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Commentary **Open Access**

A new twist to neurotransmitter receptors and cancer

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BACKGROUND

Nicotinic acetylcholine receptors (nAChRs) and beta-adrenergic receptors (β-ARs) are cell membrane receptors expressed in most mammalian cells where they function as the recipients of signals from the autonomic nervous system that maintains physiological homeostasis in the mammalian organism and regulates cell and organ responses to endogenous and exogenous signals. The neurotransmitter of the parasympathetic branch of the autonomic nervous system, acetylcholine, binds as an agonist to all members of the nAChR family, thus opening the ligand-gated ion channel of the receptors. The resulting depolarization of the cell membrane opens voltage-gated Ca^{2+}-channels (VOCs), allowing influx of additional Ca^{2+} that triggers the release of cell type-specific intracellular products via exocytosis.[1] Influx of Ca^{2+} is particularly high in response to agonist binding to the homomeric (comprised of alpha subunits only) α7nAChR due to the selectivity of its ion channel for Ca^{2+} whereas heteromeric (comprised of alpha and non-alpha subunits) nAChRs have non-selective ion channels. The mechanisms of nAChR-mediated neurotransmitter release by the central and peripheral nervous system, their role in memory, cognition and stress responses and the nAChR-mediated mechanisms of nicotine addiction have been extensively studied.[1,2]

Beta-adrenergic receptors are coupled to the stimulatory G-protein G_s that activates the enzyme adenylyl cyclase (AC) upon binding of an agonist to the receptor, leading to the formation of intracellular cyclic adenosine monophosphate (cAMP) that activates protein kinase A (PKA) and numerous PKA-dependent and independent intracellular signaling cascades in a cell type-specific manner.[3] In addition, β1 and β2-ARs can increase intracellular Ca^{2+} levels by a variety of mechanisms [Figure 1], including the PKA-induced upregulation of L-type Ca^{2+}-channels[4] and release of Ca^{2+} from intracellular stores that can also be induced by the cAMP binding protein exchange factor directly activated by cAMP (Epac).[5] Of particular importance for the regulation of cancer cells is the fact that activated PKA and/or cAMP stimulate the release of epidermal growth factor (EGF),[6] arachidonic acid (AA),[7,8] interleukins and vascular endothelial growth factor (VEGF),[9] which jointly stimulate the development,

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progression and metastasis of numerous cancers. The neurotransmitters of the sympathetic branch of the autonomic nervous system, epinephrine (Epi) and norepinephrine (Nor) are the physiological agonists for β-ARs. Epi and Nor are additionally synthesized and released by the adrenal medulla and are often referred to as "stress neurotransmitters" because psychological stress triggers their simultaneous release from the sympathetic nervous system and adrenal gland.[10,11] The release of stress neurotransmitters from the sympathetic nervous system and adrenal gland is regulated by nAChRs via Ca^{2+} influx that triggers their exocytosis.[12,13] The biology of β-ARs as it relates to cardio-vascular disease has been extensively studied and beta-adrenergic receptor antagonists (beta-blockers) and VOC blockers are widely used as therapeutics for this disease complex.[14-17]

Discoveries that nicotine induced the proliferation of human small cell lung cancer cells *in vitro*[18] while inhibiting apoptosis,[19] effects triggered by the nAChR-mediated release and re-uptake of the neurotransmitter 5-hydroxytryptamine (5-HT, serotonin),[20] first pointed to nAChRs as important regulators of a subset of cancers. Reports that β-AR agonists stimulated the proliferation of lung adenocarcinoma cells *in vitro* and that this response was inhibited by β-blockers first implicated β-ARs in the regulation of another subset of cancers.[21,22] The identification of the tobacco carcinogen nicotine-derived nitrosamine ketone (NNK) as a high affinity agonist for nAChRs[23,24] as well as β-ARs[7] subsequently provided a direct mechanistic link between the high carcinogenic potential of this agent and its interaction with neurotransmitter receptors. These studies also showed that NNK-induced β-AR signaling in lung adenocarcinoma cells and pancreatic ductal adenocarcinoma cells triggered the release of AA, resulting in the formation of cancer-stimulating AA metabolites while additionally trans-activating the epidermal growth factor receptor pathway.[7,8,25] Collectively, these early findings represented the starting point for a new domain in cancer research: the role of neurotransmitters and their receptors in the initiation, progression and drug resistance of cancer and the development of novel therapeutic and preventive strategies that target this regulatory network.[26-30]

