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Neurotransmitters and their Receptors as the Upstream Regulators of the Most Common Human Cancers and their Stem Cells

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Introduction

Cancer is a disease characterized by the dysregulated growth of cancer cells at the expense of healthy tissues, resulting in local and distant metastasis, ultimately killing the host. This is a highly coordinated process, resulting in the simultaneous stimulation of cell proliferation, cancer stem cell self-renewal, metastatic ability, angiogenesis, neuro-neogenesis and decrease in apoptosis. Studies on the mechanisms of cancer development, progression and resistance to therapy have traditionally focused on gene mutations as well as changes in the expression of genes and signaling proteins associated with the regulation of cell proliferation, apoptosis, metastasis and angiogenesis[1]. However, the highly coordinated embryonal development of the mammalian organism, its stem cells and the ability of the adult organism to respond to endogenous and exogenous signals is regulated by neurotransmitters and their receptors[2-3], suggesting that they may also be involved in the regulation of cancers and their stem cells. In support of this hypothesis, it has been shown that cancer stem cells from pancreatic cancer and lung adenocarcinoma synthesize and release the neurotransmitters acetylcholine, epinephrine (Epi), norepinephrine (Nor) and γ-aminobutyric acid (GABA), with acetylcholine, Epi and Nor stimulating their self-renewal while GABA was inhibitory[4-5].

It has been shown that smoking distorts the balance between excitatory and inhibitory neurotransmitters by nicotine-induced desensitization of the α4β2 nicotinic acetylcholine receptor (nAChR) that regulates GABA synthesis and release while upregulating the α7nAChR which regulates the synthesis and release of epinephrine and norepinephrine[6-8], a phenomenon implicated in the development of nicotine addiction[9] and tobacco-associated cardiovascular disease[10]. Since smoking is additionally a documented risk factor for the development of numerous human cancers at different organ sites (lung, pancreas, breast, colon, stomach, prostate, ovary), continued smoking after a diagnosis of cancer negatively impacts overall survival and response to therapy[11-16], and nAChRs are universally expressed in most mammalian cells, including embryonal stem cells[17], it is only logical to investigate the potential role of neurotransmitters and their receptors in the development, progression and resistance to therapy of cancer, which is the topic of this review.

Nicotine is generally considered the major psychoactive component responsible for the addictive properties of smoking[18-20]. On the other hand, the tobacco-specific nitrosamines N-nitroso-nor-nicotine (NNN) and 4(methylnitrosamino)-1-(3pyridyl)-1-butanone (N-nitroso-

nicotine ketone, NNK), that are formed from nicotine by nitrosation during the processing of tobacco and in the mammalian organism, have been identified as powerful carcinogens in animal experiments and are thought to cause cancer in humans via the induction of constitutively activating mutations in the k-*ras* gene and inactivating mutations in the tumor suppressor gene *p53*[21]. These classic concepts have however been challenged by discoveries that both tobacco-specific nitrosamines bind as agonists to nAChRs with significantly higher affinities than nicotine[22] and that NNK binds additionally as an agonist to beta-adrenergic receptors (β-ARs) with significantly higher affinity than their physiological agonists Epi and Nor [23-24]. Moreover, it was discovered that the *ras* mutations induced by NNN and NNK do not render the gene constitutively active but sensitize it to its physiological stimulators instead[25]. Accordingly, the chronic interactions of NNN and NNK with nAChRs may significantly contribute to nicotine addiction in smokers. On the other hand, chronic exposure of nAChRs to nicotine, NNN and NNK and chronic exposure of β-ARs to NNK may also cause the sensitization of K-*ras* by increasing the levels of its upstream stimulators such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), prostaglanding E2 (PGE2)[25-27] and pro-inflammatory cytokines [28] via their nAChR and/or β-AR-mediated releases.

