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Review Article

The Effects of β-Endorphin, the Autonomic Nervous System and the Environment on Suppressing the Growth and Progression of Malignant Tumors (Cancers)

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Abstract

Transplantations of β-endorphin neurons into the hypothalamus in rats suppress the growth and progression of cancers in various tissues and prevent the metastasis of tumors via the suppression of the sympathetic nervous system and the activation of the parasympathetic nervous system. A fragrant environment containing a low concentration of α-pinene induces a significant increase in the parasympathetic nervous activity in young adult females, and long-term exposure to that suppresses melanoma growth in mice. Long-term exposure to low concentrations of a homologous series of aliphatic alcohols, phenols, ketones, and their derivatives generally enhance the hypothalamic β-endorphin levels in rats. The enriched environment induces suppression of the sympathetic nervous system and/or activation of the parasympathetic nervous system through decreased leptin expression and secretion as well as releasing β-endorphin and show a suppression of tumor growth in mice.

Moderate-intensity physical activity results in tumor suppression, at least in part through the actions of hypothalamic β-endorphin, which is responsible for a physical effect known as a runner's high.

Keywords: Tumor; Cancer; Enriched Environment; Odor; Autonomic; β-endorphin; Physical Activity

Introduction

Sympathetic nerves innervating the tumor microenvironment have cancer-promoting effects on prostate cancer [1], breast cancer [2], and melanoma [3]. On the other hand, intratumoral parasympathetic/vagal nerves may have a dichotomous role in cancer progression [4,5] with cancer-promoting effects on prostate [6], gastric [7], and colorectal cancers [8] and cancer-suppressing effects on breast [2] and pancreatic cancers [9] (Table 1).

However, it is still puzzling how intratumoral parasympathetic/vagal nerves promote or suppress tumors [23].

In general, neurons express receptors for immune-derived cytokines and neurotransmitters that can affect neuronal function, and reciprocally, immune cells are equipped to respond to neuronal signals by expressing receptors for neuronal cell–derived molecules [24]. Rats with β-endorphin neuron transplants are able to stimulate parasympathetic neurons suppressing the growth and progression of prostate cancer [10], breast cancer [11,12], liver cancer [14], and colonic tumors [13] as well as the lung metastasis of mammary adenocarcinoma cells [25-27]. Olfactory stimulation with a low concentration of α-pinene induced a significant increase in parasympathetic nervous activity in young adult females [16],

Cancer/Tumour	Intratumoral Sympathetic Nerves	Intratumoral Parasympathetic/Vagal Nerves	Transplantation of β-Endorphin Neurons	Long-term Exposures to α-Pinene	Enriched Environment
Prostate	↑ [1]	↑ [6]	↓ [10]		
Breast	↑ [2]	↓ [2]	↓ [11,12]		↓ [17]
Melanoma	↑ [3]			↓ [15,16]	↓ [18.19]
Gastric		↑ [7]			
Colorectal		↑ [8]	↓ [13]		↓ [18]
Pancreatic		↓ [9]			↓ [20,21]
Liver			↓ [14]		
Lung					↓ [20]
Glioma					↓ [22]

Table 1: The effects of intratumoral sympathetic and parasympathetic nerves and various treatments, on the progression of various cancers. ↑：cancer-promoting effects. ↓：cancer-suppressing effects.

and long-term exposure to the same suppressed melanoma growth in mice [15,28]. Furthermore, an enriched environment as a model of eustress decreased the expression and secretion of leptin, released β-endorphin [29] to suppress the sympathetic nervous system and/or to activate the parasympathetic nervous system, and showed reduced tumor growth and increased remission in cancer models [18,30] (Table 1). This review describes the antitumor effects of the transplantation of β-endorphin neurons into the hypothalamus, long-term exposure to low concentration of odorants, an enriched environment, and physical activity.

Transplantation of β-endorphin neurons into the hypothalamus

The endogenous opioid peptide β-endorphin has a profound effect in the reduction in body stress, the maintenance of an active immune system, and production of analgesia and a feeling of wellbeing [25]. In the brain, β-endorphin-producing perikarya are primarily found in the hypothalamic arcuate nucleus [25,29]. β-Endorphin exhibits a notably high degree of degradation resistance in the brain and has the ability to elicit stable and long-lasting effects on distant targets [31,32]. Activation of the cyclic adenosine monophosphate system in rat hypothalamic neural stem cells differentiated these cells into primarily β-endorphin-producing neurons in culture [10]. When these *in vitro* differentiated neurons were transplanted into the hypothalamic paraventricular nucleus (PVN) of adult rats, they successfully integrated with the surrounding cells and produced β-endorphin [10,25] (Figure 1).

