5-HT₁A PARTIAL AGONISTS AS ANXIOLYTICS AND ANTIDEPRESSANTS

Jeffrey Sprouse
Pfizer Central Research
Groton

1. OVERVIEW

Agonists of the 5-HT₁A subtype of serotonin receptor have long been known to be efficacious in animal models of anxiety and depression (1). Together with the modest success of prototypes in the clinic, these observations have led to speculation as to their mechanism(s) of action. Particularly daunting has been the task of explaining how 5-HT₁A agonists would be effective in clinical states traditionally viewed as being at opposite ends of a diagnostic continuum. The solution to this puzzle may involve their partial agonist nature which theoretically could provide the optimal degree of intrinsic activity for normalizing 5-HT neurotransmission in both hypo- and hypernormal states. This article will consider the possibility of 5-HT₁A partial agonists as the desired endpoint in anxiolytic and antidepressant drug discovery and the potential therapeutic benefits of designing new molecules with various degrees of agonist potential. Where clinical data are lacking, patient outcomes will be extrapolated from laboratory experiments.

2. MONOAMINE HYPOTHESIS OF DEPRESSION

Though now many years since its original description, the monoamine hypothesis of depression still serves as a useful starting point for refining the role of the monoamine neurotransmitters in the etiology of depression and perhaps more importantly in the theoretical basis for its pharmacologic treatment. Its principle tenet is that behavioral depression is related to a deficiency of monoamines at functionally important central synapses. As a corollary, the excess of monoamines leads unavoidably to anxiety and mania. Depression and anxiety then may be represented by a continuum of neurotransmission in which low levels of neurotransmitter tone yield depression whereas high levels yield anxiety and that between these extremes lies the proper degree of tone and hence euthymia (Figure 1).
As the title of this article indicates, comments here will be restricted to high and low levels of serotonin (5-HT) neurotransmission. This is of course a greatly simplified view given that other monoamines (norepinephrine, dopamine) are completely excluded from consideration as are other neurotransmitter systems (e.g. excitatory amino acids, neuropeptides) for which there is substantial evidence of their involvement in various psychopathologies. Even within this narrowed focus, there is the troubling matter of bipolar disorder with its wide swings of mood occurring successively or co-morbid situations in which anxiety and depression simultaneously exist. One may ask where along this single continuum these complex conditions fall. Should they replace our so-called euthymic states such that “normal mood” is not static but is buffeted by minor shifts to and fro along this axis? This is a debate for which there is no satisfactory answer and (luckily for me) which can be deemed outside the scope of this discussion. Again the hypothesis and continuum serve, if nothing else, as a framework to review relevant data. Naturally not all of the pieces will fit and it is precisely this poor fit which will hopefully provoke discussion by others.

3. COUNTERBALANCED ACTIONS OF 5-HT\textsubscript{1A} AGONISTS

Interest in 5-HT\textsubscript{1A} receptors stems in part from the very central role they play in the regulation of the firing rate of serotonin-containing neurons. Central serotonergic neurons are densely clustered in a number of discrete midbrain and brainstem nuclei collectively referred to as the raphe nuclei. The firing of the raphe neurons in part establishes a tone to the nerve terminals. The quantity of 5-HT ultimately available to the postsynaptic receptors will depend on the activity of additional receptor mechanisms at the terminal that modulate release, uptake and synthesis, but the baseline is provided by the discharge rate originating in the raphe nuclei. This pacemaker function is due not only to the intrinsic membrane properties of these neurons (2) but also to autoreceptors located on the cell bodies and/or dendrites which negatively modulate firing frequency. In the case of the raphe autoreceptors, these have been shown to be of the 5-HT\textsubscript{1A} subtype using receptor binding (3) and electrophysiological (4) approaches. Activation of the autoreceptors by 5-HT itself or a 5-HT\textsubscript{1A} agonist leads to a decrease in cell firing (4) and ultimately a decrease in 5-HT release in projection areas (5).

In addition to its localization on 5-HT neurons, the 5-HT\textsubscript{1A} receptor is found on a number of other neuronal cell types, where its general function also appears to be inhibition of neuronal activity. This postsynaptic 5-HT\textsubscript{1A} receptor is most densely localized in