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REVIEW
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The Anti-tumoral Properties of Orexin/Hypocretin Hypothalamic Neuropeptides: An Unexpected Therapeutic Role

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Orexins (OxA and OxB) also termed hypocretins are hypothalamic neuropeptides involved in central nervous system (CNS) to control the sleep/wake process which is mediated by two G protein-coupled receptor subtypes, OX1R, and OX2R. Beside these central effects, orexins also play a role in various peripheral organs such as the intestine, pancreas, adrenal glands, kidney, adipose tissue and reproductive tract.In the past few years, an unexpected anti-tumoral role of orexins mediated by a new signaling pathway involving the presence of two immunoreceptor tyrosine-based inhibitory motifs (ITIM) in both orexin receptors subtypes, the recruitment of the phosphotyrosine phosphatase SHP2 and the induction of mitochondrial apoptosis has been elucidated. In the present review, we will discuss the anti-tumoral effect of orexin/OXR system in colon, pancreas, prostate and other cancers, and its interest as a possible therapeutic target.

Keywords: orexins, neuropeptides, GPCR, cancer, inflammation, gastroenterology, signaling pathway

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INTRODUCTION

Since its discovery in 1998 (1, 2), the role of orexins also named hypocretins has been extensively studied in the central nervous system (CNS) (3). Literature analysis revealed that about 2,000 articles have been published (Pubmed source, 1978 articles on July, 2018) demonstrating the great interest of "orexin" field in its role in the central nervous system. In contrast, the study of orexins in peripheral systems has been much less investigated, with only a hundred of articles published (Pubmed source, 103 articles on July, 2018). This great interest in central action of orexins was directly associated to their discovery in hypothalamus (1, 2). Orexins (OxA/hypocretin-1 and OxB/hypocretin-2) are two neuropeptides isoforms produced by the same prepro-orexin precursor (2). These two peptides have been shown to be involved in multiple CNS processes, including energy homeostasis, reward seeking, and drug addiction and the regulation of the sleep/wakefulness state which represents the major central effect of orexins, (4, 5). In human, narcolepsy type 1 (also known as narcolepsy with cataplexy) is the main pathology associated to a misregulation of orexins production caused by the loss of orexin neurons and characterized by a decreased ability to regulate sleep/wake cycles (6, 7). As mentioned above, orexins also play a role in various peripheral organs such as the intestine, pancreas, kidney, reproductive tract, adipose tissue and adrenal glands (8), although their roles remain controversial (9). Expression of orexins in peripheral tissues has been investigated using immunohistochemistry and/or RT-PCR techniques. Orexin have been detected

in gastrointestinal tract, including colon (10), and pancreas (11), adrenal glands (12), kidney (11), adipose tissues (12) and reproductive tract including testis (13), and prostate (14). It should be noted that the analysis of literature related to orexins expression in peripheral tissues, revealed a large variability in term of orexins level and/or none expression. This could be related to the used tools, in particular the specificity of antibodies and/or RT-PCR, which reflected only the presence of preproorexin transcripts. The determination of basal circulating orexins concentration indicated a range of 2–45 pM (15, 16) which was about 1,000 times less in term of concentration than the IC_{50} of orexin receptors estimated to few 10 nM (17).

Orexins mediate their biological effects by interaction with two G-protein coupled receptors (GPCRs) subtypes, OX1R, and OX2R (also named Hcrtr-1 and Hcrtr-2, respectively) (18, 19), leading to the intracellular calcium releasing involving the Gq pathway (**Figure 1**). Although stimulation of orexin receptors predominantly leads to an increase in intracellular free calcium ions level, other signaling second messengers/pathways, i.e., cAMP, MAPK-Erk1/2, PI3K-Akt and JNK are also involved in orexins actions (19).

GPCRs characterized by seven α-helices transmembrane domains, belongs to the largest family of cell surface receptors with over 800 members in the human genome which are involved in the mainly pathophysiological actions (20). Classically, it was admitted that their major physiological actions were mediated "exclusively" by the G-protein signaling pathway, including effector stimulation and/or inhibition, desensitization and cellular internalization (21, 22). However, since several years, it has seen an increasing trend that many GPCRs action can also be mediated by other transduction mechanisms leading to a rich set of new physiopathological functions (20). Among their new roles, GPCRs are often overexpressed/underexpressed in tumor cells and also involved in the progression and/or initiation of cancer by inhibiting or stimulating proliferation and/or apoptosis (23, 24). In this review, we focus on the expression and anti-tumoral properties of OX1R in different cancers as gastrointestinal cancers (colon and pancreatic cancers) and prostate cancer, including their potential roles as therapeutic targets.