Figure 1: Hypothalamic β-endorphin neurons suppress the growth and progression of tumor cells through the activation of the parasympathetic nervous system (blue areas). On the other hand, chronic neurobehavioral stress can promote the growth and progression of various tumors through sustained activation of the sympathetic nervous system（orange area) (based on [11,25]). ↑: up-regulation, ↓: down-regulation.

Ach: acetyl choline, NE: norepinephrine, EMT: Epithelial-Mesenchymal Transition.

β-Endorphin inhibits the stress response of the hypothalamus-pituitary anterior lobe-adrenal cortex (HPA) axis through interaction with corticotrophin- releasing hormone (CRH) neurons in the paraventricular nucleus (PVN), activates the

parasympathetic nervous system (PNS) and acetylcholine (Ach) release, and suppresses the sympathetic nervous system (SNS) and norepinephrine (NE) release, which then leads to the activation of innate immune cells (including NK cells) of the lymphoid organ and an increase in cytotoxic immune cells and anti-inflammatory cytokines levels in the circulation [25,27]. In the tumor microenvironment, these immune cell and cytokine changes increase tumor cell apoptosis and decrease the inflammation-mediated epithelial-mesenchymal transition (EMT), thereby suppressing cancer growth and progression [25]. In addition, chronic neurobehavioral stress or distress can promote the growth and progression of various tumors secondary to the sustained activation of the sympathetic nervous system [11] (Figure 1). Intracranial administration of β-endorphin enhances immune activity, but its effect is transient [25]. There are considerable dangers in the use of exogenous opioids in human [31]. In order to apply β-endorphin to suppressing the growth and progression of human malignant tumors (cancers), it is necessary to develop a method for safely introducing β-endorphin into the human hypothalamus without side effects [27]. In the following sections, the antitumor effects of long-term exposure to low concentrations of certain types of odorants, an enriched environment, and physical activities are discussed as natural methods for the enhancement of β-endorphin levels in the human hypothalamus.

Exposure to odorants

α-Pinene suppresses tumor growth

Olfactory stimulation by α-pinene induced a significant increase in the parasympathetic nervous activity in young adult females [16]. On the other hand, exposure to the odor of a low concentration of α-pinene (0.035 ppm; 5 h/day) for 4 weeks prior to tumor implantation with murine melanoma cells and 3 weeks after transplantation reduced the tumor volume by about 40% compared to that in the control mice [15,28]. Long-term exposure to 0.035 ppm α-pinene in mice did not significantly increase the plasma noradrenaline concentrations, which reflect sympathetic nervous activity, and a decrease in BDNF protein levels and glucose-1-phosphate concentrations was detected along with suppressed leptin expression [15,28]. Furthermore, levels of stress hormones, such as plasma corticosterone and adrenaline, did not change [15]. Leptin is a peptide hormone produced by adipose tissue before being secreted into the blood and transported across the blood-brain barrier, where it binds to a specific receptor (LepRb), which is expressed in several brain nuclei, including the arcuate nucleus and the paraventricular nucleus, and it increases sympathetic nerve activity [33-36]. Therefore, prolonged inhalation of 0.035 ppm α-pinene may suppress the sympathetic nervous system and/or activate the parasympathetic nervous system in mice brains [16]. Additionally, the numbers of NK cells, B cells, CD4+T cells, and CD8+T cells increased in the 0.035 ppm α-pinene-exposed mice [15]. NK cells are also potent producers of cytokines and chemokines such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) and are thereby essential in modulating adaptive immune responses [37]. Cytotoxic CD8+ T cells of the adaptive immune system are preferred immune cells for targeting cancer [41,42]. α-Pinene had no inhibitory effect on melanoma cell proliferation *in vitro*, suggesting that the effect of long-term exposure to 0.035 ppm α-pinene on tumor growth did not have a direct effect [15,28].

Mammalian olfactory system

The detection of odorant signals from the environment and the generation of appropriate physiological effects in response to these signals rely on the mammalian olfactory system. When volatile odorants enter the vertebrate nasal cavity and dissolve in the nasal mucus, they bind to olfactory receptors (ORs) that are localized in the cilia of olfactory sensory neurons at the olfactory epithelium [43-50]. Olfactory receptor (OR) genes are classified into two broad families, class I and class II [51]. Olfactory sensory neurons send the odor signals via their axons to the olfactory bulb, which is a neural structure of the forebrain [49,51,52]. Because olfactory sensory neurons targeting the dorsal and ventral zones make synapses primarily with mitral cells in the dorsal and ventral mitral cell layers, respectively, odor information from the dorsal zone olfactory sensory neurons is processed largely by early generated mitral cells, while late-generated mitral cells process odor information from the ventral zone olfactory sensory neurons [53] (Figure 2).