It was initially believed that neurotransmitters are only expressed in the nervous system and that their release from nerves of the autonomic nervous system regulates all involuntary cell and organ functions[29]. In addition, it was shown that cancer cells release neurotropic factors that initiate neo-neurogenesis, a process including the growth of nerve endings into the tumor tissue, thus facilitating the interaction of cancer cells with nerve-derived neurotransmitters[30]. Furthermore, *in vitro* investigations with human breast cancer cell lines revealed that cancer cells can get attracted to Nor and migrate towards this neurotransmitter via "chemotaxis"[31], a phenomenon likely responsible for the perineural invasion of the pancreatic plexus (comprised predominantly of sympathetic nerves) by pancreatic cancer cells at an early stage of cancer development[32]. However, more recent investigations found that normal epithelial cells as well as epithelial cancers also synthesize and release excitatory (acetylcholine, Epi, Nor, serotonin) as well as inhibitory (γ-amino butyric acid, GABA) neurotransmitters and regulate their own proliferation and migration via this autocrine mechanism, with the excitatory neurotransmitters stimulating proliferation and migration whereas GABA inhibits[4,17,33-37]. Nicotinic acetylcholine receptors, adrenergic receptors and GABA receptors expressed in cancer cells can thus be activated by exposure to nerve-derived neurotransmitters and by cancer-derived or surrounding epithelial cell-derived neurotransmitters while nAChRs can additionally be activated by nicotine, NNN and NNK and β-ARs by NNK. Moreover, the systemic increase in the stress neurotransmitters Epi and Nor in response to psychological stress[38] or smoking[39] represents an additional source of adrenergic receptor activation in cancer cells.

Effects of nAChRs via Serotonin-Induced Signaling in Cancer Cells

The excitatory neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is synthesized and released by neurons in the brain and by cells of the disperse neuroendocrine system in the lungs, gastrointestinal tract, pancreas and prostate[40]. Serotonin is a growth factor for neuroendocrine cancers of the lungs (small cell lung cancer, carcinoids)[37, 41], as well as pancreatic cancer[42]. It has been shown that the homomeric nAChR comprised of α7 subunits (α7nAChR) regulates the release of serotonin from small cell lung cancer cells and normal pulmonary neuroendocrine cells upon binding of nicotine or NNK to the receptor[41]. In turn, the released serotonin then binds to serotonin receptors expressed in these cells that stimulate their proliferation via the activation of intracellular signaling cascades involving Raf-1, the mitogen-activated protein kinase (MAPK) pathway and the transcription factor c-myc[37,41]. Interestingly, the activation of this pathway is inhibited at the level of Raf-1 by β-AR signaling and by phospho-diesterase inhibitors, both of which increase the intracellular levels of cAMP[43-44].

Effects of nAChRs via Stress Neurotransmitter-Induced Beta-Adrenergic Receptor Signaling in Cancer Cells

Numerous publications have described the nicotine-induced direct modulation of diverse intracellular signaling pathways (activation of proliferation and migration pathways, inactivation of apoptotic pathways) in cancer cells by nAChRs[45]. However, an important role of nAChRs is the regulation of neurotransmitter release [46]. Nicotinic receptors are ion channels that depolarize the cell membrane upon binding of an agonist to the receptor, leading to the opening of voltage-gated Ca^{2+}channels[6]. In turn, the resulting influx of Ca^{2+} triggers the release of cellular products such as neurotransmitters[37, 41, 47-48]. In analogy to this classic function, *in vitro* studies with cell lines from human lung and pancreatic adenocarcinomas and normal epithelia in which these cancers arise have shown that binding of nicotine or NNK to the homomeric α7nAChR or to heteromeric nAChRs expressing subunits α3 or α5 in combination with beta subunits caused the release of Nor and Epi, which then activated beta-adrenergic receptors that stimulated the release of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF)

