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RESEARCH ARTICLE

Bidirectional Relationship Between the Central Nervous System and Peripheral Tumours

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ABSTRACT

The brain and its central nervous system circuitry communicate with all peripheral tissues through neuroendocrine, neuroimmune and neurovascular systems as well as peripheral neuronal networks. This applies to the abnormal situation of a tumour as much as normal biological function. The central nervous system can affect tumour development and metastases though activation or dysregulation of specific brain centres. It has also become apparent that the tumour is capable of building up local autonomic and sensory nerve networks and along with adipokines, cytokines, neurotrophic factors and afferent nerve inputs which can signal back to the brain to promote cancer initiation, growth and dissemination. An attempt is made to unravel this complex of relationships with an understanding that there is a common language spoken between the elements but also with an appreciation that these mechanisms are still only partially understood.

Introduction

It has been recognised for some time that psychological stress or psychiatric illness can impact tumour incidence and development, as well as influencing the course of inflammatory disease[1]. This had been demonstrated in rodent cancer models last century. Tumours in these rodents were associate with poor survival with exposure to repeated intense stressors before tumour onset[2,3]. The underlying mechanism was unclear but the hypothalamic-pituitary-adrenal axis (HPA) was thought to be involved because of its control over stress, metabolism and immunity through the release of endocrine hormones. This theory has now been confirmed with glucocorticoids having been shown to control the dissemination of breast cancer cells in orthotropic xenograft models[4]. Activation of neuroendocrine neurons from the paraventricular nucleus (PVN) of the hypothalamus regulates the circadian and stress-induced release of glucocorticoids by the adrenal cortex [5,6] Fig 1,2. This hormone release was also shown to induce activation of glucocorticoid receptors on tumour cells in distal metastases, along with thymic involution reducing the number of T cells, accelerating tumour growth and dissemination[7,8]. So, it became apparent that the influence of psychological stress in cancer implied participation of the brain in tumorigenesis.

The role of the nervous system in these processes is not, however, confined to the central nervous system, there was found to be complementary involvement of nerve fibres and nerve cells in the tumour microenvironment (TME). The expression of nerve growth factors in tumours suggests that neural signalling can affect a cancer[9]. Cancer cells can surround and infiltrate nerves, perineural infiltration, which is associated with tumour aggressiveness and neuropathic pain[10,11]. It has also been more recently shown, in mouse models of cancer, that nerve fibres can sprout into tumours, axonogenesis. This has now been demonstrated in a range of tumour types; prostate, skin, gastric, pancreatic and breast cancer. In all these studies, tumour tissue was infiltrated by autonomic and sensory nerve fibres that release neurotransmitters that bind to receptors expressed on cancer and stromal cells[12,13]. There now appears to be a convergence central and peripheral nervous systems with bidirectional cross-talk between brain and tumour that can affect development and progression of cancer.

Hypothalamic-pituitary-adrenal axis

It has already been described how the HPA axis acts as a major neuroendocrine pathway able to transmit psychological stress from the brain to the periphery by producing blood-born glucocorticoids that reduce immunological control of cancer cells. This system begins in the paraventricular nucleus (PVN) of the hypothalamus, an important autonomic control centre in the brain responsible for control of stress, metabolism and immunity. Activation of neuroendocrine neurons of the PVN regulates circadian release of glucocorticoids by the adrenal cortex but also modulates glucocorticoid production and release under stress conditions. High levels of circulating glucocorticoids can activate glucocorticoid receptors on tumour cells of distant metastases accelerating tumour growth and dissemination[7,8]. Elevated levels of glucocorticoids found in the blood of breast cancer patients was found to disturb circadian rhythms of the adrenal output with tumour development, indicating that the HPA axis can be altered by metastasis. This was also demonstrated in breast cancer patient-derived xenograft models, suggesting bidirectional signalling. Not just brain to tumour but also tumour to brain[8].