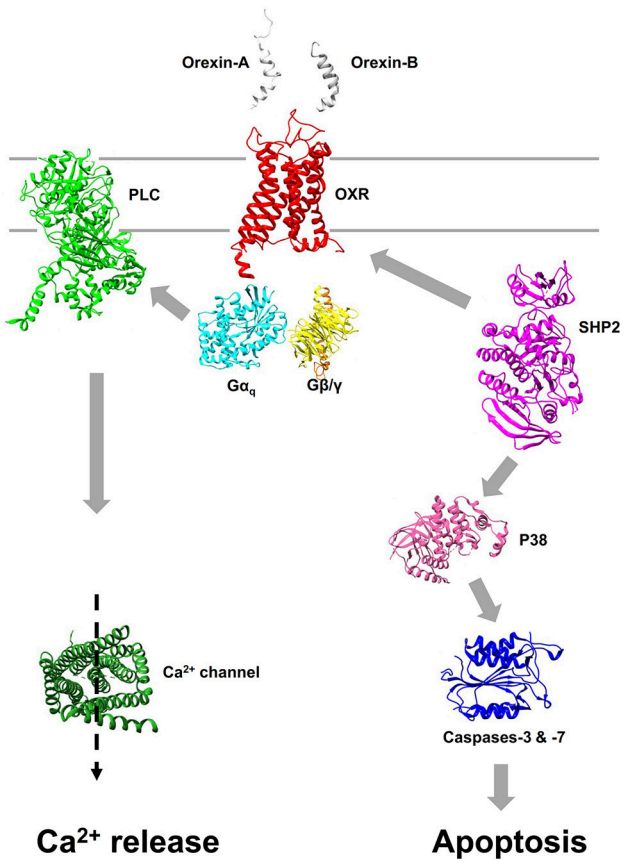

FIGURE 1 | Pro-apoptotic signaling pathway induced by orexins. Interaction of orexins with OX1R or OX2R leads to promote the dissociation of heterotrimer G_q into α_q and β/γ subunits. The canonical Ca^{2+} signaling pathway stimulated by orexins results of phospholipase C (PLC) activation mediated by α_q subunit **(Left)**. Apoptosis induced by orexins is mediated, independently of canonical Ca^{2+} signaling pathway, by the recruitment of the phosphotyrosine phosphatase SHP2 leading to the activation of p38 cascade and activation of caspases-3 and -7 *via* the mitochondria apoptosis pathway **(Right)**. All structures were obtained in Protein Data Bank (PDB).

COLON CANCERS

Colorectal cancer is the third most common cancer in men and the second most common in women, represents almost 10% of the annual global cancer incidence (25). Incidence rates of colorectal cancer show a strong positive gradient with an increasing level of economic development. Approximately 60% of patients with colorectal will present liver metastases during the course of disease (26). The only option to fight against the appearance of hepatic metastases of the colorectal cancers is the surgical resection. However, the rate of second recurrence stays of 75 % after metastasectomy (27). The patient's survival is dependent on the stage at diagnosis. It is positive for the premature lesions (Stage I), intermediate for stages II and III and poor for the metastatic stages. A post-operative chemotherapy is proposed for stages II and III. In the case of the rectal cancer, the association of a chemotherapy and a radiotherapy strongly reduced the relapse incidences and prolonged patients' survival (27). Since the 1980s, the global survival of the metastatic diagnosed patients increased by the use of new cytotoxic molecules (i.e., oxaliplatin, irinotecan), combined with anti-angiogenic and anti-EGFR molecules (28). To date, this survival was strongly increased by the combination of the three most effective chemotherapeutic agents (fluorouracil, irinotecan and oxaliplatin) (29).

