Current Topics

Recent Advances in 5-Hydroxytryptamine (5-HT) Receptor Research: How Many Pathophysiological Roles Does 5-HT Play via Its Multiple Receptor Subtypes?

Foreword

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5-Hydroxytryptamine (5-HT) is an old transmitter. It was first discovered in the late 1940s as “serotonin” which is a powerful vasoconstrictor substance extracted from blood serum, but not plasma. Soon thereafter, the substance was isolated and its structure was identified. Since then, 5-HT has been the focus of great attention for pharmacological and pathophysiological research in almost every major physiological system, including the central nervous, sensory nervous, cardiovascular, respiratory, gastrointestinal, genitourinary, and even immune systems. 5-HT is probably the most pharmacologically versatile transmitter of all neurotransmitters or bioactive substances discovered to date. Because of this versatility, it has been thought to have a role in the etiology of various diseases, including depression, schizophrenia, anxiety, migraine, hypertension, pulmonary hypertension, thrombosis, anorexia, emesis and irritable bowel syndromes.

The basis of these diversities is undoubtedly the existence of multiple 5-HT receptor subtypes. At present, seven major families of 5-HT receptors have been identified (5-HT₁–5-HT₇), and various subtypes exist in several of these receptors, at least 20 subtypes of which have been cloned. Most 5-HT receptors are G protein-coupled, heptahelical proteins, whereas the 5-HT₃ receptors are ligand-gated ion channels. Several therapeutic drugs targeting some of these 5-HT receptor subtypes have been successfully introduced into the treatment of certain diseases such as schizophrenia, neurosis, migraine, thrombosis, functional dyspepsia, or chemotherapy-induced nausea and vomiting.

In this series of mini-reviews, the current topics of 5-HT receptor research in cardiovascular, gastrointestinal, peripheral and central nervous systems are introduced by six groups including ours. In the 1st paper, Prof. Togashi's group reviews

the persistent influence of early life stress such as infant/child abuse, neglect, or parental loss on emotional regulation, focusing on the central serotonergic systems (5-HT_{1A} receptor) in rats. In the 2nd paper, Prof. Ohno and coworkers review the functional roles and mechanisms of the central serotonergic system in modulating extrapyramidal motor disorders, focusing on the crucial roles of 5-HT_{1A}, 5-HT_{2A/2C}, and 5-HT₃ and 5-HT₆ receptors. In the 3rd paper, Prof. Takeda and colleagues focus on the novel relationship between cancer- and stress-related anorexia and ghrelin dynamics involving peripheral and central 5-HT_{2B}, 5-HT_{2C} or 5-HT_{1B} receptors in both human and animal studies. In the 4th paper, Prof. Kato focuses on the important novel role of gastrointestinal 5-HT₃ receptor, the only ligand-gated ion channel among the 5-HT receptor subtypes, in the pathogenesis of intestinal inflammation, suggesting the 5-HT₃ receptor antagonists as a new class of anti-inflammatory drugs. In the 5th paper, Prof. Yamamoto's group focuses on the roles of 5-HT_{1B} and 5-HT_{2A} receptor subtypes involved in some vascular-related diseases including migraine, pulmonary arterial hypertension, and saphenous vein graft diseases. In the last paper, Dr. Machida of our laboratory describes the pathophysiological roles of 5-HT receptors expressed in vascular smooth muscle cells and endothelial cells, focusing on their signal transduction and functions in vascular biology.

It remains to be seen how many pathophysiological roles 5-HT plays via its multiple receptor subtypes. I hope these mini-reviews prove useful and valuable for future studies seeking to clarify more about its function in the etiology of various diseases, and on potential new drugs targeting 5-HT receptors as well.