Chapter 51

Triptans, 5-$HT_{1B/1D}$ Receptor Agonists in the Acute Treatment of Migraines

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The triptans belong to a class of compounds known as 5-hydroxytryptamine$_{1B/1D}$ (5-$HT_{1B/1D}$, previously 5-HT-like/5-HT_{1D} [260]) receptor agonists. Undoubtedly, these drugs have significantly advanced the acute treatment of migraine headaches (see Dechant et al. [64], Ferrari et al. [96], Humphrey et al. [148], Plosker and McTavish [238], Saxena and Tfelt-Hansen [262], Tfelt-Hansen [294], Tfelt-Hansen et al. [296], and Wilkinson et al. [322]). The idea that compounds mimicking 5-HT at craniovascular receptors should abort migraine attacks stems from the following observations (261):

1. Urinary excretion of 5-hydroxyindole acetic acid increases, whereas platelet 5-HT decreases during migraine attacks,
2. Migraine-like symptoms can be precipitated by reserpine and alleviated by 5-HT, which causes carotid vasoconstriction via the 5-HT_{1B} receptor, and
3. Ergotamine and methysergide elicit a selective carotid vasoconstriction (at least partly via the 5-HT_{1B} receptor), which is confined to cephalic arteriovenous anastomoses that seem to be involved in migraine pathophysiology (259).

Based on this reasoning, tryptamine derivatives were synthesized to achieve selectivity at the craniovascular 5-$HT_{1B/1D}$ receptors, and this culminated in the design and development of sumatriptan (149). Despite its great utility in migraine treatment, sumatriptan has certain limitations; namely, low oral bioavailability, high headache recurrence possibly owing to a short half-life, and contraindication in patients with coronary artery disease. Therefore, a number of pharmaceutical companies decided to develop newer triptans having agonist activity at 5-$HT_{1B/1D}$ receptors. Together with sumatriptan, six other such compounds (zolmitriptan, rizatriptan, naratriptan, eletriptan, almotriptan, and frovatriptan) are now available for clinical use; the development of donitriptan (156–158) seems have been stopped (for chemical structures, see Fig. 51-1). Although avitriptan (253), BMS181885 (330), and the nontriptan alniditan (128), were found effective in the treatment of migraine, these compounds are no longer in clinical development.

In this chapter we review the pharmacology of triptans and rationale for their use in migraine, the randomized clinical trials with triptans demonstrating their efficacy and evaluating the optimum dose, randomized clinical trials comparing triptans, randomized clinical trials comparing sumatriptan with other treatments, long-term studies with triptans, tolerability and safety problems with triptans, and finally the therapeutic use of triptans.

PHARMACOLOGY OF TRIPTANS

Receptor-Binding Profile

All triptans display high affinities at 5-HT_1 receptor subtypes (13,156,232,262,296) (Table 51-1). Among triptans, donitriptan appears to have the highest affinity at both 5-HT_{1B} and 5-HT_{1D} receptors and the highest efficacy at the 5-HT_{1D} receptor. Some triptans also interact with 5-HT_{1A} and 5-HT_{1F} receptors, but rizatriptan appears to be more selective for 5-$HT_{1B/1D}$ receptors. It must be remarked, however, that the nontriptan compound, alniditan, which also proved efficacious in migraine (128), showed little, if any, affinity at the 5-HT_{1F} receptor (173). Sumatriptan, zolmitriptan, eletriptan, and frovatriptan display a micromolar affinity at the 5-HT_7 receptor, which mediates smooth muscle relaxation (85,260).

Cardiovascular Effects

Systemic Hemodynamics

As described (262,296), human volunteer studies show that the triptans (75,186,265,312) slightly increase