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Is Sodium Channel Nav1.7 an Ideal Therapeutically Analgesic Target? A Systematic Review

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Abstract : Introduction: SCN9A encoded Nav1.7 is an ideal therapeutic target with minimal side effects for the pharmaceutical industry because SCN9A variants can cause both human gains of function pain-related mutations and loss of function pain-free mutations. This study reviews the clinical effectiveness of existing Nav1.7 inhibitors, which theoretically should be powerful analgesics. Methods: A systematic review is conducted on the effectiveness of current Nav1.7 blockers undergoing clinical trials. Studies were mainly extracted from PubMed, U.S. National Library of Medicine Clinical Trials, World Health Organization International Clinical Trials Registry, ISRCTN registry platform, and Integrated Research Approval System by NHS. Only studies with full text available and those conducted using double-blinded, placebo controlled, and randomised designs and reporting at least one analgesic measurement were included. Results: Overall, 61 trials were screened, and eight studies covering PF 05089771 (Pfizer), TV 45070 (Teva & Xenon), and BIIB074 (Biogen) met the inclusion criteria. Most studies were excluded because results were not published. All three compounds demonstrated insignificant analgesic effects, and the comparison between PF 05089771 and pregabalin/ibuprofen showed that PF 05089771 was a much weaker analgesic. All three drug candidates only have mild side effects, indicating the potentials for further investigation of Nav1.7 antagonists. Discussion: The failure of current Nav1.7 small molecule inhibitors might attribute to ignorance of the key role of endogenous systems in Nav1.7 null mutants, the lack of selectivity and blocking potency, and central impermeability. The synergistic combination of analgesic drugs, a recent UCL patent, combining a small dose of Nav1.7 blockers and opioids or enkephalinase inhibitors dramatically enhanced the analgesic effects. Conclusion: The current clinical testing Nav1.7 blockers are generally disappointing. However, the newer generation of Nav1.7 targeting analgesics has overcome the major constraints of its predecessors.

Keywords : chronic pain, Nav1.7 blockers, SCN9A, systematic review
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