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ESPS PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	PubMed Search:	[ ] Accept
[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This review paper has shown recent progress in the studies on opioid receptor heteromers and the effects of ligands on the receptors. The authors have suggested the advantageous effects of dualsteric ligands. This paper sheds light on pharmacology of opioid receptor heteromers and clinically relevant aspects. However, there are two major problems and a number of minor problems in the manuscript according to my accompanying suggestions.

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ESPS PEER-REVIEW REPORT

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
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[Y] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Role of opioid receptor heterodimerization in pain modulation and tolerance development The present review highlights the heteromerization process of the specific opioid receptors mu-delta already described in the literature, as well as the importance of developing pharmacological analogs (agonists and antagonists) with simultaneous "dual" activity on such receptors. As proposed, compounds presenting such dual activity would allow a more specific control of pain conditions without the related adverse effects of desensitization and tolerance that compromise the use of the most important analgesics currently available for the treatment of chronic pain, i.e., the opioid analgesics. Considering "Contents" as the first review page, deficiencies, eventual substitutions and suggestions are indicated below: Deficiencies and substitutions: 1. Heteromerization is not only associated with opioid receptors. 2. Lack of a glossary to explain or define all acronyms and important terms presented. Exemplifying: KD and Dc (page 3), FRET and BRET (page 8), NPFF (page 11); MERF (page 22); NTB (page 27). 3. Terms such as oligomerization, protomer, tolerance, anti-opioid system should be provided and follow IASP definitions, fixing the terms afterwards.

Opioid receptors have been interchangeable all through the text as: MOR, DOR, KOR; MOPr, DOPr, KOPr, as were MOP-DOP, MOR-DOR, MOR/DOR, and m-d heteromers (page 10) that difficult the flow of the reading. 4. A phrase is missing before "Intracellularly, the two receptors may also interact physically, and operate as homo- or heteromers with…"(page 7) 5. Indication of important references is lacking along text or they simply don't exist. Ex: for NPFF in the second paragraph (page 6)also, in vivo co-localization of MOR/DOR in rostro-ventral medulla (page 7). Should it be reference 29 lacking at the end of the first paragraph? (page 8). Yet, in the same page, a phrase in the second paragraph ("However, other studies found no such interactions") should finish with a reference or references. Moreover, reference #100 is indicated after #101 on page 32. On the other hand, identification of the references Yekkirala et al., 2013 and Gupta et al.,1999 on pages 21 and 32, respectively, are unnecessary. Comments and suggestions: 1. Evolutionary development of an anti-opioid system in superior animals certainly has been acquired to counterbalance an excessive (endogenous) opioid tonus. Can't it be expected that blocking partially or an integral part of such a system with dual compounds as proposed would compromise the proper functioning of the whole system? In other words, it would mean development of yet unknown adverse side effects associated with proposed compound's, a subject not discussed in the review. 2. In some places the text doesn't flow rationally. For instance, there is an interval in the text between the description of the anti-opioid system and the proposed dual compounds, leaving the intent (of the review) in the air. Moreover, illustration in Figure 1, which is supposed to help the understanding of the whole system's functioning doesn't give information on "who is who" in the balance (white rectangle= opioid system?). Besides, the upper arrow shouldn't be bidirectional? 3. Considering a strict chemical terminology, the term "bivalent" ligands in the illustration of Fig. 2 wouldn't be better to be substituted by "dual" ligands? The term "bivalent" is also used in the phrase "In short, as all bivalent ligands described to date…" (page 24) instead of dual ligands. 4. The term "Resensitization" under an arrow at the left front in illustration of Figure 3 could be substituted by realocation (in the membrane). Resensitization is the consequence of receptor re-integralization in the membrane. 5. The sequence of phrases in conclusion is truncated. Suggestions: "Research on opioid receptors has been… "- phrase 1. "The discovery of opioid receptor heteromers has…"- phrase 2. "This review h