Sympatho-adrenal system

Stress conditions, as well as activating the HPA axis, can also increase production and release of catecholamines, adrenaline and noradrenaline, from the adrenal medulla[14]. The medulla has been shown to be controlled by the adrenergic splanchnic division of the sympatho-adrenal system (SAS) that originates in the central nervous system (CNS). Interaction of both neuroendocrine pathways can amplify their effects, either by regulating each other or by being modulated by adrenergic signalling pathways in the CNS[15,16]. The PVN regulated HPA axis can be activated by catecholamines released from noradrenergic neurons of the nucleus of the solitary tract or the locus coeruleus-noradrenergic system in the brainstem[17]. Involvement of the SAS was first shown in cancer in an orthotropic ovarian cancer xenograft model where mice were subjected to stressors. Inhibition of the β-adrenergic pathway blocked tumour growth despite the HPA axis still being active[18]. Total resection of the adrenals, discontinuing HPA and SAS influence, does not prevent stress-induced development of syngeneic mouse adenocarcinomas, indicating other mechanisms of brain participation in the regulation of cancer[19]. The PVN has a central role, highly innervated by a neuronal population influenced by projections from diverse brain areas, including; Suprachiasmatic nucleus (SCN), nucleus of the solitary tract, lateral hypothalamus (LH), amygdala, hippocampus and prefrontal cortex (PFC). All of which have been shown to have a role in regulating

cancer[17]. Figure 1.