and arachidonic acid, leading to increased cell proliferation [23-24]. Similar investigations with gastric and colon cancer cells reported nicotine-induced cell proliferation involving beta-adrenergic receptor activation and upregulation of the arachidonic acid metabolizing enzyme cyclooxygenase 2 (COX-2)[27, 34, 49]. These findings are in accord with the physiological function of beta-adrenergic receptors. Beta-adrenergic receptors are seven trans-membrane receptors coupled to the stimulatory G-protein Gs that activates adenylyl cyclase upon binding of an agonist to the receptor[50]. In turn, activated adenylyl cyclase catalyzes the formation of intracellular cyclic adenosine monophosphate (cAMP) which activates protein kinase A (PKA) and phosphorylates the transcription factor cAMP response element binding protein (CREB)[50]. It is well established that beta-adrenergic receptors induce the release of EGF[51], arachidonic acid[23-24,52], VEGF[28], and pro-inflammatory cytokines [28], all of which can contribute to the development, progression and resistance to therapy of numerous cancers. In addition, it has been shown that agonist binding to β-ARs can transactivate the EGFR directly[53-54]. It is therefore not surprising that binding of nicotine or NNK to the α7nAChR activates signaling proteins such as Raf, AKT the MAPK pathway and Src as well as arachidonic acid metabolizing enzymes in cancer cells[45], all of which are classic downstream effectors of the EGFR[55-56]. However, this is not (as often concluded in the cancer research literature) a direct effect of Ca^{2+} influx via the nACHR and associated Voltage-gated Ca^{2+} channels but instead an indirect response via the detour of Ca^{2+}-induced Epi/Nor release which then causes the β-AR-induced release of EGF, VEGF, arachidonic acid and pro-inflammatory cytokines, each of which in turn activates its associated signaling pathways. This is an important distinction as it identifies β-AR-induced cAMP signaling as the one key step that can be easily targeted for successful adjuvant cancer therapy by repurposed drugs such as beta-blockers, GABA and positive allosteric modulators of GABA-B-Rs currently in use for the management of cardiovascular disease, nutritional supplementation and drug addiction, respectively. A non selective beta-blocker such as propranolol should thus be the preferred therapeutic for cancer patients with incidental cardiovascular disease as this agent blocks all beta-adrenergic receptors, including β2ARs which are the predominant β-ARs in most cancer cells[57]. By contrast, the use of a selective β1-AR antagonist would be contra-indicated in such patients, because this would lead to the reactive upregulation of β2-ARs[58], thus stimulating the cancer cells. As propranolol would suppress blood pressure and heart function below physiological levels in cancer patients without incidental cardiovascular disease, these individuals should be given GABA or allosteric modulators of the $GABA_B$-R instead. The use of selective $GABA_B$-R agonists such as baclofen which have a higher affinity to the receptor than GABA should be avoided because preclinical investigations have shown that chronic baclofen down-regulates this receptor, resulting in tumor promoting effects[59].

Effects of nAChRs via GABA-Induced Inhibition of Adenylyl Cyclase

Gamma-amino butyric acid (GABA) is the major inhibitory neurotransmitter in the brain where its release is activated by the heteromeric nACHR expressing α4 and β2 subunits[60]. Chronic exposure to agonists such as nicotine, acetylcholine or the tobacco-specific nitrosamines in smokers desensitizes this receptor, thereby inhibiting GABA release. Desensitization of the α4β2 nAChR in the brain is an important contributor to the development of nicotine addiction in smokers[60].

In epithelial cells and epithelial cancers which synthesize and release GABA via identical mechanisms as the brain, GABA inhibits cell proliferation and migration[31, 59, 61-64]. However, when its upstream regulatory α4β2nAChR is desensitized due to chronic exposure to agonists in tobacco products, GABA release is inhibited, leading to suppression of the GABA system[9,20]. Preclinical studies with pancreatic cancer xenografts in mice and *in vitro* with pancreatic cancer cell lines have shown that chronic exposure to nicotine reduces the levels of systemic GABA in vivo[47] while additionally decreasing intracellular and secreted GABA in pancreatic cancer cells and their extracellular environment i*n vitro*[65]. On the other hand, treatment of pancreatic cancer cells with GABA inhibited cell proliferation even in the presence of stimulation with the β-AR agonist isoproterenol by blocking the formation of intracellular cAMP[63]. The tumor inhibiting effects of GABA were abolished by gene knockdown of GABA-B receptors (GABA-B-Rs)[63]. These findings are in accord with the physiological function of receptors (including the GABA-B-R) coupled to the inhibitory G-protein Gi, which inhibits the activation of adenylyl cyclase, thus blocking the formation of its downstream effector, cAMP[50, 66]. In similar experiments, GABA also inhibited the cAMP-driven proliferation of small airway epithelial cells and lung adenocarcinoma cell lines via GABA-B-R induced inhibition of cAMP formation[67] and inhibited the growth of xenografts from these cell lines[62]. GABA supplementation in the drinking water prevented the development of pancreatic cancer and pancreatic intra-ductal neoplasia in a hamster model of pancreatic cancer induced by NNK and alcohol consumption [68], an effect accompanied by significant reductions in the pancreatic levels of cAMP, interleukin 6 and multiple phosphorylated signaling proteins associated with cell proliferation[68]. The potential tumor suppressor function of GABA via Gi-coupled GABA-B-Rs suggested by these preclinical data is supported by clinical findings