Tumor-suppressor genes and oncogenes was identified as key genes whose mutations or altered expression are associated with colorectal cancer (30). Colon cancer initiation and progression, which are under these genes control, are also regulated by growth factors or hormones present in the tumor environment which action are mediated trough tyrosine kinase receptors or G protein-coupled receptors (GPCRs) (31). Many GPCRs were

similarly expressed in normal colon epithelial cells, others are overexpressed and some of them are ectopically expressed in cancer cells (31–36). The peptide hormones mediated-growth effects such as gastrin (34) or neurotensin (33), serine proteases such as thrombin (35) or trypsin (37) or lipids such as lysophosphatidic acid (38) or prostaglandin E2 (39) are promoted through GPCRs. Activation of these GPCRs activation leads tumoral growth via G protein transduction pathways and/or by transactivating the tyrosine kinase epidermal growth factor receptor (EGFR) (40, 41). The environment of primary colon tumors is rich in growth factors, however the existence of growth inhibitory factors for colon cancer is not well documented. In order to determine these inhibitory factors, the screening of the ability of different peptide hormones and neuropeptides to inhibit colon cancer growth was investigated (42). Twenty-six peptides were tested, including orexins which were present in few peripheral tissues including the gastrointestinal tract (10). The screening, using the human colon cancer cell line HT-29 grown in standard trophic conditions shows that only the two related peptides OxA and OxB was able to inhibit tumoral cell growth (42). Orexins do not modify cell cycle and proliferation, but activate cell death by apoptosis with a plasma membrane phosphatidylserine externalization, chromatin condensation and DNA fragmentation (42–44). Only OX1R, and not OX2R, is expressed in HT-29 cells and is involved in the orexin-induced apoptosis. Orexins promote cell death described by a mitochondrial cytochrome c release and caspase-3 and caspase-7 protease activations (42, 44). The ability of orexins to activate a robust apoptosis has been shown in 9/10 (90%) different human colon cancer cell lines (44). Conversely, orexins do not trigger apoptosis in explant cultures of human normal colonic mucosa demonstrating that the orexin-induced apoptotis appeared during the colonic epithelial cell oncogenesis (44). However, preproorexin and OxA has been detected in normal total colon (10, 11). In contrast, no detection of preproorexin was observed in normal and tumoral colonic epithelia (44). Moreover, in preclinical models, the tumoral development of xenografted tumor from HT-29 cells which expressed OX1R or HCT-116 cells which do not expressed OX1R were identical (44). These observations indicate that endogenous OxA, present in colon but not in colonic epithelium, have no impact on tumoral development.

The drug resistance occurrence is a primary cause of chemotherapy failure. The 5-fluorouracil (5-FU) represents the "gold standard" molecule used in treatment of colon cancer. The OX1R expression was investigated in the HT-29-FU colon cancer cell line model, developed after a long-term 5-FU exposure clonal cells resistant against the drug (45). The OX1R expression, orexins-induced apoptosis and subsequent growth inhibition were similar in resistant HT-29-FU cells and sensitive initial HT-29 cells (44), suggesting that orexins-induced apoptosis persists in resistant cells (44). Moreover, OX1R is expressed in 100% of primary colorectal tumors resected from patients (38 different colorectal cancers) whatever their stages and in 10 hepatic metastases and in human colon cancer cell lines established from lymph nodes, ascite, and lung metastases tested (44).

The efficiency of *in vivo* orexin treatment was addressed using human colon cancer cells xenografted in nude mice. When human colon cancer cells were xenografted in nude mice, daily OxA administration strongly slowed the tumor growth and even reversed the development of established tumors when administered 7 days after cell inoculation. After a 15-days orexins treatment, the tumor volume is decreased by 80% (**Figure 2**) (44). It was shown that orexins treatment reduces tumor growth *in vivo* by promoting apoptosis, through activation of caspase-3 (44).