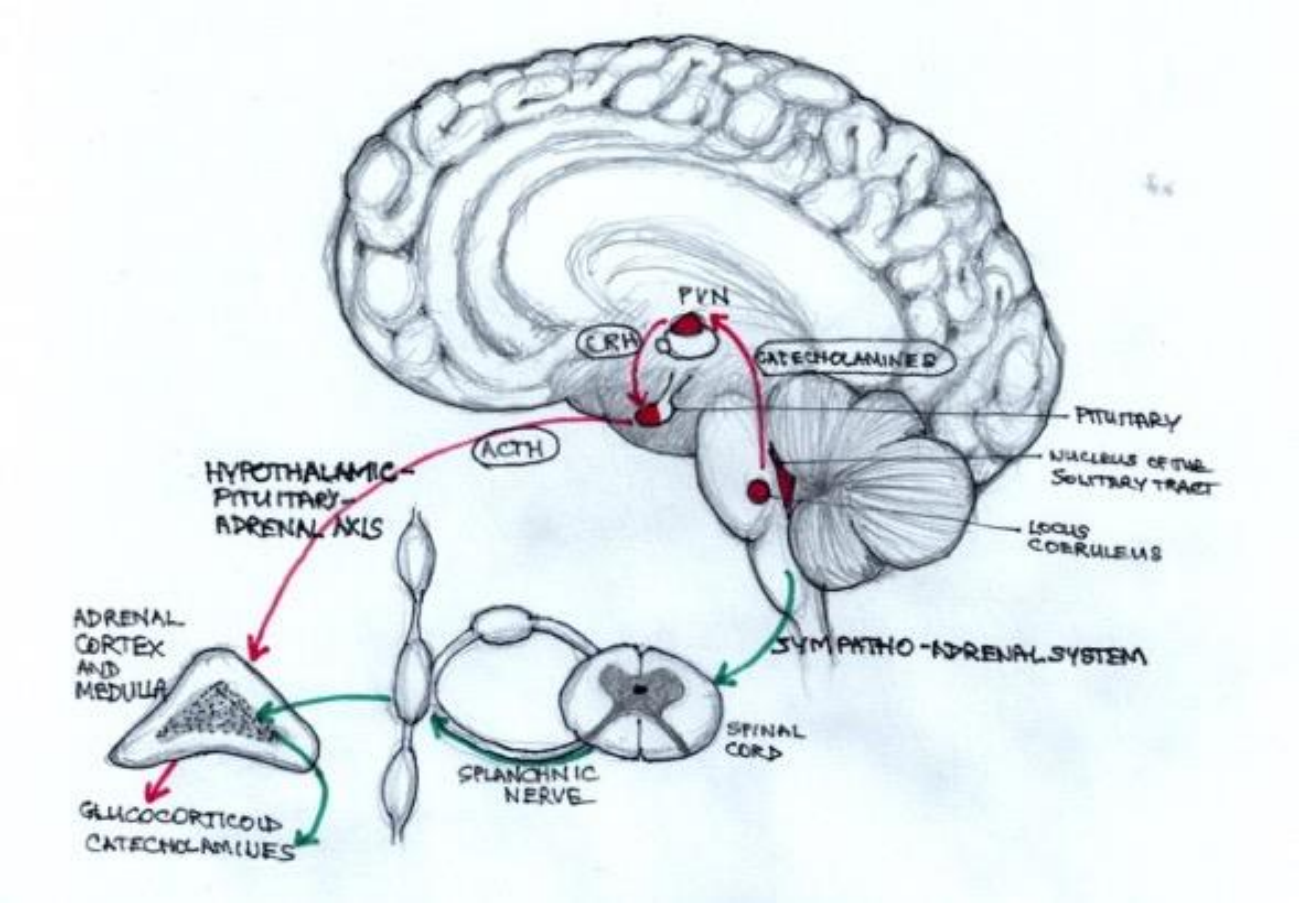

Figure 1. Central neuroendocrine pathways controlling tumour progression

Hypothalamic-pituitary-adrenal (HPA) axis red

The HPA axis can be stimulated by catecholamines secreted by noradrenergic neurons arising from the nucleus of the solitary tract and the locus coeruleus in the brainstem. Activation results in corticotropin-releasing hormone (CRH), secreted by neurons in the PVN of the hypothalamus, that travel to the anterior pituitary inducing release of adrenocorticotropic hormone (ACTH). This, in turn, stimulates production of glucocorticoids by the adrenal cortex and release into the circulation. Glucocorticoids promote tumour and metastatic growth upon binding to glucocorticoid receptors on tumour cells. There is also a reduction in immunological control through involution of the thymus and subsequent reduction in lymphocytes. Glucocorticoids can also reduce support of the HPA axis by deactivating glucocorticoid receptor-expressing neurons in the PVN.

Sympatho-adrenal system (SAS) green

Activating signals from the CNS, through interneurons, stimulate the splanchnic nerve of the autonomic nervous system that innovate the adrenal medulla promoting production of catecholamines and release into the vascular system. At the tumour, these neurotransmitters bind to β-adrenergic receptor expressing cancer and stromal cells promoting cancer cell proliferation and dissemination.

Brain areas and their neural connections influencing tumour development

THE SUPRACHIASMATIC NUCLEUS OF THE ANTERIOR HYPOTHALAMUS

The suprachiasmatic nucleus (SCN) generates the central circadian rhythm and controls individual rhythms in peripheral tissues modifying their physiological responses, including the autonomic nervous system, endocrine systems and sleep-wake cycles[20,21]. Cancer patients are more prone to disruptions of their circadian rhythms and associated behaviours, such as anxiety, depression and fatigue, either as a direct consequence of stress related to disease or alterations in circadian rhythm control[22]. Conversely, disturbance of circadian rhythms can promote disease, including cancer[23-25]. For example, light-at-night can increase the incidence of breast tumours through dysregulation of the circadian expression of genes regulating

immunity and metabolism. Shift work has been associated with an increased incidence of prostate, colon and lung cancer[23,26-28], as well as metabolic diseases. The SCN contains a diverse population of neurons and neurotransmitters that participate in peripheral control. Photic information is received by the retina and is transmitted to the SCN through excitatory glutamatergic fibres of the retinohypothalamic tract triggering cAMP signalling controlling clock genes of the SCN. The SCN modifies activity of the PVN of the hypothalamus and a range of other target organs through neural and humoral signalling[29,30]. Serotonergic projections from mid brain raphe nuclei modifies the SCN inducing phase shifts in response to light. Neurotransmitter GABA modulates activity of the SCN by inhibiting autonomic neurons in the PVN in a day-night fashion, regulating cyclic secretion of melatonin by the pineal gland to control the sleep-wake pattern. Melatonin is known to be influential in stimulating immune responses[31] and reduced secretion promotes cancer development through its effects on innate and adaptive immunity[32-34]. Interaction between the SCN and autonomic nervous systems shows how the clock mechanism impacts cancer development beyond the HPA axis and the SAS. This has led the International Agency for Research on Cancer to classify night-shift work as a probable carcinogen[35].

Lateral hypothalamus

The LH has some control over the autonomic nervous system, regulation of feeding behaviour and wakeful cycles, and as such is part of a reward system. A site for integration of autonomic and endocrine responses, a motivation-cognition interface with relays to major hypothalamic nuclei and regulation of pituitary function.