that high levels of GABA-B-R expression in cancer tissue is predictive of better clinical outcomes in patients with non-small cell lung cancer (NSCLC)[69]. Additional support for this interpretation comes from observations that diabetes caused by the destruction of pancreatic beta-cells that are the main site of insulin as well as GABA production in the pancreas[70-71] is a documented risk factor for pancreatic cancer[12]. Similarly, pancreatitis of any etiology, including smoking and alcohol abuse, which destroys endocrine and exocrine cells of the pancreas resulting in pancreatic GABA deficiency[72], is a risk factor for pancreatic cancer[12].

Effects of Psychological Factors

The cancer promoting effects and negative impact on therapeutic responses of psychological stress via systemic increases in the levels of Nor and Epi and the resulting activation of beta-adrenergic receptor signaling have been documented in numerous animal models of human cancers that are adenocarcinomas, including adenocarcinoma of the lungs, pancreas, colon, prostate, breast, liver and ovary[64, 73-81]. On the other hand, it has been shown that experimental stress reduction by environmental enrichment inhibited the growth of lung adenocarcinoma xenografts in mice via reduction in systemic levels of stress neurotransmitters, leading to reduced beta-adrenergic receptor activation while simultaneously increasing the levels of GABA and opioid peptides, both of which inhibit the activation of adenylyl cyclase by their Gi-coupled receptors[5]. Environmental enrichment also inhibited the growth of pancreatic ductal adenocarcinoma (synonym: pancreatic cancer) xenografts in mice[82].

GABA-B receptors (GABA-BRs) and opioid receptors (ORs) are coupled to the inhibitory G-protein Gi that counteracts the cancer stimulating effects of Gs-coupled receptors by blocking Gs-mediated signaling by inhibiting the enzyme adenylyl cyclase necessary for the formation of intracellular cAMP[83-84]. Stress reduction by environmental enrichment also increased the sensitivity of pancreatic cancer xenografts in mice to chemotherapy with gemcitabine and 5-fluorouracil[82]. In accord with these preclinical investigations, chronic psychological stress is associated with higher cancer risk and poorer cancer survival in people[85] and severe psychological stress due to loss of a parent during childhood or later in life significantly increases the risk of pancreatic cancer[86] whereas incidental beta-blocker therapy that is widely used for the management of cardio-vascular disease, has improved survival and response to cancer therapy in patients with prostate cancer[87], breast cancer[88], colon cancer[89], NSCLC[90] and ovarian cancer[91]. In addition, preclinical data in human urothelial bladder cancer cell lines have shown that Epi, Nor and nicotine significantly stimulated cell proliferation, a response suppressed below base levels by propranolol[92]. Propranolol also strongly suppressed the growth of unstimulated urothelial cancer cells , indicating that similar to other epithelial cancers, urothelial cancer cells stimulate their own growth via the autocrine synthesis and release of Nor and Epi. A population-based cohort study additionally showed that chronic therapy with propranolol significantly reduced the risk for the development of cancer of the head and neck, stomach, colon and prostate[93] and propranolol is now successfully used as adjuvant to classic chemotherapy of metastatic breast cancer[94]. In addition, the tumor suppressor function of the Gi-coupled GABA-B receptor discovered in preclinical models of NSCLC and pancreatic cancer [63, 67] has been supported by clinical investigations that showed significantly improved clinical outcomes in NSCLC patients whose cancer over-expressed the GABA-B receptor[69].

Regulation of Cancer Stem Cells by Neurotransmitter Receptors.

