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Review

Lipid signaling cascades of orexin/hypocretin receptors

Jyrki P. Kukkonen*

Biochemistry and Cell Biology, Department of Veterinary Biosciences, POB 66, FIN-00014, University of Helsinki, Finland

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ABSTRACT

Orexins – orexin-A and orexin-B – are neuropeptides with significant role in regulation of fundamental physiological processes such as sleep-wakefulness cycle. Orexins act via G-protein-coupled OX_1 and OX_2 receptors, which are found, in addition to the central nervous system, also in a number of peripheral organs. Orexin receptors show high degree of signaling promiscuity. One particularly prominent way of signaling for these receptors is via phospholipase cascades, including the phospholipase C, phospholipase D and phospholipase A_2 cascades, and also diacylglycerol lipase and phosphoinositide-3-kinase pathways. Most analyses have been performed in recombinant cells; there are indications of some of these cascades in native cells while the significance of other cascades remains to be shown. In this review, I present these pathways, their activation mechanisms and their physiological significance.

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1. Introduction

Orexin/hypocretin receptors (OX_1 and OX_2 receptors) belong to the G-protein-coupled receptor (GPCR) superfamily. They play a key role in the regulation of many physiological processes, especially in the wakefulness/sleep pattern (reviewed in Refs. [1,2]). Orexin receptors show very diverse signaling originating from multiple G-protein species (and possible other signal transducers) and ranging from ion channel activation/inhibition to hormone release, cell differentiation and even cell death (reviewed in Refs. [2–4]). One striking feature of orexin receptor signaling is its coupling to generation of lipid messengers via phospholipases. This is not surprising for GPCRs but the rich spectrum of phospholipase activation by orexin receptors may be less usual.

Lipids and lipid-derived molecules represent a vast and very diverse group of bioactive compounds. These compounds can have different sources: some are absorbed from the diet, some are mere metabolites of these or the body's own compounds, and some are actively produced for their physiological role in, e.g. signaling. The most classical cascades producing lipid derivatives for signaling purposes are instigated by reactions catalyzed by phospholipases, which themselves are targeted by particular signal pathways from, e.g. GPCRs. The knowledge of the diversity of these, as well as other, lipid pathways (reviewed in Ref. [5]) and the actions downstream of these, has increased tremendously. At the same time we need to admit that our understanding of the intricacies of the lipid signaling networks is still very limited.

In this review, I present the known (and speculated) lipid signaling pathways of orexin receptors and their physiological significance.

2. Overview of orexin receptors signaling

We have presented a general overview of orexin receptor signaling in some recent reviews [2–4]. All in all, the data available indicate that orexin receptor signaling is very multifaceted and complex. However, most of the analytic data originate from studies with recombinant cell lines, which makes conclusions of the significance of the findings somewhat unclear.

Orexin receptors couple, at least, to the G-protein families of $G_{i/o}$, G_q and G_s, and possibly also to β-arrestin, dynein light chain Tctex-types 1 and 3 and the protein phosphatase SHP-2 (reviewed

Abbreviations: 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; anandamide, *N*-arachidonoylethanolamine; CNS, central nervous system; $cPLA_2$ and $iPLA_2$, cytosolic (Ca^{2+}-dependent) and intracellular (Ca^{2+}-independent) PLA_2, respectively; DAG, diacylglycerol; DAGL, DAG lipase; DOG, dioctanoylglycerol; ERK, extracellular signal-regulated kinase; GPCR, G-protein-coupled receptor; GPL, glycerophospholipid; IP_3, inositol-1,4,5-trisphosphate; KB-R7943, a NCX inhibitor; lysoGPL, lyso(glycero)phospholipid; lysoPA, lysophosphatidic acid; MAFP, methyl arachidonyl fluorophosphonate; NAPE, *N*-acyl-phosphatidylethanolamine; NSCC, non-selective cation channel; OX_1, orexin 1 receptor; OX_2, orexin 2 receptor; PA, phosphatidic acid; PC, phosphatidylcholine; PC-PLC, PC-specific PLC; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide-3-kinase; PI, phosphatidylinositol; PIs, phosphatidylinositols (including differentially phosphorylated species PI, PIP, PIP_2 and PIP_3); PIP, phosphatidylinositolmonophosphate; PIP_2, phosphatidylinositol-4,5-bisphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PKB, PKC and PKD, protein kinase B, C and D, respectively; PLA_1, PLA_2, PLB, PLC and PLD, phospholipase A_1, A_2, B, C and D, respectively; pyrrophenone, a $cPLA_2\alpha/\zeta$ inhibitor; TRP (channel), transient receptor potential (channel); U73122, a PLC inhibitor.

