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Medicine in focus

Is the inhibition of nicotinic acetylcholine receptors by bupropion involved in its clinical actions?

Hugo R. Arias*

Department of Pharmaceutical Sciences, College of Pharmacy, Midwestern University, 19555 N. 59th Avenue, Glendale, AZ 85308, USA

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ABSTRACT

In this mini review we will focus on those molecular and cellular mechanisms exerted by bupropion (BP), ultimately leading to the antidepressant and anti-nicotinic properties described for this molecule. The main pharmacological mechanism is based on the fact that BP induces the release as well as inhibits the reuptake of neurotransmitters such as a dopamine (DA) and norepinephrine (NE). Additional mechanisms of action have been also determined. For example, BP is a noncompetitive antagonist (NCA) of several nicotinic acetylcholine receptors (AChRs). Based on this evidence, the dual antidepressant and anti-nicotinic activity of BP is currently considered to be mediated by its stimulatory action on the DA and NE systems as well as its inhibitory action on AChRs. Considering the results obtained in the archetypical mouse muscle AChR, a sequential mechanism can be hypothesized to explain the inhibitory action of BP on neuronal AChRs: (1) BP first binds to AChRs in the resting state, decreasing the probability of ion channel opening, (2) the remnant fraction of open ion channels is subsequently decreased by accelerating the desensitization process, and (3), BP interacts with a binding domain located between the serine (position 6′) and valine (position 13′) rings that is shared with the NCA phencyclidine and other tricyclic antidepressants. This new evidence paves the way for further investigations using AChRs as targets for the action of safer antidepressants and novel anti-addictive compounds.

1. Introduction

Clinical depression is a chronic illness that affects approximately 5–8% of the population of American adults or about 15 million people each year (NIMH, 2008). Those suffering from depression experience symptoms such as persistent feelings of sadness, hopelessness, worthlessness, and loss of interest in typical daily activities. If this disorder is left untreated, the patient may eventually develop thoughts of suicide or engage in suicidal behavior. This common mental health disorder is the leading cause of disability in the USA and other developing countries. People from all ethnic, socio-economic, sex, and age groups are susceptible to depression.

Although we do not have a clear view of the causes underlying mental depression, genetic and/or epigenetic factors might be involved (Levinson, 2006; Caspi et al., 2003). For example, the latest evidence from brain imaging studies supports the view that the familial component is very important in the development of this disease (Peterson et al., 2009). Fig. 1 shows that the cortical thickness of right brain hemispheres from nondepressed persons with family history of depression (high-risk group) is thinner than that from persons without family history of depression (low-risk group). However, a familial trait is not necessary of genetic origin, and might also be consequence of changes in the environment when children are growing up with parents or grandparents who are depressed. Fortunately, depression is a CNS disorder that when properly treated, the symptoms will diminish or disappear completely. This opens up the possibility for a patient diagnosed with depression to lead a healthy, typical lifestyle. Antidepressants have been used therapeutically to treat depression for many years. However, it is still unclear exactly how these drugs work. Several antidepressants prevent the reuptake of specific neurotransmitters from the synaptic cleft, leaving them available for interaction with receptors on the postsynaptic neuron. Some other antidepressants inhibit the enzymes (i.e., monoamine oxidase, MAO) involved in monoamine degradation, increasing the concentration of biogenic amines including serotonin (5-HT), norepinephrine (NE), and dopamine (DA). Depending on their mechanisms of action and on their structural features, there are currently nine main cate-

Abbreviations: Bupropion (BP), (±)-2-(*tert*-butylamino)-1-(3-chlorophenyl) propan-1-one; DA, dopamine; DAT, dopamine transporter; NE, norepinephrine; NET, norepinephrine transporter; NDRI, norepinephrine-dopamine reuptake inhibitor; 5-HT, 5-hydroxytryptamine (serotonin); ACh, acetylcholine; NCA, noncompetitive antagonist; AChR, nicotinic acetylcholine receptor; MAO, monoamine oxidase; TCAs, tricyclic antidepressants; VTA, ventral tegmental area; [^{3}H]TCP, [piperidyl-34-^{3}H(*N*)]-*N*-(1-(2 thienyl)cyclohexyl)-3,4-piperidine; PCP, phencyclidine.

* Tel.: +1 623 572 3589; fax: +1 623 572 3550.
E-mail address: harias@midwestern.edu.

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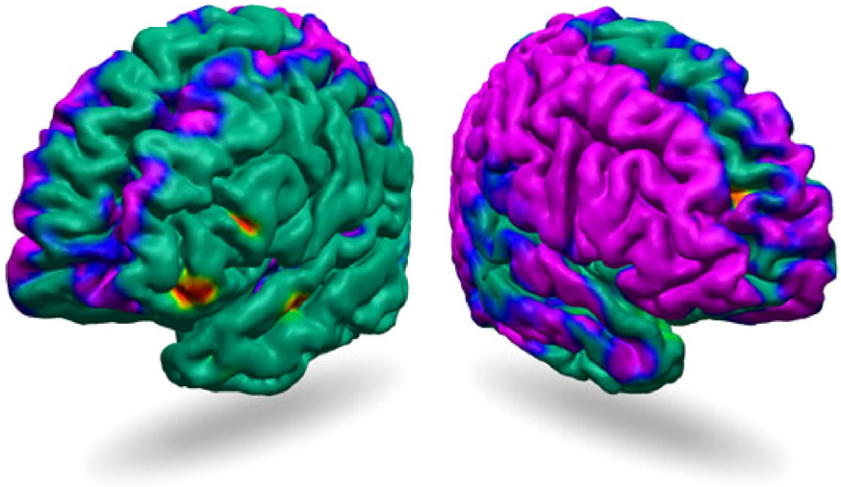