The glomeruli in the dorsal olfactory bulb are involved in innate olfactory responses, whereas those in the ventral domain of the olfactory bulb are required for memory-based olfactory responses [43,46-49].

Figure 2: Schematic diagram of the proposed olfactory circuits for suppressing tumor growth by long-term exposure to low concentration of α-pinene in mice. (based on [15,16,49,52,54]).

The intensity of glomerular activity was classified and indicated by symbols as follows: modest,○; very strong,◎.

Class I ORs: class I olfactory receptors. class II ORs: class II olfactory receptors.

↑: upregulation, ↓: downregulation. L: lateral, M: medial, A: anterior, P: posterior.

Blue areas: an olfactory circuit presumed to be mediated by activation of the parasympathetic nervous system.

Orange areas: an olfactory circuit presumed to be mediated by activation of the sympathetic nervous system.

A homologous series of fatty acids and aliphatic aldehydes activate glomeruli clustered in the anteromedial domain of the dorsal olfactory bulb [52]. Moreover, a homologous series of aliphatic alcohols, phenols, ketones and their derivatives activate glomeruli clustered in the lateral domain of the dorsal olfactory bulb [52]. In general, long-term exposure to low concentration of odorants, such as alcohols, phenols, ketones, and their derivatives, increased rat hypothalamic β-endorphin levels relative to those in the control rats [55,56]. In addition, β-endorphin levels in the rat hypothalamus increased with longer periods of exposure to the odor of 2,6-dimethoxyphenol [56]. The information from odorants is conveyed from the olfactory bulb to the primary olfactory cortices including the anterior olfactory nucleus, piriform cortex, olfactory tubercle, cortical amygdala, and entorhinal cortex by mitral cells and tufted cells [57-62]. In mice, the odor of 2-phenylethanol, aliphatic alcohols, elicited attraction, whereas the odor of isopentylamine, aliphatic amines, elicited aversion [54]. The caudal third of the posterolateral cortical amygdala is activated by the innate attractive odors, such as 2-phenylethanol, whereas, the anterior cortical amygdala may only be activated by odors that elicit innate aversive behaviors [54]. Chirality as well as the functional groups of the odorant have a decisive influence on the physiological effects of the odorant [63]. The cortical amygdala plays a critical role in generating innate odor-driven behaviors, but this does not preclude its participation in learned olfactory behaviours [54]. α-Pinene very strongly activated glomeruli clustered in the lateral domain of the rat dorsal olfactory bulb (alcohol/phenol-responsive domain) (◎), which probably reflects parasympathetic nerve activity [16], and it elicited two modest responses in glomeruli clustered in the anteromedial domain of the rat dorsal olfactory bulb (fatty-acid-responsive domain) (○), which may reflect sympathetic nerve activity [52] (Figure 2).

Odorants enhance hypothalamic β-endorphin levels

Dried bonito broth (Katsuo-dashi), which is an important seasoning in Japanese cuisine and is used to reinforce the flavor of foods and lend a characteristic flavor to Japanese dishes, has umami and a unique aroma and stimulates the reward system of the brain [64,65]. Dried bonito (Katsuobushi) is simmered, smoked, and fermented skipjack tuna [66]. One of the predominant smoke components is 2,6-dimethoxyphenol (MW:154), which is a characteristic thermal degradation product from hardwood with antioxidant activity [67]. The mice that experienced the bonito bouillon-flavored diet from the birth-to-weaning period had a greater preference for bonito bouillon than those consuming the bonito bouillon-flavored diet after weaning or consuming a normal diet from birth [68]. These phenomena are consistent with an increase in rat hypothalamic β-endorphin levels with increasing exposure time to a typical bonito-flavored compound, 2,6-dimethoxyphenol [56,67]. The effects of long-term exposure to 17 individual odorants on hypothalamic β-endorphin production were investigated in rats housed in a cage with a wire bottom, from which air could enter and exit freely, with the walls and ceiling lid made of clear acrylic plastic [55]. Among 17 odorants, muscone (1; ketones), the highest molecular weight (MW:238), showed the highest enhancement effect of β-endorphin levels in the rat

hypothalamus, followed by santalol (2; α-santalol:β-santalol = 2:1; alcohols), 1,3,5-trimethoxy benzene (3; phenol derivatives), linalool (4; alcohols), nerolidol (5; alcohols), α-terpineol (6; alcohols), benzyl acetate (7; alcohol derivatives) and l-menthol (8; alcohols) [55] (Figure 3).

