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Neuroreceptor imaging in depression

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ABSTRACT

The in vivo study of receptor binding potential in the human brain is made possible by positron emission tomography (PET) imaging. Here we review PET studies of neuroreceptor function in mood disorders — specifically, major depressive disorder (MDD) and bipolar disorder (BD). We concentrate on the most widely studied receptors of the serotonergic and dopaminergic systems. Specifically, the serotonin 1A (5-HT_{1A}), serotonin 2A (5-HT_{2A}), serotonin 1B (5-HT_{1B}), dopamine 1 (D1), and dopamine 2/3 (D2/3) receptors. We also review PET studies of the serotonin transporter (5-HTT), the dopamine transporter (DAT), monoamine oxidase A (MAO-A), and the muscarinic 2 receptor (M2). On the basis of the PET literature as well as supporting genetic studies, postmortem data, and preclinical models of depression, and several models of how monoaminergic function is altered in mood disorders are discussed with respect to inflammation, endocrine dysfunction, depression subtypes, and altered neurocircuitry.

Contents

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Introduction

Positron emission tomography (PET) makes use of the radioactive decay of positron-emitting nuclides to measure cerebral blood flow, metabolic activity or protein binding, in vivo. In vivo receptor function is best represented by the binding potential (BP), defined as the product of the density of receptors available to bind the radioligand (B_{avail}) and the affinity of the radioligand for its receptor ($1/K_D$), where K_D is the dissociation constant (Mintun et al., 1984). Stated differently, BP is the ratio of specifically bound to free tracer at equilibrium in a region of interest in the brain. In the context of PET, three different reference concentrations generally have been used to calculate this ratio and therefore there are three ways that the term "BP" is used in the PET literature.

The BP_F refers to the ratio at equilibrium of the concentration of specifically-bound radioligand in the brain to the concentration of free radioligand in the brain (Innis et al., 2007). In order to estimate the concentration of the unbound radioligand in the brain, the concentration of free radioligand in the plasma is measured from arterial blood samples obtained during the scan. Here the assumption is that under conditions of passive diffusion the concentration of free radioligand in the plasma equals the concentration of free radioligand in the brain. In practice, however, the free fraction of radioligand in the plasma cannot always be distinguished from protein-bound radioligand in the plasma. Thus a second method for assessing the BP involves calculation of BP_P: the ratio of specifically-bound radioligand in brain tissue to free plus protein-bound radioligand in plasma at equilibrium (Innis et al., 2007). In other words, BP_P is not corrected for the fraction of the tracer that is bound to plasma proteins. In mathematical terms, $BP_P = C_T - C_{ND}/C_P$ where C_T and C_{ND} denote mean radioactivity concentrations in the region of interest and reference region (see below), respectively, and C_P denotes the equilibrium concentration of radiotracer in the plasma.

The calculation of BP_F and BP_P necessitates arterial plasma sampling and tracer kinetic modeling and therefore the non-displaceable BP (BP_{ND}), which approximates BP_F and BP_P for certain radioligands, is usually used where possible. BP_{ND} is the ratio of free plus specifically-bound radiotracer to free plus nonspecifically bound (non-displaceable) radiotracer in brain tissue at equilibrium (Innis et al., 2007). BP_{ND} is calculated using a reference region, i.e. a region of the brain with negligible density of the receptor of interest. Thus BP_{ND} is the ratio of activity in a region where the target receptor protein is abundantly expressed to activity in a control region that is essentially devoid of the target receptor protein. A limitation of the BP_{ND} parameter is that a group difference can be driven by an abnormality in either the target tissue or the reference tissue. Here, the assumption is that the non-displaceable binding does not differ between the experimental and control subject samples.

In addition, the relative contributions of receptor density and receptor affinity to the BP parameter vary according to whether the radiotracer is an agonist or an antagonist. Antagonists bind with equal affinity to receptors in both high and low affinity states and thus largely measure receptor density while agonists bind preferentially to receptors in the high affinity state and are therefore sensitive to both receptor density and affinity. The majority of radioligands developed to date to measure receptor binding in the brain have been antagonists (Table 1).

Another potential measure of receptor or enzyme function is volume of distribution (V_T), which refers to the ratio of the concentration of the radioligand (at equilibrium) in the brain tissue (C_T) to the concentration of the radioligand in plasma (C_P) (Innis et al., 2007). V_T is used as a measure of receptor binding when no adequate reference region in the brain is available because of the ubiquity of the receptor under study. Because the total concentration of radioligand in the brain tissue (C_T) is composed of specifically bound (C_S), non-specifically bound (C_{NS}) and free radioligand (C_{FT}), the nomenclature V_S is used to signify that the volume of distribution reflects the ratio of the specifically-bound radiotracer in the brain to the concentration of the radiotracer in the plasma. V_S can be regarded as essentially equivalent to BP_F or BP_P (Innis et al., 2007).

In this review we focus on PET studies of neuroreceptor function in mood disorders — specifically, major depressive disorder (MDD) and bipolar disorder (BD). We concentrate on the most widely studied receptors of the serotonergic and dopaminergic systems: the serotonin 1A, serotonin 2A, dopamine 1, and dopamine 2/3 receptors. We also include studies of the serotonin transporter, the dopamine transporter, monoamine oxidase A (MAO-A), the serotonin 1B receptor, and the muscarinic 2 receptor. In the Results section, below, we present an overview of the findings for each receptor. In the Discussion section, we consider the possible reasons for the inconsistencies in the literature (where they exist) and refer to converging or diverging evidence from preclinical, postmortem, and genetic studies. Finally, we construct a simplified model of the role played by each receptor in affective illness and construct a heuristic integrated model of neuroreceptor function in mood disorders.

Methods

Relevant studies were identified through a MEDLINE search, National Library of Medicine, NIH (http://www.pubmed.gov) and cross-referenced papers in the field. Search terms used included the following: "PET", "bipolar disorder", "major depressive disorder", "5-HT_{1A}", "5-HT_{2A}", "5-HT_{1B}", "serotonin transporter", "monoamine oxidase A", "dopamine receptor", and "dopamine transporter". To our knowledge, all papers that compared mood disorder subjects to