The OX1R-driven apoptosis even though calcium pathway could not be explained only by the classical Gq-mediated calcium response. Two tyrosine-based motifs (ITIM) were identified in OX1R which have a crucial role in OX1R-driven apoptosis (**Figure 1**) (43, 48). The ITIM is not considered to be a GPCRs' signature, but represents a hallmark of immune inhibitory receptors (49). After activation of OX1R by orexins, the two ITIMs are phosphorylated on tyrosine residue (43, 48). It should be noted that the classical Gq-mediated activation of phospholipase C is not involved in this process. When orexins promoted tyrosine phosphorylation of ITIMs, OX1R recruits and activates the phosphotyrosine phosphatase SHP2 which is crucial in the orexin-induced apoptosis process (43, 48). The intracellular signaling pathway downstream of SHP2 includes the p38 mitogen-/stress activated protein kinase phosphorylation, which leads to the proapoptotic protein Bax translocation in the mitochondria, the apoptosome formation, caspase-3 and caspase-7 activation and cell death (**Figure 1**).

PANCREAS CANCER

Pancreatic ductal adenocarcinoma (PDAC) is the tenth most common cancer sites in terms of frequency and is the fifth cause of cancer mortality (50, 51). Moreover, the projection cancer incidence and deaths in 2030 indicate that this cancer could become the second cause of cancer-related death (52). Invasive PDAC which carries a very poor prognosis (5-year survival rate $< 8\%$), is rarely surgically resectable and $<20\%$ of patients undergoing a curative surgery. In addition, PDAC is one of the most chemotherapeutic drug-resistant tumors (53). The high therapeutic resistance of PDAC can be explained by immunodepression, hypoxic microenvironment and a pronounced fibrotic reaction consisting of proliferating stromal cells together with collagen-rich extracellular matrix (53). This fibrotic stroma can account for more than 80% of the tumor mass (54), has been shown to limit the delivery of therapeutics, and contribute to tumor progression and drug resistance (55). Despite increased knowledge in the etiology of PDAC, successful therapeutic strategies are still very poor.

Recently, the OX1R expression was detected in 70/73 human PDAC (96 %) and in 83/103 human pancreatic neuroendocrine tumors (46). It should be noted that OX1R was not expressed in normal pancreas (acini and ducts) except in the Langerhans islets (**Figure 3A**) in which orexins could play a role in insulin secretion (8). This expression in tumoral tissue was independent of patient age, gender, tumor size, and lymph

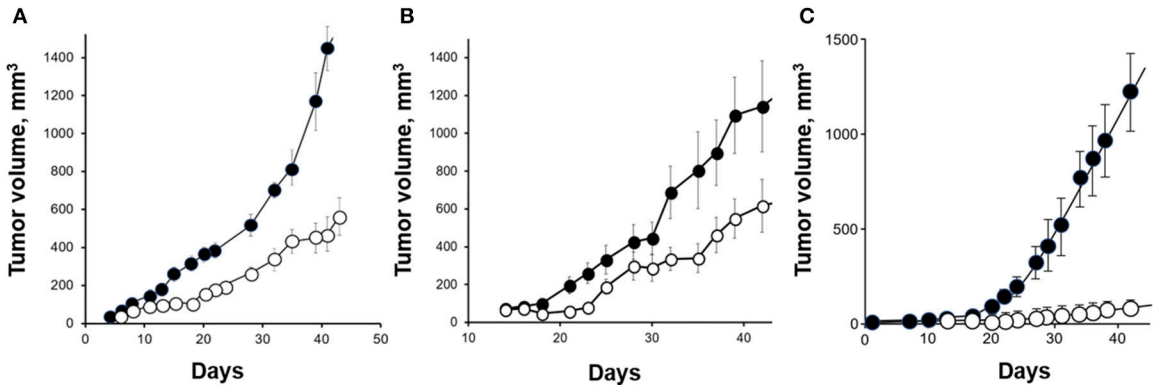

FIGURE 2 | Anti-tumoral effect of OxA in preclinical mouse models. **(A)** Nude mice were xenografted with the colon adenocarcinoma cell line, HT-29 and then, treated by 1 μmoles of OxA/Kg intraperitoneally (ip) injected. The tumor development was determined by measurement. **(B)** Nude mice were xenografted with the pancreatic adenocarcinoma cell line, AsPC-1, and ip injected with 1 μmoles of OxA/Kg. **(C)** Nude mice were xenografted with the prostate cancer cell line, DU145 and treated with 1 μmoles of OxA/Kg. (•), control mice injected with PBS; (○), treated mice injected with OxA. The sources of graphs were based on Voisin et al. (44), Dayot et al. (46), and Chartrel et al. (47).

