Aromas Influencing the GABAergic System

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Aromas have a powerful influence in people's everyday life and are known to exhibit an array of pharmacological properties, including anxiolytic, anti-stress, relaxing, and sedative effects. Numerous animal and human studies support the use of aromas and their constituents to reduce anxiety-related symptoms and/or behaviours. Although the exact mechanism of how these aromas exert their anxiolytic effects is not fully understood, the GABAergic system is thought to be primarily involved. The fragrance emitted from a number of plant essential oils has shown promise in recent studies in modulating GABAergic neurotransmission, with GABAA receptors being the primary therapeutic target.

aromas essential oils volatile chemicals constituents GABAergic GABAA receptor anxiolytic sedative

1. Introduction

The sense of smell with aromas is common in everyday life, and these aromas can elicit neurological, cognitive, or behavioural responses [1]. For example, it is not uncommon for a smell to evoke a previous visual memory [2]. Aromatic plants and oils have been used as incense, perfumes and cosmetics, for medicinal and culinary purposes, and in religious rituals since time immemorial. Sprigs of juniper are still burnt in Tibetan temples in the East for purification, as are frankincense used during Roman Catholic mass in the West [3] (p. 11).

In recent times, studies have revealed inhalation of certain aromas exerts psychophysiological effects on humans [4]. Numerous animal and human studies have demonstrated anti-anxiety effects from the inhalation of various aromas [5][6][7] and other studies have elucidated the purported mechanism of action of these aromas exerting their anxiolytic effects [1].

Aromas are volatile chemicals < 300 Da that are detected by the olfactory system [4]. Aromas first dissolve into the mucus lining of the nasal cavity and then bind to olfactory receptors in the olfactory epithelium, generating an action potential within the receptor neuron [2][4]. An electrical signal is created and sent to the olfactory bulb for primary processing and then for final processing in various brain regions such as the amygdala, hippocampus, orbitofrontal cortex, and thalamus [2]. The olfactory neuroanatomy is intertwined with the primary emotional areas, including the amygdala, hippocampus, and orbitofrontal cortex via extensive reciprocal axonal connections [7]. It is also thought that these aromas may exert direct effects on neuronal receptors in the brain by crossing the blood-brain barrier [4].

The brain regions most crucial in regulating negative emotions such as anxiety are a set of limbic structures with the amygdala being a focal point [8]. A common finding from a variety of clinical anxiety disorders including social anxiety disorder, post-traumatic stress disorder (PTSD), obsessive compulsive disorder, phobias, and panic disorder is hyperactivity of the amygdala in response to negatively valanced stimuli [9]. Of particular interest is the brain GABAergic system, which is central to the regulation of anxiety. γ-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system (CNS) and is said to be utilised by one-third of CNS neurons as their primary neurotransmitter [8]. GABAergic neurotransmission in the amygdala is important in regulating anxiety-related behaviours [8]. For instance, administration of benzodiazepines reduces amygdala activation in the presence of negative emotional stimuli. In addition, infusions of GABA or GABA receptor agonists into the amygdala decreases measures of anxiety in several animal species [8]. The hippocampus is another limbic structure that has reciprocal connections with the amygdala, projects to the hypothalamus affecting the release of adrenocorticotropic hormones, and has been implicated in dementia [10], anxiety disorders, and PTSD [11]. Animal studies using dementia models have revealed early loss of GABAergic interneurons resulting in hippocampal hyper-excitability, and neuroimaging studies in patients with dementia have reported hyper activity in the hippocampus [12]. Many dementia patients experience high levels of anxiety. In addition, several molecular and biochemical changes in the GABAergic system have been reported in the dementia brain, in particular a reduced expression of GABAA receptors in hippocampal neurons [13]. Thus, the GABAergic system undergoes significant remodelling in the dementia brain, and administration of exogenous agents that bind to GABA receptors may prove a useful tool in inhibiting typical GABA-related phenotypes, such as anxiety [14].

Neuronal inhibition of GABA is mediated via GABA receptors with GABAA receptors being important in controlling excitability of the brain and modulating anxiety [15]. GABAA receptors are a superfamily of pentameric ligand-gated ion channels that are widely distributed in the brain [15], consisting of five subunits arranged pseudo-symmetrically around a central pore with each subunit comprising of an extracellular, intracellular, and transmembrane domain [16]. The five subunits are made up of two α, two β, and one γ subunit, typically γ2, as approximately 75–80% of all GABAA receptors contain γ2 [17]. Each one of the subunits has a distinct cellular and reginal distribution in the brain with some cell types expressing few, most, or all GABAA receptor subunits [15]. Two binding pockets for GABA in GABAA receptors are formed at the extracellular interface between adjacent α and β subunits. The pockets are formed by loops A-C of the β subunit at the principle side and loops D-F of the α subunit at the complementary side [15]. Benzodiazepines are a class of anxiolytic compounds that bind to GABAA receptors at the interface between adjacent α and γ2 subunits enhancing flux of GABA-induced chloride ions, resulting in neuronal hyperpolarization and allosteric modulation of these receptors [15][17]. GABAA receptors are chloride ion channels that open in response to GABA and are influenced via medications such as benzodiazepines, barbiturates, and, more recently, via inhaling certain aromatic compounds.