It was initially thought that nAChRs and β-ARs expressed in non-neuronal cells and cancers derived from them were exclusively stimulated by the autonomic nervous system or by exposure to tobacco products. However, more recent studies have shown that numerous non-neuronal cells and the cancers derived from them synthesize and release their own acetylcholine[31] and are also able to synthesize and release Nor and Epi in response to acetylcholine self-stimulation or exposure to exogenous nAChR agonists.[32-36] In addition, it has been shown that polymorphisms in genes CHRNA3 (encodes the α3 nAChR subunit) and CHRNA5 (encodes the α5 nAChR subunit) as well as a copy number variation that duplicates the α7nAChR gene CHRNA7 are associated with an increased risk for lung cancer[37-39] and that single nucleotide polymorphisms in the β2-AR gene are associated with adverse clinical outcomes of pancreatic cancer.[40]

An important aspect of cancer regulation by neurotransmitters and their receptors is the significant influence of the mood on this regulatory network [Figure 1]. Preclinical investigations have thus shown that experimentally induced psychological stress or treatment with stress neurotransmitters have strong promoting effects on the majority of the most common human cancers via direct activation of cAMP-dependent intracellular signaling pathways by stress neurotransmitters downstream of β1 and β2-ARs[29,32,41-45] and the simultaneous suppression of the tumor suppressor gene *p53* by beta-arrestin-1 signaling downstream of β2-ARs.[46] Moreover, chronic experimental stress suppressed the synthesis and release of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).[41,42] These findings are in accord with the reported suppression of the GABA system by chronic psychological stress[47] and in anxiety disorders such as posttraumatic stress syndrome.[48,49] GABA is the main inhibitory neurotransmitter in the mammalian body and inhibits the AC-dependent formation of cAMP as well as the activation of voltage-gated Ca^{2+}-channels[50] under physiological conditions by activating inhibitory G-protein (G_i) signaling downstream of G_i-coupled GABA-B-receptors. In light of findings that the GABA-B receptor has tumor suppressor function in pancreatic[42,51-53] and non small-cell lung cancer (NSCLC)[35,41,54,55] while GABA also inhibits the *in vitro* growth of breast cancer and colon cancer,[47,56] suppression of GABA by psychological stress has significant tumor promoting effects on these cancers.

Similar to chronic stress, smoking also increases the levels of cancer stimulating stress neurotransmitters[57] while suppressing cancer inhibiting GABA,[2] effects caused by the neuroadaptation of nAChRs to chronic nicotine, NNK and N'-nitrosonornicotine (NNN). In conjunction with the mutational activities of NNK and NNN at the *K-ras* and *p53* genes,[58] the resulting prevalence of cancer stimulating beta-adrenergic receptor signaling contributes significantly to the increased cancer risk of smokers.

NOVEL FINDINGS

Three publications[59-61] from the Research Institute of Pharmacological Sciences, College of Pharmacy, Seoul National University (Seoul, Republic of Korea) have recently revealed additional mechanisms of nAChR and β-AR-mediated lung cancer promotion that can potentially be exploited for the targeted prevention and therapy of lung cancer and numerous other cancers. These studies showed that NSCLC tissues from smokers expressed significantly higher levels of the phosphorylated insulin-like growth factor-1 receptor (IGF-1R) than NSCLCs from nonsmokers and that the nicotine-derived carcinogen NNK promoted NSCLC tumorigenesis *in vitro* and in a mouse model by inducing exocytosis of insulin-like growth factor 2 (IGF-2) that phosphorylated the IGF-1 receptor, effects inhibited by the neuronal nAChR antagonist mecamylamine, dyhydropyridine blockers of L-type VOCs as well as by antagonists for β1-and β2-ARs.[59] The investigators reported that the observed IGF-1R phosphorylation was caused by β-AR-mediated stimulation of IGF2 transcription.[61] However, the molecular mechanisms of this effect have yet to be defined. Based on the inhibitory effects of mecamylamine and VOC blockers on EGF-1R phosphorylation, nAChRs were the upstream regulators of this β-adrenergic cascade by stimulating the release of Nor and Epi. In accord with established mechanisms of stress responses (nAChR-mediated opening of VOCs causing release of stress neurotransmitters by exocytosis from the sympathetic nervous system and adrenal glands), experimental chronic stress had significant tumor promoting effects on urethane-induced mouse NSCLC and on the development of this cancer type in transgenic $Kras^{G12D/+}$ mice via IGF-2-mediated activation of the IGF-1R signaling cascade.[60,61] In both animal models these effects were inhibited by the general beta-blocker propranolol or the dihydropyridine VOC blockers amlodipine or nifedipine. Propranolol also significantly prevented the development of NNK-induced lung tumors in A/J mice, an effect accompanied by suppression of phosphorylated IGF-1R.[61] The authors conclude that beta-blockers and VOC blockers should be further explored for the prevention of lung cancer, a concept that could rapidly move into clinical trials because these drugs are already widely used for the long-term management of cardiovascular disease.