node metastasis (46). The use of AsPC-1 cell line derived from human PDAC revealed that OxA was able to strongly inhibit cell growth by the SHP2-induced apoptosis (46). Moreover, the treatment by OxA of tumor slices obtained from patients and maintained in culture, induced the activation of caspases-3 in tumoral tissue demonstrating that OxA was able to induce apoptosis in PDAC (46). In preclinical model consisting in sub-cutaneous xenografted AsPC-1 cells in nude mice, OxA reduced significantly the tumor growth (**Figure 2B**). This tumor regression was also observed in tumors established 14 days prior OxA treatment (46). For translational studies, the patient-derived xenograft (PDX) model was frequently used. In such models, the tumoral fragments, or the isolated cells from the patient's cancer were implanted in immunodeficient mice, OxA was also able to drastically reduce the tumor growth derived from PDAC indicating its potential therapeutic interest (46). Previously report revealed the expression of OxA in endocrine pancreas (11). However, the presence of endogenous OxA does not seem to be involved in anti-tumoral effect of exogenous OxA since the tumoral development of xenografted tumor from AsPC-1 cells which expressed OX1R or HPAF-II cells which do not expressed OX1R were very similar (46). Moreover, the concentration of circulating orexins was very low (about 40 pM) to functionally activate OX1R.

As mentioned in the introduction, orexins and their receptors have been extensively studied in CNS notably in sleep regulation. In this context, many academic and pharmaceutical laboratories have focused their researches in the development of molecules able to improve sleeping regulation, in particular, in insomnia (57, 58). A lot of antagonists were developed and sub-divided into two classes named single orexin-receptor antagonists (SORAs) and dual orexin-receptor antagonists (DORAs). Among them, the SORA small molecule SB-408124 or SB-334867 was shown to be specific of OX1R (59, 60) and JNJ-42847922 specific of OX2R (61). However, the main molecule development, in particular antagonists, was related to the sleep-wakefulness actions of orexins leading to the design of DORA such as SB-649868, almorexant (ACT-078573) (62) and suvorexant (MK-4305) for which the U.S. Food and Drug Administration (FDA) approved the use for the treatment of insomnia (63). In parallel, the development of OXR agonists was substantially much lower. Despite some attempts, no OX1R agonist was actually available (64) and only few OX2R agonists have been developed such as the non-peptidic molecules YNT-185 (65), OX2R-agonist 26 (66), and the peptide agonist SB-668875 (67) but these molecules are poorly documented.

Surprisingly, the use of suvorexant or almorexant on PDAC cell line, AsPC-1 revealed that these molecules inhibited the cellular growth by apoptosis induction (46). Almorexant appearing to be more potent than suvorexant to induce this inhibitory effect. Moreover, intraperitoneal injections of almorexant in xenografted mouse model, induced a significant reduction in tumor size (>50%) similar to the anti-tumoral effect of OxA in the same conditions (46). As shown in **Figure 1**, OxA and OxB activated two signaling pathways, including: (1) the canonical intracellular Ca^{2+} release effect mediated by the Gq protein which was totally inhibited in the presence of SORA and/or DORA (46) and; (2) the recruitment of SHP2 mediated by the phosphorylation of ITIM sites leading to the intrinsic apoptosis mediated by the p38 signaling pathway which was not affected by DORA (46). Recently, structure-function relationship analysis of OxB evidenced that some residues of the peptide discriminated between proapoptotic and calcium pathways (17). Likewise, almorexant which binds to OX1R with the similar affinity than OxA could discriminate these two signaling pathways demonstrating the existence of two independent molecular activation of the OX1R. These observations, suggest that almorexant (and also suvorexant) belong to ligand-biased family (68). Therefore, OX1R antagonists, which was prescribed for insomnia could be used in the anti-tumoral therapy as full agonist.