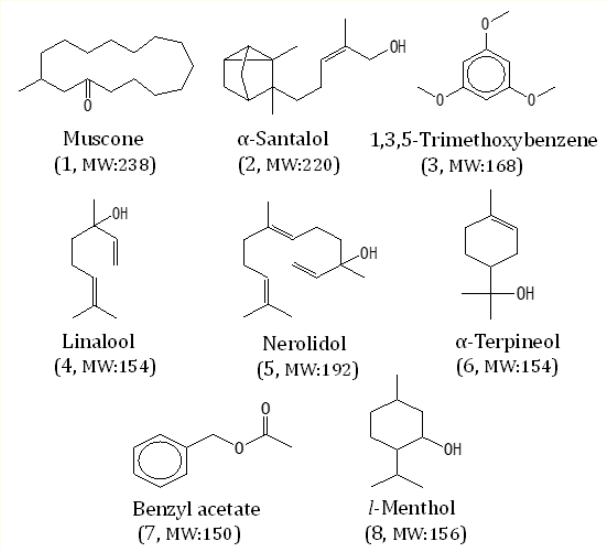

Figure 3: Odorants (1-8) that increase rat hypothalamic β-endorphin levels with long-term exposure.

In particular, long-term exposure to low concentrations of muscone (1) increased the hypothalamic β-endorphin levels in rats approximately twofold compared to those in the control group [55]. Moreover, there were no significant changes in the plasma corticosterone levels, which are the major stress hormones [55]. These results suggest that long-term exposure to these low concentrations of high molecular weight odorants causes an increase in hypothalamic β-endorphin levels without stress-induced stimulation of the hypothalamus pituitary anterior lobe-adrenal cortex (HPA) axis in rats [55,69]. Moreover, long-term exposure to 7-methyl-3,4-dihydro-2H-1,5-benzodioxepin-3-one (MW:178; calone; heterocyclic compound), vanillin (MW:152; aldehydes), citral (MW:152; aldehydes), methyl anthranilate (MW:151; amines), limonene (MW:136; monoterpene hydrocarbons), guiacol (MW:124; phenols), indole (MW:117; amines), cis-3-hexenol (MW:100; alcohols), and acetic acid (MW:60; fatty-acids) did not increase the hypothalamic β-endorphin levels in rats [55]. Long-term exposure to the highly volatile odorant compounds that have a molecular weight less than 150 did not increase the hypothalamic β-endorphin levels in rats, presumably because the highly volatile compounds volatilized under these experimental conditions [55]. Generally, long-term exposure to low concentrations of a homologous series of aliphatic alcohols, phenols, ketones and their derivatives activates glomeruli clustered in the lateral domain of the dorsal olfactory bulb (alcohol/phenol-responsive domain) [52], and subsequently activates the caudal third of the postero-lateral cortical amygdala [54], and then enhances the hypothalamic β-endorphin levels in rats [55] (Figure 3).

β-Endorphin levels in the rat hypothalamus might be further increased not only by the mixing of multiple effective odorants but also by using a fixative such as triethyl citrate (MW:276; bp=294°C) to prevent the volatilization of the odorants [70].

Enriched environment

Mice in an enriched environment showed reduced tumor growth and increased remission in breast cancer [17,71], melanoma cancer [18,19], colon cancer [18], pancreatic cancer [20,21], glioma cancer [22], and lung cancer [20] models. Stress most commonly refers to distress, which diminishes NK cell function and suppresses the expression of the cytokine genes involved in the recruitment and activation of NK cells [72]. In contrast, eustress is associated with milder and/or briefer challenges that elicit positive or healthy adaptive responses [72].

Stress is transmitted to the hypothalamus via the cerebral cortex, and activates the hypothalamus-sympathetic-adrenal medullary system (SAM) axis and hypothalamus-pituitary anterior lobe-adrenal cortex (HPA) axis [73-75]. An enriched environment as a model of eustress regulates adipose NK cells via a hypothalamic BDNF-sympathoneural-adipocyte IL-15 (Interleukin 15) (HSA) axis [76] and displays a tumor-resistant phenotype [20] (Figure 4).

Enriched environments enhanced the cytotoxicity of NK cells and the CD8+ cytotoxic T lymphocytes *in vitro* and increased mobilization of these cells from the spleen in melanoma model mice [30]. The blockade of β-adrenergic signaling abolished the effects of the enriched environment on the NK cells and attenuated the antitumor effect of the enriched environment [20]. Hypothalamic BDNF activates the sympathetic nervous system (SNS) innervating WAT to release norepinephrine into WAT and

Figure 4: The proposed antitumor mechanism of an enriched environment as a model of eustress (based on [18,20,29,30,72,76,77]).