It contains a small number of a discrete neuronal type, the orexinergic neuron, responsible for a neuropeptide, orexin (hypocretin) which directly connects to the sympathetic nervous system, and along with the SCN and PVN stimulates the HPA axis in response to psychological stress[36]. Hypothalamic orexinergic neurons are an infrequent neuronal subtype but influential in aspects of physiological control of nociception and wakefulness through projection to specific brain areas. The most common site of receptors is the Locus Coeruleus (LC) but the paragigantocellularis, ventral tegmental area, dorsal raphe nucleus and periaqueductal grey matter are also involved. These areas are responsible for co-regulation of nociception and arousal. These findings indicate that orexin excitatory tone to the LC is required for a combination of nociception and wakefulness with activity, and may be of evolutionary significance by providing higher levels of alertness and less pain perception with flight or fight situations[37].

This direct connection to the autonomic sympathetic nervous system and control of wakefulness/sleep has been shown to maintain bone marrow homeostasis, while sleep disturbances decease orexin release, enhancing monocyte numbers[38]. These monocytes are capable of reaching, and possibly regulating the tumour immune microenvironment, which may explain increased cancer incidence and mortality in patients with altered sleep patterns[39]. In response to sleep disturbance, tumour growth was increased in a syngeneic lung cancer mouse model which was mediated by recruitment of tumour-associated macrophages[40]. Further, a syngeneic breast cancer mouse model has shown abnormal orexinergic neurons in the LH altering sleep and glucose metabolism though activity of neural sympathetic circuits[41] Fig 3.

Ventral tegmental area

The midbrain ventral tegmental area (VTA) which plays a role in reward, motivation and aversion is richly innervated with dopaminergic neurons. There is interaction between dopaminergic, glutamate and GABA neurons in the VTA to modulate reward-related behaviours. This interactive brain information processing is frequently altered in schizophrenia, leading to behavioural and cognitive dysfunction[42]. Schizophrenia has a higher cancer mortality rate that has been attributed to reduced screening, care and comorbidities but neuroleptic medications, designed to block dopamine receptors could be partly responsible for this promotion of tumour growth[43]. On the other hand, activation of VTA dopaminergic neurons prevented the growth of mouse melanoma through downregulation of sympathetic adrenergic innervation of myeloid-derived suppressor cells in the marrow, decreasing immunosuppression, but also emphasising the complexity and interrelations of neurons signalling pathways in cancer[44].

The subventricular zone

It has been recognised that autonomic fibres in the tumour microenvironment can regulate tumour dissemination. Recently it has become apparent that neural progenitors from the CNS, that express doublecortin (DCX^+), infiltrate prostate tumours and metastases in which they initiate neurogenesis. In a mouse prostate cancer model, oscillations of DCX^+ neural progenitors within the subventricular zone (SVZ) are associated with disruption of the blood-brain barrier with DCX^+ cells released into the circulation. These cells then infiltrate the tumour,

generating new adrenergic neurons. In humans, the density of DCX^+ neural progenitors are associated with aggressiveness and recurrence of prostate adenocarcinoma and reveal a unique crosstalk between the CNS and prostate tumours[45].

Amygdala, hippocampus and prefrontal cortex

The amygdala, hippocampus and prefrontal cortex (PFC) are involved in modulating cognitive processes, emotions and behaviour and are disrupted in cognitive decline and psychiatric disorders[37]. The amygdala is a core centre for processing fearful or threatening stimuli, detection of threats and actuation of appropriate fear related behaviours in response to threatening or dangerous stimuli. The hippocampus is a medial temporal lobe structure found in all mammalian species. It plays a role in spatial navigation, learning and memory. It provides a representation of the relationship between objects and events in space and time[46]. The PFC is prominent in primates and is critical for higher-order cognitive processing and emotional regulation. It is organised into sub-regions. Dorsolateral - involved in cognitive function such as; executive control, attention and working memory. Ventromedial-involved in emotional and motivational regulation.

The CNS is the seat of adaptation to psychological stress though activation of neuroendocrine axes but brain architecture can be remodelled as a consequence of life stressors, hence, the amygdala, hippocampus and MPC can undergo alteration of neural structures and dendritic interconnections through chronic stress. Neurotransmission by glutamate has been found to regulate progression of gliomas and breast-to-brain metastases[47,48] and it has been suggested that these alterations in glutamate neurotransmission is the mechanism of the stress-induced changes in these brain structures. The abundance of glutamatergic neurons in these brain structures implicates their role in brain-cancer cross talk. Figure 2.

