Donitriptan, a Unique High-Efficacy 5-HT$_{1B/1D}$ Agonist: Key Features and Acute Antimigraine Potential

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ABSTRACT

We hypothesized that the limited acute therapeutic effectiveness of tryptamine derivatives in alleviating migraine headache could be explained by the relatively low intrinsic activity of these agents at 5-HT$_{1B/1D}$ receptors. Donitriptan is a novel arylpiperazide 5-hydroxytryptamine (5-HT) derivative which was designed to exploit the higher potency and efficacy properties of 5-HT compared to tryptamine at 5-HT$_{1B/1D}$ receptors.

In vitro, donitriptan has subnanomolar affinity for nonhuman and human 5-HT$_{1B/1D}$ receptors and micromolar affinity for the 5-HT$_{1P}$ subtype. Donitriptan potently inhibited forskolin-induced cAMP formation and enhanced specific GTP$^{35S}$ specific binding to a greater extent than tryptamine derivatives and equivalent to 5-HT in C6 cells expressing human 5-HT$_{1B}$ or 5-HT$_{1D}$ receptors. Donitriptan produced more potent and larger amplitude increases in hyperpolarizing Ca$^{2+}$-dependent K$^+$ current than sumatriptan in guinea pig isolated trigeminal ganglion neurons, and was more potent than tryptamine derivatives in eliciting contractile responses in rabbit isolated saphenous vein rings.

In vivo, donitriptan evoked more potent, longer-lasting and greater amplitude carotid vasoconstrictor responses than tryptamine derivatives in anesthetized pigs; and in contrast to sumatriptan, naratriptan or zolmitriptan, produced long-lasting, dose-dependent decreases in unilateral carotid blood flow in conscious dogs at doses from 0.63 mg/kg p.o. without affecting heart rate or behavior. Oral donitriptan also evoked hypothemic responses in guinea pigs suggesting that the compound gains access to the brain.

Donitriptan is thus a selective, potent 5-HT$_{1B/1D}$ receptor agonist which can be distinguished from tryptamine derivatives in consistently exerting high intrinsic activity at these receptors in a series of vascular and neuronal models relevant to migraine. Advantages in terms of therapeutic effectiveness in the acute relief of migraine headache over currently available triptans can be expected to include greater response rates and consistency of pain relief, a lower incidence of migraine recurrence and better tolerability. The acute anti-migraine potential of the first high efficacy 5-HT$_{1B/1D}$ agonist of its kind, donitriptan, is currently being investigated in man.