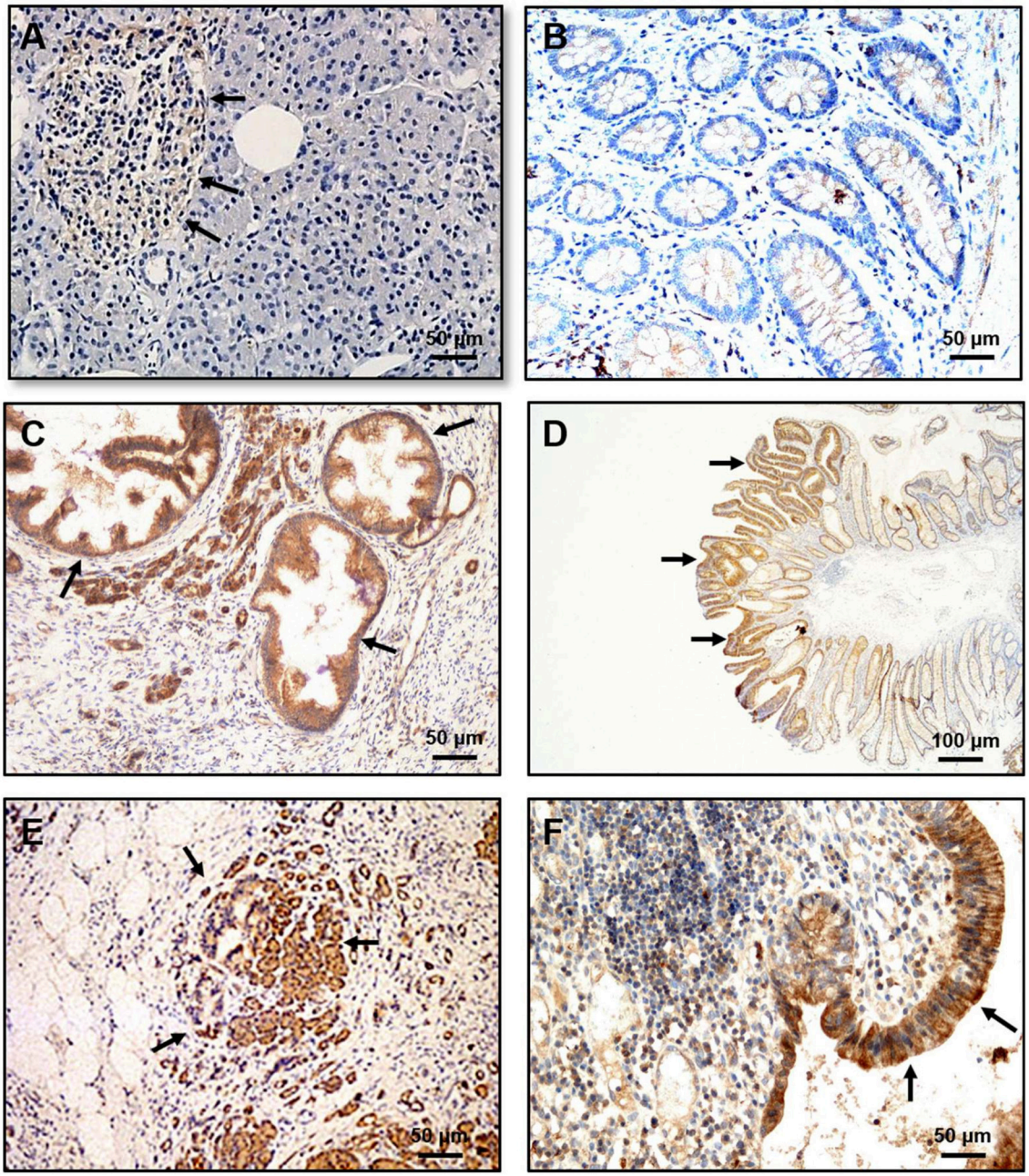

FIGURE 3 | Immunohistochemical expression of OX1R in PanIN, dysplastic colonic polyp, pancreatitis and ulcerative colitis (UC). **(A)** OX1R was not detected in the normal pancreas either in normal duct and acinar cells. **(B)** OX1R was not detected in colonic mucosa. **(C)** OX1R was expressed in PanIN lesions. **(D)** OX1R was expressed in dysplastic cells present in colonic polyps. **(E)** OX1R immunostaining of colonic mucosa from patients with pancreatitis. **(F)** OX1R immunostaining of colonic mucosa from patients with UC. Arrows indicated the OX1R expression. Bar = 50 µm for **(A, B C, E, F)**; Bar = 100 µm for **(D)**. The sources of graphs were based on Voisin et al. (44), Dayot et al. (46), and Messal et al. (56).