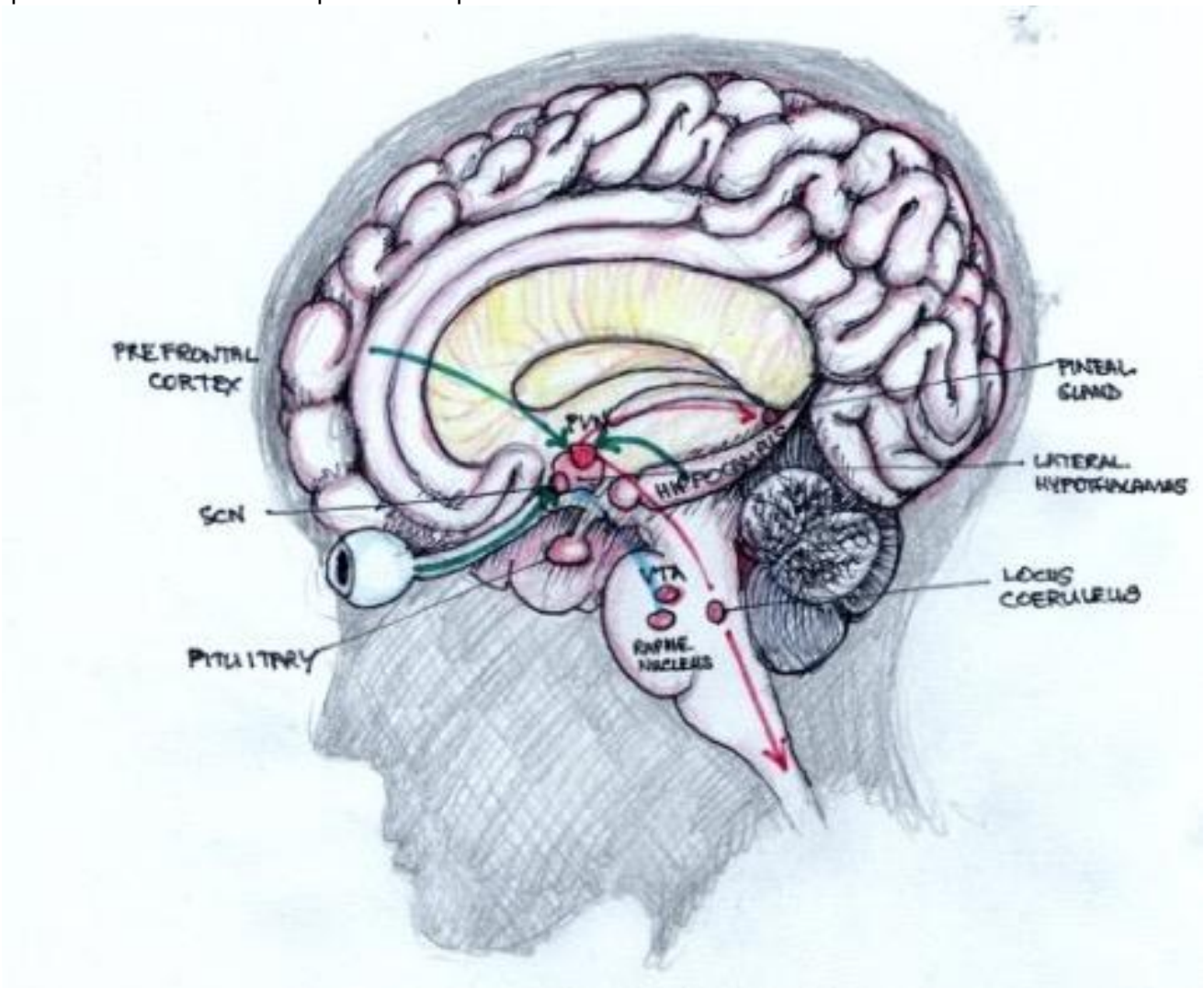

Figure 2. Brain areas and their neural projections participating in tumour development and progression