Cancer stem cells (CSCs) have been identified as a small population of cells with stem cell characteristics inside the tumor tissue. They express a variety of stem cell markers and have the ability for self-renewal that increases the stem cell population while additionally being able to differentiate into more differentiated cancer cells[95]. CSCs are widely believed to drive the growth, progression, metastasis and resistance to therapy of cancer[95]. Interestingly, it has been shown that human pancreatic cancer stem cells isolated by cell sorting or selective culture conditions expressed nAChRs with subunits alpha3, 4, 5 and 7 and that they synthesized and released Epi, Nor and GABA into the culture medium[96]. Chronic exposure to nicotine induced stem cell self-renewal via the activation of the stem cell-specific sonic hedgehog (SHH) pathway by increasing the release of both stress neurotransmitters while reducing the levels of GABA[96]. Treatment of the cells with GABA completely reversed these effects[96]. Cancer stem cells isolated from human non-small cell lung cancer cell lines of adenocarcinoma histology responded with increased self-renewal to epinephrine, an effect accompanied by increases in intracellular cAMP and induction of the stem cell marker SHH, its downstream effector, the GLi1 protein, and the stem cell marker aldehyde dehydrogenase-1 (ALDH-1)[5]. These stem cell stimulating effects of Epi were inhibited by treatment with GABA or the opioid peptide dynorphin B via their respective Gi-coupled receptors, which inhibited the formation of intracellular cAMP[5].

Collectively, these *in vitro* findings suggest an important regulatory function of stress neurotransmitters for cancer stem cells and inhibitory actions of GABA and opioid peptides on these cells. In support of this interpretation, stress reduction by environmental enrichment significantly reduced the growth of NSCLC xenografts of adenocarcinoma histology in mice, an effect accompanied by a decrease in the serum levels of corticosterone, Epi

and Nor, increase in serum levels of GABA and the opioid peptides met-enkephalin, dynorphin A and dynorphin B and significant reductions in the tumor levels of stem cell markers SHH and ALDH-1 as well as multiple signaling proteins associated with cell proliferation whereas apoptosis-inducing signaling proteins p53 and cleaved caspase-3 were increased[5].

The self-renewal of cancer stem cells in the MCF7 breast cancer cell line was significantly induced by single dose treatments with nicotine, an effect accompanied by increased levels of the cancer stem cell markers ALDH-1, and Notch and inhibited by the selective α7nAChR antagonist α-bungarotoxin[97]. Using the same cell line, another laboratory reported nicotine-induced resistance to doxorubicin chemotherapy in cancer stem cells[98]. It has been shown that several estrogen-responsive (including MCF7) and non estrogen responsive breast cancer cell lines stimulated their own proliferation via the synthesis and release of arachidonic acid *in vitro* and that this effect was inhibited by the cyclooxygenase inhibitor aspirin and the β-blocker propranolol[99]. Collectively, these findings indicate that in analogy to findings in lung and pancreatic adenocarcinoma cell lines and their stem cells, breast cancers (which are also adenocarcinomas) and their stem cells regulate their proliferation via the autocrine nAChR-mediated release of Epi/Nor, which then activate the AA cascade downstream of β-ARs.

Beta-adrenergic receptors also have a key regulatory role in infantile hemangioma, a vascular tumor that originates from hemangioma stem cells (HemSCs). Propranolol has thus been shown to inhibit the proliferation and viability while increasing apoptosis of HemSCs *in vitro* by inhibiting cAMP formation[100]. Moreover, propranolol decreased the volume of blood vessels and blood circulation in a mouse model of hemangioma[100]. Another laboratory has reported that propranolol inhibited angiogenesis in HemSCs by down regulating VEGF[101], indicating that HemSCs stimulate their own proliferation via an autocrine mechanism that involves the synthesis and release of Epi and/or Nor which then activated VEGF production via beta-adrenergic receptor signaling. In accord with these preclinical findings, propranolol has become the leading and highly successful therapeutic for human infantile hemangioma[102].

