MS01-3 Ramelteon: a novel melatonin receptor agonist for the treatment of sleep disorder

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Ramelteon, a selective MT_1/MT_2 receptor agonist, was discovered in a research for safer treatment of sleep disorder. Ramelteon showed extremely high affinity to MT_1 and MT_2 with Ki of 14 and 112 pM, respectively, and agonist activity with EC_{50} of 21 pM for human MT_1. Ramelteon increased slow wave sleep (SWS) in freely-moving cats ($\geq$ 0.001 mg/kg) during daytime, and also increased SWS along with reduction of sleep latency in freely-moving monkeys ($\geq$ 0.03 mg/kg) during nighttime when melatonin secretion is high. The effect of ramelteon was longer-lasting and more potent than that of melatonin in both animals. EEG power spectrum analysis in monkeys revealed that zolpidem (30 mg/kg)-induced SWS contained increment of high frequency activity, showing qualitative difference from naturally occurring sleep whereas ramelteon-induced SWS showed indistinguishable pattern from naturally occurring sleep. Ramelteon facilitated re-synchronization of circadian rhythm of locomotor activity disrupted by 8-h phase advance of light-dark cycle in rats. In phase 3 clinical trials with adults and aged population, ramelteon (4, 8 and 16 mg) showed reduction of sleep latency and increment of total sleep duration in both objective evaluation by SPG and subjective report in sleep lab, without causing tolerance by repeated administration or rebound insomnia. In contrast to benzodiazepines, ramelteon did not show drug dependence in human or adverse effects on learning/memory and motor activity. From these results, ramelteon is expected to be a safe treatment for sleep disorder by inducing physiological sleep.