* Tel.: +358 9 191 57024; fax: +358 9 191 57033.
E-mail address: jyrki.kukkonen@helsinki.fi.

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in Refs. [2,3]). Further downstream of the receptors, responses such as activation of phospholipases (below), modulation of second messenger levels (lipid-derived messengers, cAMP, Ca^{2+}), activation Ser/Thr and Tyr kinases, activation/potentiation of non-selective cation channels (NSCCs) and voltage-gated Ca^{2+} channels and inhibition and activation of K^+ channels have been seen. In the long run, effects seen involve activation of transcription factors and resultant plastic changes; even cell death is seen in some cell types (reviewed in Refs. [2–4]). For some responses signal cascades between the receptor and the response measured can be traced, but in many cases the pathways are not properly mapped. Remarkably, it seems that orexin receptors may preferentially utilize distinct signal cascades in each tissue/cell type. The molecular mechanisms behind this are not known, but an obvious guess would suggest that tissue-specific expression of signal transducers and distinct signal complex formation explains the behavior.

2.1. Orexin receptors and calcium

Ever since their cloning, orexin receptor were known to strongly couple to Ca^{2+} elevation in a manner sensitive to the phospholipase C (PLC) inhibitor U73122 [6,7]. This led to the conclusions that the receptors would be of the G_q-coupled type with PLC-driven inositol-1,4,5-phosphate (IP_3) generation and Ca^{2+} release. While the PLC coupling was soon verified by direct measurements [see, e.g. Section 3.3 and (Ref. [8])], also other properties of the Ca^{2+} elevations were discovered. We were able to show that the primary response to OX_1 orexin receptor stimulation was indeed a Ca^{2+} influx, of the type "receptor-operated" as it did not require release from Ca^{2+} stores or IP_3 [8,9]. In addition, orexin receptors couple to the more regular store-operated Ca^{2+} influx, which follows from the IP_3-dependent Ca^{2+} store discharge [10]. Most of the investigations have been performed in recombinant Chinese hamster ovary-K1 (CHO) cells but neither the channel nor its activation mechanism is fully known, although transient receptor potential (TRP) family NSCCs make good candidates. In the central nervous system (CNS) neurons, similar non-selective cation fluxes are seen. For details, see Section 3.4 and [2–4].

3. Phospholipases

Phospholipases by definition are enzymes that hydrolyze (membrane) glycerophospholipids (GPLs). Phospholipases fall in the principal classes of phospholipase A, B, C and D (PLA, PLB, PLC and PLD). Of the interest for this review are the recognized signaling phospholipases PLA_2, PLC and PLD (Fig. 1A and B).