The brain can promote tumour development and progression mainly orchestrated by elements of the hypothalamus; paraventricular nucleus (PVN), suprachiasmatic nucleus (SCN), and lateral hypothalamus (LH). Glutaminergic projections (green) from the hippocampus and prefrontal cortex (PFC) act on the PVN to regulate the hypothalamic-pituitary-adrenal (HPA) axis. Photic information from the retina is transmitted in the retinohypothalamic tract as part of the optic nerve which leaves at the chiasma to enter the suprachiasmatic nucleus (SCN). This is the central control of circadian rhythm, influencing circadian patterns of physiological response in individual cells and tissues throughout the body. Dysregulation can be carcinogenic. GABAergic projections then pass from the SCN to the PVN. Serotonergic projections (blue) also pass from the midbrain Raphe nucleus to fine tune PVN function. Adrenergic projections (red) pass from the PVN to the pineal gland to regulate melatonin secretion. Melatonin limits tumour growth through effects on innate and adaptive immunity, and inhibiting proliferation and increased apoptosis of cancer cells. Orexinergic projections from the LH connect to autonomic neurons, through orexin secretion. Deceased secretion enhances the number of circulation monocytes and their infiltration into the tumour microenvironment (TME). Rich innervation of the midbrain ventral tegmental area (VTA) with dopamine, glutamine, and GABAergic neurons also affects peripheral tumour development.

The tumour and the tumour microenvironment

The role of the CNS in tumour development has become clearer, however, the impact of the tumour on brain functioning has been overlooked until recently. Cognitive disorders such as anxiety and depression are frequently reported in cancer patients and this was thought to be due to the negative psychological impact of the cancer or its treatment and rarely attributed to a direct effect of the tumour on the brain. However, evidence is emerging that tumours might directly regulate brain activity by releasing adipokines, neurotrophic factors or pro-inflammatory cytokines, or through sensory neurons that signal back to the CNS.

Leptin, adiponectin and ghrelin, adipokines, produced by adipocytes regulate appetite by binding to specific receptors mainly in the hypothalamus[49] but these receptors are also expressed on cancer and stromal cells[50]. Leptin decreases appetite and weight while increasing energy expenditure. This increases levels of adiponectin that regulates glucose and lipid metabolism and ultimately insulin sensitivity. Obese individuals with higher levels of leptin develop leptin resistance leading to lower levels of adiponectin and are more prone to cancer[51]. Tumour-associated adipocytes release adipokines that activate cancer cell proliferation, dissemination and are associated with tumour aggression. In breast cancer, the increased expression of leptin and leptin receptors has been identified as a marker of tumour progression[50,52]. Leptin receptors are expressed in the hypothalamus, hippocampus, PFC and leptin receptor-expressing neurons can affect VTA dopaminergic and LH orexinergic neurons that have some control over tumour growth and progression through modification of tumour angiogenesis or immune cell trafficking from the marrow, respectively[36,44,49].

On the other hand, hypothalamic brain-derived nerve factor (BDNF) expressing neurons downregulate adipocyte-derived leptin, while increasing adiponectin through activation of β-adrenergic innervation of adipose tissues, causing inhibition of proliferation and growth in melanoma and colon cancer models[53]. This hormone/hypothalamic BDNF-expressing neuronal crosstalk is another example of bidirectional connection between peripheral issues and brain areas[54].

Peripheral nervous system innervation of the TME with ultimate connection to the CNS and brain provides a communication channel for the tumour to impact brain activity. Sensory innervation of the TME stimulates tumour initiation and progression[55-57]. For example, formation and progression of basal cell carcinomas are dependent on sensory innervation[55]. Apart for efferent signalling stimulating tumorigenesis, afferent sensory nerve signalling to the CNS is illustrated by cancer-associate pain[58]. In another example, peptidergic PVN innervation from viscero-sensory relays can support activation of HPA axis in response to visceral disease[17], and in brain tumours, olfactory sensory stimulation can participate in glioma genesis through activity of olfactory receptor neurons[59].

In the case of melanoma, nociceptive neurons interact with tumour cells increasing neurite outgrowth, response to noxious ligands and neuropeptide release. One such neuropeptide, calcitonin gene-related protein (CGRP) was found to increase exhaustion of cytotoxic $CD8^{+}$T cells, which limits their capacity to eliminate melanoma. Peripheral nervous system innovation affecting immunosurveilance[60]. Figure 3.