Conclusions and Future Directions

Despite of intense cancer research, the mechanisms of development, progression and resistance to therapy of cancer remain poorly understood. The main emphasis of past and present preclinical and clinical cancer research has focused on studying cancer cells: which genes are altered (mutated, overexpressed, under expressed, hyperactive, hypoactive) in cancer cells? Which signal transduction pathways and proteins associated with cell proliferation, migration and apoptosis are altered (mutated, overexpressed, under expressed, hyperactive, hypoactive) in cancer cells? These investigations are highly valuable and have identified a multitude of potential cancer therapeutic targets inside the cancer cells that are currently utilized for personalized cancer therapy. However, cancer mortality still remains high and further improvements are needed. As is summarized in this review, the numerous abnormalities expressed in cancer cells represent the adaptive responses of these cells to disturbances at the level of their upstream regulators. Contrary to the widely held belief that cancer is a disease caused by unregulated growth, it is instead a highly coordinated process characterized by the simultaneous stimulation of cell proliferation, migration, angiogenesis and neuro-neogenesis and inhibition of apoptosis. The principal tools in the mammalian organism capable of regulating such highly coordinated processes are the neurotransmitters and their receptors, which regulate the embryonic development of the mammalian organism and its ability to adapt and respond to endogenous and external stimuli[2]. However, this elaborate fine-tuned regulatory network becomes distorted when the balance between excitatory and inhibitory neurotransmitters is disturbed and /or the expression and sensitivity of their receptors is modulated. As summarized in this review, there is growing evidence that neurotransmitters and their receptors and exogenous agents that interact with these receptors are the upstream regulators, which orchestrate all aspects of the complex processes that enable cancer cells to grow at the expense of healthy tissue and disseminate to distant organs in a coordinated fashion. Although nAChRs are in many cases at the top of this regulatory pyramid, efforts to prevent or treat cancer by inhibiting their function by pharmacological, molecular or immunological means are ill advised because these receptors regulate too many vital cell and organ functions and their therapeutic incapacitation would have severe side effects. However, the beta-adrenergic cAMP-signaling pathway that is indirectly activated by nAChRs in cancer cells represents a perfect target for this approach in cancers associated with increased blood levels of Epi/Nor and/or cAMP. The non-selective beta-blocker propranolol is an established therapeutic for cardiovascular disease[103] and can be easily re-purposed for this approach. Propranolol should thus be the preferred therapeutic for cancer patients with incidental cardiovascular disease as this agent blocks all beta-adrenergic receptors, including β2ARs which are the predominant β-ARs in most cancer cells[57]. By contrast, the use of a selective β1-AR antagonist would be contra-indicated in such patients, because this would lead to the reactive upregulation of β2-ARs[58], thus stimulating the cancer cells. As propranolol would

Table 1. Agents and psychological factors that inhibit the development, progression and resistance to therapy of cAMP-driven cancers.

Agent	Mechanisms of Action	Source
Gamma-amino-butyric acid (GABA)	Inhibits cAMP formation via G_i-coupled GABA-B-Receptors	Endogenous: increased by stress reduction/happiness; Nutritional: Red Wine, tomatoes, blue and black berries, dietary supplement
Opioid peptides: Dynorphins, endor -phines, enkephalins Opioids: Opium, Morphin Hydrocodone Oxycodone Fentanyl Methadone	Inhibit cAMP formation via G_i-coupled opioid receptors (mu, kappa, delta)	Endogenous: increased by stress reduction/happiness Substance abuse, anesthesia, analgesia Cough Suppression Management of addiction
Cannabinoids	Inhibit cAMP formation via G_i-coupled cannabinoid receptors (CB1, CB2); CB2 receptor-Mediated β-endorphin release	Substance abuse, medical marihuana, synthetic cannabinoid receptor agonists
Valerian	Increases endogenous GABA synthesis by induction of GAD enzymes	Non prescription herbal root extract used as sleep aid and anxiolytic
GABA-B-R PAMS	Positive allosteric modulators of GABA-B-Receptors increase sensitivity of the receptor even in the presence of low GABA levels	Therapeutics for addiction
Stress Reduction/ Happiness	Increase endogenous GABA and opioid peptides while reducing epinephrine/norepinephrine	Methods to achieve this psychological state vary for each individual

