropion was suspected as being a major contributor.

In this publication, we synthesized and studied bupropion and the optically active metabolites in a series of cellular-based assays and animal behavioral tests. We showed that the (*S*,*S*)-hydroxybupropion metabolite was potent as an inhibitor of the $\alpha 4\beta 2$ nicotinic receptor, one of the most prominent nicotinic receptors in the human brain. The (*S*,*S*)-hydroxybupropion metabolite was also more potent in a standard model of depression (forced swim test), suggesting that the metabolite may be the active component for depression.

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