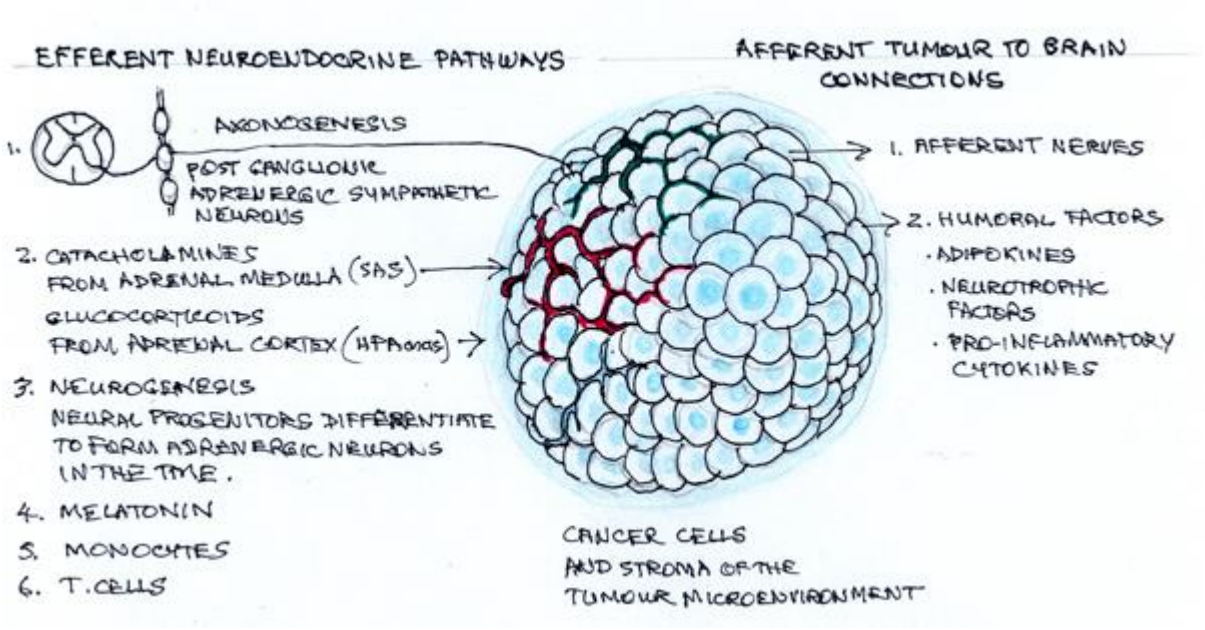

Figure 3. The tumour microenvironment

Efferent brain to tumour neuroendocrine pathways.

1. Axonogenesis. Tumour-generated autonomic network develops through outgrow of pre-existing adrenergic and cholinergic nerve fibres to regulate tumour and stromal cells of the TME
2. Through the vascular system catecholamines and glucocorticoids reach the TME. Neurotransmitters bind to β-adrenergic receptors expressed on tumour and stromal cells promoting proliferation and dissemination.
3. Neurogenesis. Neural progenitors differentiate to form adrenergic neurons in the TME
4. Adrenergic PVN neurons regulate melatonin secretion from the pineal gland. Melatonin limits tumour growth through effects on innate and adaptive immunity and by inhibiting proliferation and increasing apoptosis of tumour cells.
5. Monocytes can infiltrate the TME. A decrease of orexin levels in response to sleep disturbance enhances the number of circulating monocytes and their infiltration into the TME.
6. Effects on immunity alters T cell numbers and function

Afferent tumour to brain connections

1. Sensory innovation of the TME sustains tumour progression. It can relay information to the brain with the parabrachial nucleus acting as a relay transmitting information to the hypothalamus and amygdala, mediating cancer-induced pain, anorexia and cognitive and behavioural disturbances.
2. Adipokines from adipocytes, neurotrophic factors and pro-inflammatory cytokines enter the circulation to reach the brain.

Conclusion

A central processing unit is an obvious requirement of the human organism. Receiving information from the peripheral organs and external environment and sending out commands. There is, however, also a peripheral nervous system, arising from the neural crest and its units migrating to the periphery in embryonic life. It has been given an important sentinel role with some autonomy to allow for rapid adaption to changing nutritional requirements of tissues and organs and in response to the changing external environment. There needs to be strong links of communication between the two systems. This applies to normal physiology and in daily routine patterns of behaviour and response it is able to follow a regular circadian pattern. The tumour is an abnormal addition to the peripheral tissues and it is able to take advantage of the adaptability of the peripheral systems by plugging into this complex of sensors, effectors and signalling pathways utilising this adaptive system for its own ends, proliferation and dissemination.

There needs to be an appreciation of the macro-neuro-environment as well as the TME and its intra-tumoral network that sustain cancer development with targeted therapeutics to improve response or overcome resistance to current cancer therapies. The brain and its response within the social environment also need to be taken into consideration.

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