3.1. Orexin receptors and phospholipase A_2

The name "PLA_2" indicates that the enzymes hydrolyze the GPL *sn*2 ester bond. However, many of the enzymes belonging to this family may show less specificity for the *sn*2 bond over *sn*1, and they may thus act as PLA_1, PLB or lyso-PLA enzymes (reviewed in Ref. [11]). When PLA_2 enzymes hydrolyze the *sn*2 bond, the products are a free fatty acid and a *sn*2 lysophospholipid [lysoGPL]. The fatty acid in the *sn*2 position is often unsaturated (mono or poly); the most classical, though not really the sole product of PLA_2 reaction, is arachidonic acid (AA). The family of PLA_2 enzymes is the largest among phospholipases, and it is divided in several subfamilies (reviewed in Ref. [11]). While the enzymes within a subfamily are related to each other, the different subfamilies are not necessarily related to each other. The class IV and VI enzymes are usually associated with intracellular signaling. Class IV is known as $cPLA_2$ ("c" for cytosolic and also Ca^{2+}-dependent). It harbors members IVA-F (a.k.a. $cPLA_2\alpha$, -β, -γ, -δ, -ε and -ζ) (reviewed in Refs. [11,12]). The most investigated form is IVA ($cPLA_2\alpha$). This enzyme is activated by Ca^{2+} and phosphorylation by protein kinase C (PKC), extracellular signal-regulated kinase (ERK) and some other

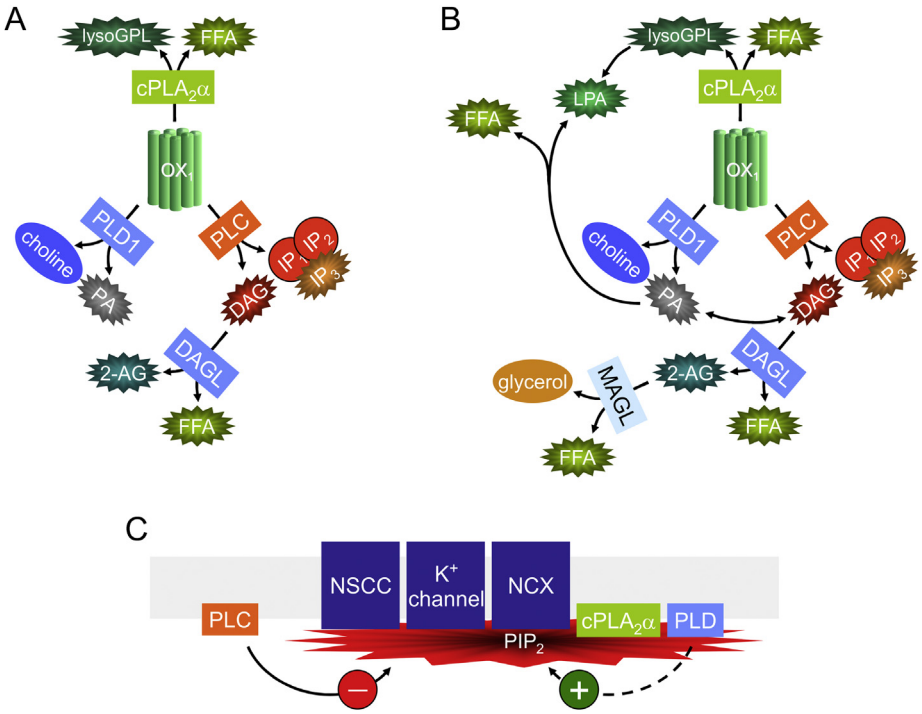

Fig. 1. Phospholipase signaling and signal pathway interaction. (A) OX_1 receptor stimulation-induced phospholipase pathways in CHO cells. (B) Some possible conversions of the lipid messengers. Please observe that the same messengers (e.g. DAG) from different pathways may not be equal (different fatty acid composition). (C) PIP_2 and signaling. NCX and some K^+ channels require PIP_2 for activity and some NSCCs are inhibited and some are stimulated by PIP_2. PIP_2 is required by PLD and it also stimulates $cPLA_2\alpha$. PLC hydrolyses PIP_2 and thus reduces PIP_2 levels while PLD signaling increases PIP_2 synthesis. FFA, free fatty acid. Responses downstream of PIP_2 metabolism are not shown (i.e. PLC and PI3K cascades).

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