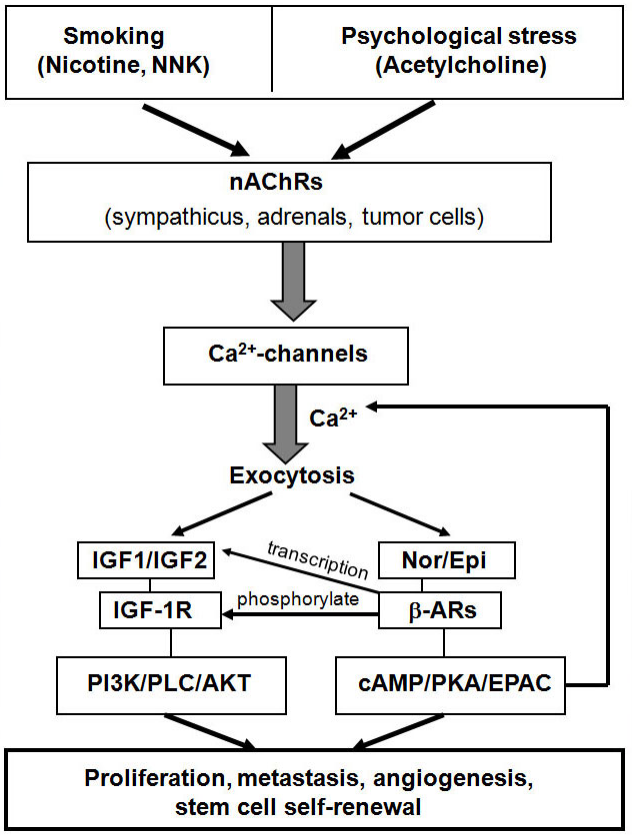

Figure 1: Working model illustrating the mechanistic interactions of nicotinic acetylcholine receptors, Ca^{2+}-channels, beta-adrenergic receptors and the IGF pathway in cancers associated with smoking and psychological stress. NNK: nicotine-derived nitrosamine ketone; nAChRs: nicotinic acetylcholine receptors; IGF-1R: insulin-like growth factor-1 receptor; PLC: phospholipase C; AKT: protein kinase B; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A

CONCLUSIONS AND FUTURE DIRECTIONS

The reported activation of the IGF-1R signaling cascade in NSCLC and their normal epithelial precursor cells by the joint actions of nAChRs, VOCs and β-ARs adds a novel aspect to the mechanisms of cancer regulation by neurotransmitter receptors. While cancer research on the regulatory function of these receptors has mostly interpreted their modulation of intracellular signaling pathways as direct events downstream of the receptors,[20,24,30,45,62,63] the cited three publications[59-61] instead take into consideration the physiological role of nAChRs and β-ARs in the release of cell type-specific products by exocytosis [Figure 1] in response to increased intracellular Ca^{2+}. In addition to IGF-2, β-AR-I agonists also induced the release of AA, EGF, VEGF, interleukin-6 as well as several cancer stem cell markers.[36,64-66] In turn, these effects can be caused by elevated systemic levels of stress neurotransmitters in response to stress or tobacco exposure, by direct binding of NNK in tobacco products to β-ARs, or by medications that are beta-adrenergic agonists. In addition, epithelial cancer cells and their respective cancer stem cells synthesize and release their own Epi and Nor upon activation of nAChRs by nicotine or nicotine-derived nitrosamines.[33,36] The proposed re-purposing of beta-blockers and Ca^{2+}-channel blockers for lung cancer prevention would therefore inhibit

differentiated cancer cells as well as cancer stem cells.