PROSTATE CANCER

With about 71,000 new cases of prostate cancer in France each year, this cancer represents the most commonly diagnosed malignant tumor for men in the Western world, far ahead lung cancers and colorectal cancers (69). Despite the progress in screening, prostate cancer is the second cause of cancer-related mortality (70) and is associated with resistance to chemo-hormonal therapy in the metastatic setting. It should be noted that, more one in nine men will disclose a prostate cancer during his life. Because androgens stimulate the tumor growth, androgen ablation therapy represents the first line of treatment of advanced

cancer inducing an effective tumoral regression (71). However, over the years an androgen resistance named castration-resistant prostate cancer (CRPC) develops. The cause of this resistance remains still unclear, but some investigations revealed an overexpression/amplification of androgen receptors (AR), a gain-of-function of AR, a production of AR variants having constitutive properties, an overexpression of co-factors of AR and an intra-tumoral production of androgen (72). In addition to the major role of the androgen/AR system in prostate cancer, various GPCRs are involved in the development and progression of prostate cancer (73). These GPCRs include gonadotropin hormone receptors [luteinizing hormone receptor (LHR) and follicle-stimulating hormone receptor (FSHR), peptide receptors neurotensin receptor (NTR), bombesin receptor (BBR), endothelin-1 receptor (ETR), oxytocin receptor (OXTR), and ghrelin receptor (GHSR)], protease receptors [thrombin receptors (PARs)] and neuropeptide receptors [neuropeptide Y receptor (NPYR)], vasoactive intestinal peptide receptor (VPAC), and pituitary adenylyl cyclase activating peptide (PAC1). This partial list of GPCRs and their ligands promoted proliferation, migration, invasion, mitogenic signaling, and neuroendocrine differentiation of prostate cancer cells (73–81). Moreover, GPCRs expressed and/or overexpressed in prostate cancer are able to engage a cooperative crosstalk with growth factor receptors such as epidermal growth factor receptor (EGFR) (82). This transactivation mediated by GPCRs such as PAR receptors leads to the cleavage of EGF-like transmembrane ligands [EGF, transforming growth factor α (TGFα) …] by cancer cells. Thereby, a soluble biologically active growth factor was produced and induced mitogenic effects mediated by EGFR (40). In contrast, few GPCRs were involved in the inhibition of growth and/or in apoptosis of prostate cancer cells. The gonadotropin-releasing hormone receptor (GnRH) was expressed in human malignant prostate tumors where its activation induced an anti-tumoral activity mediated by p38 MAPK and protein tyrosine phosphatase (73). However, nothing is known about neuropeptides and their receptors in anti-tumoral properties in prostate cancer. OX1R but not OX2R was highly expressed in high grade advanced prostate cancer (CaP) whereas this expression was much lower in low grade cancer (83). Inversely, in benign prostatic hyperplasia (BPH), OX1R expression was mostly absent and mainly confined in scattered cells (83). It should be noted that OX2R seemed to be expressed in BPH, which was associated with a decrease of OxA serum concentration (84). The expression of OxA and its precursor was found in "fiber-like" stroma of prostate cancer tissues which did not correspond to nerve and smooth muscle fibers (83). In normal tissue, OxA was expressed in follicular exocrine epithelium (14) and also in hyperplastic epithelium. However, large areas of prostate epithelium were not immunoreactive (14). Moreover, the presence of OxA was never detected in cancerous foci whatever the cancer grade (83). Taken together these observations suggested that OX1R which is expressed in cancer cells was probably not activated by endogenous OxA produced by the prostate stroma and/or delivered by the blood circulation (83). OX1R was expressed in androgen-unresponsive cell line, DU145 in which OxA or OxB induced a significant apoptosis (83). In addition, OX1R was also expressed in androgen-responsive cell line LNCaP in which OxA induced an up-regulation of OX1R gene expression and inhibited cell survival (85). *In vivo* studies using xenografted mouse model with DU145 cells revealed that daily intraperitoneally injection of OxA induced a strong reduction of tumor volume (**Figure 2C**).

