Editorial

Putting migraine to sleep: Rexants as a preventive strategy

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The orexinergic system comprises the neuropeptides, orexin A and B, which are exclusively produced in the posterior, lateral and paraventricular parts of the hypothalamus (1–3). Orexins act via G-protein-coupled OX1 and OX2 receptors on projections to the prefrontal cortex, thalamus and other subcortical areas to promote arousal (4) and exert modulating effects on nociceptive neurotransmission, thermoregulation, neuroendocrine and autonomic functions (5–7). These areas are known to modulate basal- and dural-evoked nociceptive activation in the trigeminocervical complex (TCC) (8–10). The premonitory phase of a migraine may include symptoms such as yawning, food cravings and changes in wakefulness (11), which are thought to be regulated to a significant extent by the hypothalamus and its orexinergic neurons. Recent neuroimaging data have further implicated this region of the brain (12). On this background, would manipulation of orexin receptors be useful in migraine?

Filorexant (MK-6069) is a dual (OX1 and OX2) receptor antagonist (DORA) that has been developed for insomnia (13); indeed a related compound, suvorexant, has now been approved for that purpose (14). A placebo-controlled study is reported in this issue of the Journal with filorexant 10 mg in the preventive treatment of episodic migraine, four to 14 migraine days a month, dosed once daily in a parallel group study with 120 treated with active and 115 with placebo. A migraine day was defined as a headache day with one associated symptom, such as aura, nausea, vomiting, photophobia or phonophobia, and a headache day as a day with 30 minutes or more of headache, or headache of any duration that was treated. A migraine attack was defined as two consecutive migraine days, while pain continuing for more than two days was considered another attack. The primary endpoint was the mean monthly “migraine” days over the three months of treatment compared to baseline. There was no significant difference between placebo (–1.3) and active (–1.7). For headache days the outcome was similar (–1.2 vs –1.7, respectively). A higher proportion of patients on filorexant (13% vs 4%) reported somnolence.

The endpoint was clearly negative, although as a test of the overall mechanism the matter remains unresolved. Filorexant would be expected to produce somnolence (14). So it was dosed once daily to minimise that side effect. If, as with most preventives currently used, one needs to cover the entire 24 hours with a treatment, then the single daily dosing was an unfortunate choice. This notwithstanding, there is no other sensible way to study the DORA class since daytime somnolence is simply not an option for the development of a new medicine. There are some other issues in the study which are disappointing. The authors used a very broad definition of migraine by current standards (16), so assuming Table 2 uses that definition, it remains unclear how many migraine days compared to probable migraine days were present in the population. Moreover, some patients included seemed to have rather many non-migraine days, two patients even being included with more than 14 days at baseline. There is an arbitrary cutoff of any attack after two days with a third day being considered another attack; I am not sure what the biological basis for that division may be. From a general quality viewpoint these things may not have altered the outcome reliability since the baseline ≥50% response rate is 21%, which is well in line with what would be expected (17,18).

All things considered, the rexants in their dual receptor manifestation may not be for migraine, although given what we know of cluster headache, its predilection for nocturnal attacks and neurobiology (19), a controlled trial would seem entirely reasonable. Laboratory data suggest this road is not over for orexin biology (20). Experimental data very much suggest targeting individual orexin receptors (9,21); this

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may just be the first act of a more interesting biological drama.

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None declared.

**References**