There is an ongoing international discussion on the potential usefulness of beta-blockers for cancer intervention, with numerous preclinical studies reporting significant cancer inhibition whereas clinical investigations have generated controversial data with some even reporting cancer promoting effects.[28,29,64,67-71] The potential usefulness of beta-blockers for adjuvant cancer treatment has additionally been discussed in depth based by comprehensive reviews of published preclinical and clinical literature.[67,72,73] By contrast, the current review analyzes mechanistic aspects of G_s-coupled receptors and their physiological inhibitors and their modulating effects on cancer. The discrepancies between preclinical and clinical findings are thus not only triggered by the potential sensitization of β-ARs in response to long-term beta-blocker therapy (decades of treatment in people as opposed to a few weeks in experimental animals), but also by the potential impact of factors unrelated to β-ARs. Preclinical studies that have employed agonists of receptors coupled to the inhibitory G-protein G_i (GABA-B receptors, opioid peptide receptors) for the inhibition of β-AR-mediated progression of adenocarcinoma of the lungs and pancreas *in vitro* and *in vivo* have repeatedly shown that increases in intracellular cAMP and the associated activation of its downstream effectors are key molecular events that activate β-AR-driven development and progression of both cancers and can be successfully inhibited by agonists of G_i-coupled receptors that inhibit the formation of cAMP by blocking the activation of adenylyl cyclase.[41,42,51,54,55,66,74-76] A host of non-β-AR receptors coupled to the stimulatory G-protein G_s increase intracellular cAMP,[3,77] a reaction not inhibited by beta-blockers but effectively counteracted by agonist-induced signaling of G_i-coupled receptors. There is also a host of non-beta-adrenergic agents that increase intracellular cAMP directly. Among such agents are caffeine, theophylline and theobromine contained in numerous beverages, weight loss medications, sweets and candies. These naturally occurring phosphodiesterase inhibitors block the enzymatic breakdown of cAMP which then accumulates inside the cells. In addition, pharmacological phosphodiesterase inhibitors are widely used for the therapy of chronic obstructive pulmonary disease because of their anti-inflammatory and broncho-dilating properties. None of the clinical investigations on beta-blockers and cancer conducted to date have adjusted their data to exclude the cancer promoting effects of such non-beta-adrenergic agents.

Beta-blockers should not be used for the general prevention/therapy of cancer because they are selectively effective only in cancers that are stimulated by beta-adrenergic agonists. In fact, without prior testing of patients for increased stress neurotransmitter and cAMP levels, beta-blocker treatment is contra-indicated because it can promote certain cancers due to the fact that cAMP functions as a tumor promoter in some cancers while acting as a tumor suppressor in others. It has thus been shown that cAMP inhibits the growth/progression of squamous cell carcinoma,[78] small cell lung carcinoma,[79,80] medulloblastoma and basal cell carcinoma.[81] The arbitrary use of Ca^{2+}-channel blockers for cancer prevention and therapy is equally ill advised. While preclinical investigations have identified cancer preventive effects of Ca^{2+}-channel blockers in a large spectrum of cancers,[82-84] these agents not only suppress molecular targets studied in these cancers but additionally inhibit the release of Nor and Epi from sympathetic nerves,[85] thereby suppressing the beta-adrenergic receptor-mediated formation of cAMP. In turn, this effect can selectively promote the development and progression of cancers in which cAMP has tumor suppressor function.

In summary, successful cancer prevention and improved therapeutic outcomes can be achieved by strategies that aim to maintain/restore cAMP homeostasis. Too much cAMP will promote the development and progression of cAMP-driven cancers (e.g. adenocarcinoma of the lungs, pancreas, colon, stomach and prostate) while too low cAMP levels will increase the risk for development and progression of cancers in which cAMP has tumor suppressor function (e.g. small cell lung cancer, squamous cell carcinoma, medulloblastoma, basal cell carcinoma). In analogy to the long-term management of diabetes by insulin injections that are based on blood glucose testing, this approach requires routine testing of cAMP levels. Beta-blockers will only be beneficial if elevated levels of Nor/Epi indicate hyperactive β-AR signaling.

Authors' contributions
H.M. Schuller contributed solely to the paper.

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Conflicts of interest
There are no conflicts of interest.

Patient consent
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