suppress blood pressure and heart function below physiological levels in cancer patients without incidental cardiovascular disease, these individuals should be given GABA or allosteric modulators of the $GABA_B$-R instead. The use of selective $GABA_B$-R agonists such as baclofen which have a higher affinity to the receptor than GABA should be avoided because preclinical investigations have shown that chronic baclofen down-regulates this receptor, resulting in tumor promoting effects[59]. Over the counter nutritional GABA supplements are widely used for the management of anxiety, insomnia and muscle spasms[104] and over the counter valerian extract ,which stimulates the endogenous synthesis of GABA[105], is a widely used sleep aid and anxiolytic agent[106-107]. On the other hand, numerous members of the opioid family commonly used for anesthesia, analgesia and cough suppression (table 1) inhibit cAMP by activating Gi-coupled opioid receptors and would therefore be suitable for the adjuvant therapy of cAMP-driven cancers. In fact, the synthetic opioid methadone used for the management of drug addiction has recently been shown to have antineoplastic effects in numerous preclinical cancer models[108-110]. Cannabis (medical marihuana) and synthetic cannabinoids that are used for pain management also decrease intracellular cAMP via activation of Gi-coupled cannabinoid receptors[111] and have been shown to inhibit the growth of colon cancer , breast cancer, pancreatic cancer, prostate cancer and adenocarcinoma and large cell carcinoma of the lungs in preclinical studies[112-113]. Positive allosteric modulators of the GABA-B-R, currently being developed for the treatment of addiction[114], represent another class of pharmaceuticals that can be re-purposed for cancer intervention as they selectively enhance cancer inhibiting signaling via the Gi-protein coupled to this receptor even in the presence of subnormal GABA levels. All of these agents can be used by clinical oncologists as off-label adjuvants to enhance responsiveness to conventional cancer therapy in susceptible cancers and to prevent recurrences after surgical resection and successful chemotherapy. Agonists for additional Gi-coupled receptors such as the metabotropic glutamate receptors (mGluR2, 3, 4, 6, 7 and 8)[115] should also be explored as potential targets for adjuvant cancer therapy. Furthermore, strategies for stress reduction by psychological and/or pharmacological means need to be an essential component of cancer prevention and therapy. It is, however, important to consider, that the cancer intervention approach suggested in this review will only be successful if the attending physician ensures that the patient is not exposed to medications, lifestyle factors, foods and beverages that increase intracellular cAMP by a variety of mechanisms (table 2). It can only be hoped that the extensive preclinical literature on the cancer inhibiting effects of cAMP reduction in the most common human cancers and their stem cells will finally trigger the clinical application of this promising concept.

Table 2. Agents and psychological factors that increase intracellular cAMP) which is formed downstream of G_s-coupled receptors via activation of adenylyl cyclase.

Type of Agent	Mechanism of Action	Source
Epinephrine (Epi) Norepinephrine (Nor)	Increase cAMP via adrenergic G_s-coupled receptors	Asthma/allergy medications, endogenous adrenaline in response to stress, strenuous exercise
Caffeine, Theophylline Theobromine Phosphodiesterase inhibitors (e.g. rolipram, roflumilast	Increase cAMP via inhibition of phosphodiesterases	Coffee, Caffeinated drinks, weight loss products, Green tea, peppermint tea, asthma and COPD therapeutics, Cocoa, chocolate. Anti-inflammatories for the therapy of COPD
Nitrosamines	Cause cancer by causing point mutations in the K-ras gene that sensitize the gene	All smoked and processed meat products Tobacco products
Concentrated Alcohol (e.g whiskey, wodka, rum, gin)	Increases cAMP via increased activity of adenylyl cyclase that forms cAMP	Cocktails, alcohol shots
Psychological stress Nicotine, NNN, NNK	Increase the release of Epi/Nor that activate G_s-coupled receptors, Suppress GABA and endogenous opioid system which decrease cAMP via Gi-coupled receptors	Anxiety, depression, socio-economic stress, work stress. Hectic lifestyle Death of a close relative Tobacco products, nicotine replacement therapy
Estrogens Vitamin A Beta-carotene Retinoids Glucocorticoids	Increase cAMP via non-genomic signaling of G_s-coupled signaling via non-genomic signaling of Gs-coupled receptors	Therapeutics for menopause and some birth control pills; Beer contains high levels of plant estrogens Vitamin supplements, carrots And other yellow vegetables Anti-inflammatories Anti-allergenics

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