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Therapeutic targeting of biomolecules other than cell membrane receptors

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ABSTRACT

Within this paper, a spotlight has been put on an area of the pharmacology that describes the therapeutic applications of targeting proteins and other biomolecules instead of targeting the membrane receptors. This will give a more panoramic image about the future of the pharmacology from a pharmacodynamic view and will open more doors in regard to both pharmacological applications and therapeutic implications.

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KEYWORDS

Pharmacological target;
Endogenous biomolecule;
Future therapies;
Cell membrane receptor;
Pharmacology;
Therapy.

INTRODUCTION

Pharmacology, as a multidisciplinary science at the interface between medicine, pharmacy, biology and chemistry, is now nearly 7000 years old[1]. It has often been linked to principles such as agonists and antagonists that describe a pharmakon that binds to cell membrane receptors either to stimulate or to block it, in order to obtain therapeutic effects. These concepts are frequently described is literature[2, 3] in the context of different diseases and disorders including cancer[4,5], allergy[6], pain[7], gastrointestinal disorders[8], immunology[9], autonomic functions[10], cardiovascular diseases[11,12], psychiatric disorders[13,14] and pulmonary disease[15]. Although such concepts are important, they do not give the complete image of the modern pharmacology in regard to the novel therapeutic targets that are emerging with the new findings in biology, genetics, proteomics, cell biology and others related fields.

These receptors and their ligands, in addition to the interactions between them, have been studied not only in humans but also in some animal and insect models, which allowed a good understanding of the related structural and functional properties[16]. The fact that pharmacology has been focusing on such concepts has made the other therapeutical possibilities somehow underestimated. In fact, pharmacology as a therapeutic approach is not limited to the modification of the membrane receptor status or excitability, yet it has divers possibilities beyond that. Indeed, recent studies about diseases mechanisms, cellular functions and biomolecules properties have put more lights on the possible new elements that would constitute targets for the future therapeutic approaches.

THE INCREASING IMPORTANCE OF TARGETING THE EMERGING ELEMENTS OTHER THAN MEMBRANE RECEPTORS

To describe a panoramic view of the therapeutic targets, we need to further identify, understand and in-

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vestigate more pharmacological targets such as enzymes, intracellular messengers and structural proteins. Divers publications strongly illustrate the increasing importance of considering endogenous molecules, other than membrane receptors, as promising pharmacological targets for the future therapies. Herein, a variety of examples can be given.

Enzymes inhibitors represent good examples. For instance the possible use of phosphodiesterase 10A inhibitors for the treatment of psychotic symptoms[17], the use of angiotensin converting enzyme inhibitors[18] as antihypertensive drugs[19], the carbonic anhydrase inhibitors such as acetazolamide, dorzolamide, and methazolamide used as diuretics[12] and some drugs used to treat vascular system disorders such as inhibitors of phosphodiesterase type V[20], all describe the inhibition of endogenous enzymes as therapeutic approaches which suggest that other enzymes implicated in pathological processes would be ideal targets for future therapeutic approaches.

Furthermore, drugs that act within the synapses such as serotonin and noradrenaline re-uptake inhibitors, that are used as antidepressants[21], influence the neurotransmitters activities without any interactions with their receptors, other medicines including anti-inflammatory, antipyretic analgesics[22], drugs used in dermatology as topical agents, and in cosmetology[23] and agents targeting calcitonin gene related peptide which target the neuroinflammatory process[24] represent also descriptive examples of drugs or compounds that do not interact with cell membrane receptors.

Importantly, due to the divers functions they are involved in[25-28], G protein coupled receptors (GPCRs) are among the most important targets in the modern pharmacology[26, 29]. They have been coupled to a variety of intracellular reactions and enzymatic interactions[30-35] that involve key molecules such as β-arrestins[26,36] and adenylyl cyclase[34]. Therefore, targeting those molecules represents new perspectives for future therapies[37] that will interact with enzymes and other elements involved within the transduction of the GPCRs signal without interacting with the cell membrane receptor itself.

PERSPECTIVES AND CHALLENGES

This line of thought will surely open new doors to divers applications in different fields due to the multi-aspects it covers.

Another aspect has to be considered, it is the struggles that may exist between a proven pharmacodynamic activity of a compound and the use of that compound as a drug. Indeed, a compound that is active on cell culture or enzymatic reaction for example may not be active *In vivo* because pharmacokinetic factors such as metabolism or membrane transport may deactivate it or considerably decrease its bioavailability.

On the other hand, in microbiology and parasitology, used drugs target metabolic systems or structural elements of the agents causing the disease[38-42] thus, we may extrapolate from these systems interactions, mimic the pathways and develop drugs that target human cells for example in cancer or in autoimmune diseases after describing the similarities between the human cell functions and dysfunctions, and those observed within bacteria and parasites.

CONCLUSION

Taken in consideration the facts that many membrane receptors ligands used in therapies have side effects[7,19,43-46] and also the existence of factors that may influence the membrane receptors functions[47], will further encourage the development of alternative therapies mainly those targeting intracellular proteins, synaptic enzymes and cellular messengers in regard to the concept such as safety pharmacology[48, 49] and pharmacovigilance[50-53] to find out drugs with more efficacy and a better safety profiles.

Hopefully, new advances such as properties of certain chemicals that may influence some cellular bio-properties[54], advances in medicinal plants and pharmacognosy[55-59] will provide new data and tools to further study and elucidate the functions of cells and tissues, natural and synthetic compound properties and diseases processes; toward developing new therapies beyond targeting cell membrane receptors.

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