SB-236057-A: A Selective 5-HT\textsubscript{1B} Receptor Inverse Agonist

Claire Roberts, Jeanette Watson, Gary W. Price, and Derek N. Middlemiss

Psychiatry Centre of Excellence for Drug Discovery,
GlaxoSmithKline, Harlow, Essex, UK

Key Words: 5-HT\textsubscript{1B} receptor—5-HT release—Inverse agonist—SB-236057-A.

ABSTRACT

5-HT\textsubscript{1B} autoreceptors are involved in the control of extracellular 5-HT levels from both the terminal and cell body regions of serotonergic neurons. In this manuscript we review the pharmacological and pharmacokinetic data available for the selective and potent 5-HT\textsubscript{1B} receptor inverse agonist, SB-236057-A (1’-ethyl-5-(2’-methyl-4’-(5-methyl-1,3,4-oxadiazolyl-2-y1)biphenyl-4-carbonyl)-2,3,6,7-tetrahydrospiro {furo[2,3-f]indole-3,4’-pipe-ridine} hydrochloride). SB 236057-A has been shown to have high affinity for human 5-HT\textsubscript{1B} receptors (pK\textsubscript{i} = 8.2) and displays 80 or more fold selectivity for the human 5-HT\textsubscript{1B} receptor over other 5-HT receptors and a range of additional receptors, ion channels and enzymes. In functional studies at human 5-HT\textsubscript{1B} receptors SB-236057-A displayed inverse agonism (pA\textsubscript{2} = 8.9) using \textsuperscript{35}S\textsuperscript{GTP}\gamma S binding, and silent antagonism (pA\textsubscript{2} = 9.2) using cAMP accumulation. SB-236057-A also acted as an antagonist at the 5-HT terminal autoreceptor as measured by \textsuperscript{3}H5-HT release from electrically stimulated guinea pig and human cortical slices.

In the guinea pig, pharmacokinetic analysis demonstrated that SB-236057-A was bioavailable and according to \textit{in vivo} pharmacodynamic assays it enters brain and has a long duration of action. Importantly no side effect liability was evident at relevant doses from anxiogenic, cardiovascular, sedative or migraine viewpoints.

\textit{In vivo} microdialysis studies demonstrated that SB-236057-A is an antagonist in the guinea pig cortex but has no effect on extracellular 5-HT levels \textit{per se}. In contrast, SB-236057-A increased extracellular 5-HT levels in the guinea pig dentate gyrus. This increase in 5-HT release was comparable to that observed after 14 days of paroxetine administration.

SB-236057-A has been a useful tool in confirming that, in either guinea pigs or humans, the terminal 5-HT autoreceptor is of the 5-HT\textsubscript{1B} subtype. It appears that acute 5-HT\textsubscript{1B} receptor blockade, by virtue of increased 5-HT release in the dentate gyrus, may provide a rapidly acting antidepressant.