Orange areas: Activation of the sympathetic nervous system. Blue areas: Suppression of the sympathetic nervous system and/or activation of parasympathetic nervous system. Arrowheads: inducing or projecting.

Blunted-bar heads: Inhibiting. ↑: up regulation/activation/increase. ↓: down regulation/inhibition/decrease.

decreases leptin expression and secretion, while increasing the adiponectin level [30]. Leptin secreted from adipocytes activates pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus to release β-endorphin and α-melanocyte-stimulating hormone (α-MSH) [29]. Leptin binds to its receptor on the tumor cell, promoting the activation of different signaling pathways that, in turn, lead to the proliferation and invasion of tumor cells [78]. In contrast, the marked drop in circulating leptin is causally associated with an anticancer phenotype [30] (Figure 4).

Physical activity

Daily exercise of less than 60 min/day, which caused eustress, had a significantly higher impact on tumor reduction after exercise training in mice, compared to that of more than 60 min/day or voluntary wheel running, which caused distress [79,80]. The effects of exercise on the tumor reduction and hypothalamus β-endorphins in rodents are briefly summarized in table 2.

Physical Activity	Intensity	Stress Level	Tumor Growth	Hypothalamic β-Endorphin	Ref.
Voluntary wheel running	~ 2 km/day	Distress	±		[72]
Dailly exercise of >60 min/day		Distress	±		[79]
Dailly exercise of <60 min/day		Eustress	↓		[79]
Involuntary wheel running of 20 m/min for 1h/day (28 days)	1.2 km/day	Eustress		↑	[81]

Table 2: Effects of exercises on tumor growth and hypothalamus β-endorphin in rodents.

↑: Increase, ↓: Reduction, ±: No change.

For most people, moderate-intensity exercise, 30 min/day, 5 days/week, can adapt the autonomic nervous system to parasympathetic dominance, translating to a lower heart rate at rest [82]. Exercise, reducing the risk and progression of cancers, affects the cytokine profile and changes the distribution and function of tumor-competitive immune cells, through epigenetic modifications [83]. Exercise was shown to increase global DNA methylation, downregulate the expression of Dnmt genes in prostate cancer cells, decrease DNA methyltransferases mRNA expression in the tumor tissue, and leave unchanged the global level of histone H3 lysine acetylation [84,85]. Moderate-intensity physical activity in

rodents may trigger shifts in the tumor infiltration of macrophages, neutrophils, natural killer cells, and cytotoxic and regulatory T lymphocytes, resulting in tumor suppression [79].

Swim training retarded the development of Ehrlich tumors in mice through a reduction in macrophage infiltration and neutrophil accumulation [86]. Swimming significantly attenuated tumor growth in CT-26 tumor-bearing mice through inhibiting tumor angiogenesis and downregulating the expression of hypoxia inducible factor-1α (HIF-1α), vascular endothelial growth factor A (VEGFA), and its receptor VEGFR2 [87]. Hypothalamic β-endorphin is responsible for a physical effect known as a runner's high [81-89]. The amount of β-endorphin in the hypothalamus obtained from rats in the involuntarily exercised group, who exercised every day for one hour at the speed of 20 m/min (1.2 km per day) for 28 days was much higher than those in the non-exercising and control groups [81]. Moreover, there were no significant changes in the plasma corticosterone levels, which are involved in stress responses [81]. These results suggest that moderate-intensity physical activity in rats at least partially might result in tumor suppression through an increase in the hypothalamic β-endorphin levels without stress-induced stimulation of the hypothalamus–pituitary anterior lobe–adrenal cortex (HPA) axis (Table 2).

Conclusions

Transplantation of β-endorphin neurons into the hypothalamus, long-term exposure to low concentrations of α-pinene, an enriched environment, and moderate-intensity physical activity in rodents suppress the sympathetic nervous system and/or activate the parasympathetic nervous system, and through production of β-endorphin, they reduce the growth and progression of malignant tumors (cancers). The mammalian autonomic nervous system and hypothalamic β-endorphin levels could be identified as targets for cancer prevention and therapy and might aid in the development of future mechanistic studies. Therefore, cancers are potentially preventable through the daily decisions we make regarding the environment and physical exercise. As an example, under a doctor's guidance, using cosmetics, air fresheners, and masks containing odorants that increase hypothalamic β-endorphin levels and inhaling their odors for a period of time could prevent and/or treat cancers easily and inexpensively.

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Informed Consent Statement

The author read and approved the final manuscript.

Data Availability Statement

Not applicable.

Conflicts of Interest

The author declares that they have no conflicts of interest.

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