Fig. 1. Side views of the right and left hemispheres of the brain (modified from Peterson et al., 2009). The colors represent the differences in cortical thickness between the groups with (high-risk group) and without (low-risk group) family history of depression. Blue and purple represent the thinning of the cortex, with purple regions having the greatest thinning. Green areas show no significant differences between the two groups.

gories of antidepressants (reviewed in Baldessarini, 2001; Arias et al., 2006a): (1) MAO inhibitors (e.g., phenelzine), the oldest used antidepressants, (2) selective 5-HT reuptake inhibitors (e.g., fluoxetine), (3) selective NE reuptake inhibitors (e.g., reboxetine), (4) dual NE-5-HT reuptake inhibitors (e.g., venlafaxine), (5) tricyclic antidepressants (TCAs), which are classified based on their common structure, and although they are old antidepressants some of them inhibits both the 5-HT and NE transporters (e.g., amitriptyline, imipramine, doxepin, and clomipramine), whereas some others are considered as specific NE reuptake inhibitors (e.g., desipramine and nortriptyline), (6) 5-HT type 2 receptor inhibitors (e.g., trazodone), (7) α_2-adrenergic antagonist and 5-HT type 2 and 3 receptor inhibitors (e.g., mirtazapine), and (8) natural antidepressants (e.g., hyperforin), whose mechanisms of action are still unclear. Finally, (9) bupropion (BP) [(±)-2-(*tert*-butylamino)-1-(3-chlorophenyl)propan-1-one] (see its molecular structure in Fig. 2) is a unique antidepressant whose aminoketone structure differs from that for other antidepressants in the market and functionally is classified as a dual NE-DA reuptake inhibitor (NDRI). In this mini review we will focus on those molecular and cellular mechanisms exerted by BP regarding its antidepressant and anti-nicotinic activities.

The most accepted mechanism of action for BP is that this antidepressant inhibits the catecholamine reuptake in presynaptic neurons, modulating the concentrations of the neurotransmitters DA and NE in the synaptic cleft. Fig. 3 shows the most accepted mechanism of action for BP as a NDRI. However, the affinity of BP for these neurotransmitter transporters is only moderate (see Table 1), and there is not clear-cut evidence explaining the dual antidepressant and anti-nicotinic modes of action elicited by BP. In this regard, the combined inhibition of nicotinic acetylcholine receptors (AChRs) and neurotransmitter transporters produced by BP might account for its clinical efficacy in smoking cessation therapy and as an antidepressant. Moreover, the contribution of the BP-induced AChR inhibition to its clinical action could be two-fold important: as part of the side effects (i.e., dry mouth, nausea, and insomnia) elicited by BP and/or as part of its clinical outcome. Thus, a better understanding of the interaction of BP with the AChR in different conformational states to determine its noncompetitive inhibitory mechanism is crucial to develop safer and more efficient antidepressants and/or anti-nicotinic drugs. In this regard, the interaction of BP with AChRs in different conformational states was recently determined by functional and structural approaches (Arias et al., 2009).

2. Bupropion is a catecholamine transporter inhibitor

Bupropion has been used for long time as an antidepressant (Wellbutrin®) as well as in the pharmacotherapy for smoking cessation (Zyban®) (Wilkes, 2006; Dwoskin et al., 2006). BP, as well as other more specific antidepressants, can be used for the treatment of atypical depression, which is associated with interpersonal deficits such as rejection sensitivity and social avoidance (reviewed in Levitan, 2007). It has also recently been used "off-label" for the treatment of attention deficit hyperactivity disorder (ADHD) (reviewed in Slatkoff and Greenfield, 2006; Covey et al., 2008), and it is the only antidepressant with high efficacy to prevent depressive relapse for seasonal affective disorder (SAD) (reviewed in Stahl et al., 2004). Finally, BP has showed positive effects as an adjunct for weight loss in nondepressed, obese individuals (Anderson et al., 2002). From the clinical point of view, BP only produces minor side effects including dry mouth, nausea, and insomnia, lacking major events produced by other antidepressants such as sexual dysfunction, weight gain, and sedation (reviewed in Stahl et al., 2004). These therapeutic properties have been discovered and adopted on the basis of the many pharmacological properties that this molecule exhibits. For instance, BP has been considered to be a dual NDRI (Fig. 3), a vesicular monoamine transport enhancer (Rau et al., 2005), an anti-inflammatory agent against the actions of cytokines such as tumor necrosis factor-α, a cytochrome P450 CYT2D6 inhibitor (Wilkes, 2006), and a noncompetitive antagonist (NCA) of several AChRs (see Section 5). Currently, BP constitutes an important pharmacological tool for biomedical research given its proved capacity to inhibit DA and NE reuptakes.

The first neurochemical studies on the central mechanisms of BP suggested that the antidepressant activity of BP is not merely due to MAO inhibition or biogenic amines release from nerve endings (Ferris et al., 1982). In this study, the authors showed that BP was a weak inhibitor of catecholamine transporters, but its selective blockade of the DA transporter (DAT) *in vivo* could be correlated with mild stimulation of the CNS in rodents. These and other properties, such as the lack of desensitization of β-adrenergic receptors in rat cerebral cortex, served to postulate BP as an "atypical" antidepressant with different modes of action of those for MAO inhibitors and TCAs. Shortly thereafter, new studies reinforced these observations by discriminating the antidepressant activity of BP from MAO inhibition (Ferris et al., 1983). Although in this study it was clear that DA neurons have to be present for BP to exert its effects on the CNS, they found that at antidepressant doses of BP, the DA turnover