OTHER CANCERS

Like the peripheral biological role of orexins that remains still under discussion (86), OXR expression and orexins actions in cancer have been poorly documented (87). Several lines of evidence indicated that OX1R/OX2R were expressed in various cancer cells, but their actions depended on the cancer types. It should be noted that the OXR expression was mainly determined using a great variety of antibodies (produced by various manufacturers) some of them have been identified as non-specific, in particular for anti-OX2R antibody which also recognized OX1R. In the same manner, the use of antibodies to detect the presence of OxA and/or OxB peptides in tissues was also questionable. Nevertheless, the possibility of OXR expression by other solid tumors is always under investigation. OX1R was expressed in neuroblastoma in which orexins treatment induced apoptosis (42). OX1R was also identified in cortical adenomas but its relation to apoptosis was not investigated (88, 89). In human hepatocellular carcinoma tissues (90), in gastric cancer cell lines, SGC-7901 and BGC-823, OxA seemed to enhance the proliferation and inhibited the apoptosis which is mediated by the ERK or AKT signaling pathway (91, 92), respectively. Moreover, OxA and cholecystokinin (CCK) inhibited the migration of colorectal cancer cell line, HT-29 mediated by heterodimerization of OX1R and CCK1R (93). In addition, OX2R was expressed in human pheochromocytomas and PC12 cells in which OxA and OxB stimulated (94) or inhibited (95) catecholamine secretion, in endometrial endometrioid carcinoma in which OxA and OxB had no effect on proliferation and/or apoptosis (96), and in human adrenocortical NCI H295R cells where OxA induced the phosphorylation of ERK1/2 and p38 (88). Taken together these observations indicated that OX1R and OX2R were expressed in various cancers. In contrast, in the corresponding healthy tissues such as colonic epithelium and pancreatic acini, OX1R was not expressed [**Figure 3** and (49)]. It may be noted that OX1R is expressed in Langerhans's islets (**Figure 3**). In this context, an important question arises: is OX1R expressed at early stages of cancer development? As shown in **Figure 3**, the dysplastic cells present in colon polyps or pancreatic intraepithelial neoplasia (PanIN) lesions highly expressed OX1R indicating that the expression of the receptor occurred at a very early stage (46). Chronic inflammation, including intestinal bowel disease (IBD), pancreatitis, hepatic fibrosis… or metabolic syndrome which is close to chronic inflammation, represent a high-risk factor in the development of cancer (97). What is the role of OX1R expression in inflamed tissues? Various studies have demonstrated that orexins exercised neuroprotection effects and reduced cerebral neuroinflammation associated to post-stroke trauma (98, 99). Recently, Ogawa

et al. demonstrated that OxA alleviated the survival of mice with endotoxin shock characterized by a systemic inflammation (100). Some reports revealed a relationship between orexinergic system and metabolic syndrome disorder (101). In ulcerative colitis (UC) and pancreatitis, OX1R was highly expressed in inflamed areas (**Figure 3**). Moreover, OxA was able to induce an anti-inflammatory effect in mice models reproducing UC or pancreatitis (56, 102). A recent study indicates a higher prevalence of immunopathological diseases, including purpura, multiple sclerosis, systemic lupus erythematosus, psoriasis, Crohn's disease, or ulcerative colitis, in narcoleptic patients (103). Besides, the anti-tumoral properties of OXR/orexins system, orexins could play an important role in chronic inflammation.

CONCLUSION

These last two decades, orexins/OXR system has been extensively studied in CNS in particular in the regulation of sleep/wake. These intensive and fruitful investigations lead to development of therapeutic molecules which are prescribed to treat insomnia. Beside this innovative research in CNS, the orexins/OXR system has a potential benefit in peripheral physiopathology, especially in cancer, and chronic inflammatory diseases. These promising perspectives open up new fields of application in the development of new therapeutic agonist molecules (including peptides, small non-peptidic molecules, and functional agonist antibodies) and/or the use of molecules already developed such as almorexant, suvorexant.… In the future decade, the orexins/OXR system could constitute a crucial curative target in human cancers.

AUTHOR CONTRIBUTIONS

SD, VG, PN, VR, and AnC have participated in the work and has proofread the manuscript. AlC and TV have written the manuscript. AlC was the head of the "from inflammation to cancer in digestive diseases" group.

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