2. Current Insights

The use of aromatic plants and oils for medicinal purposes is well established, and it is clear from the literature that aromas have known psychophysiological effects within areas of the brain associated with stress and anxiety

modulation. The brain regions most crucial in regulating anxiety are a set of limbic structures, including the amygdala and hippocampus, which are intertwined and intimately connected with the olfactory neuroanatomy via extensive reciprocal axonal connections [7][8]. The amygdala and hippocampus are commonly associated in anxiety disorders, PTSD, and dementia [9][10][11]. Studies have supported the role of GABAergic neurotransmission in the amygdala in regulating anxiety-related behaviours [8]. The hippocampus has reciprocal connections with the amygdala, projects to the hypothalamus affecting the release of adrenocorticotropic hormones [10], and has been associated with significant remodeling of the GABAergic system in the dementia brain where hippocampal neurons have reduced expression of GABAA receptors [12]. Neuronal inhibition of GABA is mediated via GABA receptors with GABAA receptors at the forefront in controlling excitability of the brain and modulating anxiety [15]. The use of exogenous agents that bind to GABA receptors may prove a useful tool in inhibiting typical GABA-related phenotypes, such as anxiety [14].

Aromas found in common beverages, food, spices, volatile organic compounds, popular botanicals, and their constituents were reviewed for their anxiety reducing and sedative properties acting upon the GABAergic system. Numerous animal and human studies have confirmed anxiolytic and sedative effects from the inhalation of essential oils and or aromatic compounds [5][6][18][19]; however, only few have directly examined the effect on GABAA receptors. The aromas shown to potentiate a GABAA receptor response were lavender, whisky fragrance, and aged whiskey. Studies, however, have shown that oral administration of agarwood essential oil potentiating GABAA receptor function and regulating GABAA receptor gene expression [20] and aqueous coffee extract and coffee components elicited a GABAA receptor response in *Xenopus* oocytes [21]. Despite the lack of direct studies on GABAA receptors, some of the main chemical constituents present in the essential oils and/or aromatic compounds have been evaluated for their GABAA receptor response. Monoterpenes (α-pinene [22][23], linalool [24], borneol [25], linalool oxide [26], thymol [27], carvacrol [24], citronellol, and hinokitiol [22]), alcohol (1-octen-3-ol [24]), lactones (jasmine lactone and lactone derivatives [26]), esters (ethyl phenylpropanoate [28] and methyl jasmonate [26]), cyclic ketone (*cis*-jasmone [26]), and ethoxy [28] have all shown to potentiate a GABAA receptor response.

Studies using pharmacological agents that interact with the GABAergic system have shown that essential oils and their constituents have GABAergic involvement. Koo et al. [29] and Komori et al. [30] evaluated the influence essential oils inhalation may have on the GABAergic system via in vivo GABA transaminase assays and GABA activity. Results confirmed that exposure to *A. gramineus* and *V. officinalis* inhalation inhibited GABA transaminase and raised GABA levels, confirming the role these essential oils have on the GABAergic system. In addition, Soni et al. [31] reports in their review of the medical utility of lavender that lavender exerts a similar action to benzodiazepines and increases the effects of GABA in the amygdala, although more recent studies have confirmed that the serotonergic system is involved [32]. Flumazenil, a specific GABAA receptor antagonist, is used to determine anxiolytic-like occurring through the GABAergic system [33]. Co-administration of aristolen-1(10)-en-9-ol (from *N. chinensis*) and flumazenil, a specific GABAA receptor antagonist, or 1,8-cineole (present in *L. Camara* and *E. globulus*) and flumazenil reversed the effects of aristolen-1(10)-en-9-ol and 1,8-cineole implying an effect on GABAA-benzodiazepine receptors [34][35]. Terpinen-4-ol (present in *compound anshen, Lavandula spp.* and *T. vulgaris*) inhibiting 3-mercapto-propionic acid (3-MP), a glutamic acid decarboxylase inhibitor, induced convulsions

demonstrating GABAergic involvement but did not reverse flumazenil confirming that terpinen-4-ol does not act on the same binding site as benzodiazepines [36].

Animal studies have used various behavioural modeling to assess anxiety and the involvement of the GABAergic system. The elevated plus maze is a widely used behavioural model that has predictive validity [37][38] that is specifically suited to evaluate anxiolytic substances that act via the GABAA-benzodiazepine receptor complex [39][40]. More than half of the animal studies examined in this research on essential oils used the elevated plus maze test. Despite variability in the inhalation duration of the essential oil, positive results were obtained in all elevated plus maze studies except for two. The first showed no anxiolytic effect from inhalation of *I. verum*; however, its main component, *trans*-anethole, did show anxiolytic effects [41]. The second showed an anxiogenic effect from a continual two-week exposure to *C. limon* essential oil vapour [42]. It is probable that chronic exposure to the essential oil was responsible for the anxiogenic effect, as Komiya et al. [43] demonstrated anxiolytic effects in an elevated plus maze from exposure to *C. limon* essential oil vapour for 90 min.

Of the clinical studies reviewed, there were a multitude of anxiety-related states where essential oil inhalation was applied, including pre- and post-operative anxiety, anticipation anxiety, during treatment anxiety, first-stage labour anxiety, and experimental and cognitive test anxiety. Orange [44][45], lavender [46][47], and eucalyptus [48] essential oils were used for preoperative anxiety; orange [49] and geranium [50] essential oils were used for post-operative anxiety and orange essential oil during treatment anxiety [51]; orange [52] and geranium [53] essential oils were used for first-stage labour anxiety; orange [51][54] and lemongrass [55] essential oils for experimental anxiety; and orange [56] essential oil for anticipation anxiety. There was considerable heterogeneity in the essential oil concentration, quantity applied, exposure time and mode of delivery. The concentration of the essential oil and quantity applied varied from 2–100% and 2–80 drops respectively with exposure time ranging from 3–35 min, or continual with majority of studies applied once per day, although one study was applied twice daily for three days. The mode of delivery ranged from electrical dispenser, nebuliser, to neutral support (cotton swab, medical patches, paper tissue, gauze, surgical mask, and aroma pads) with the latter making up the majority. Considering the heterogeneity of the available data from the clinical studies reviewed, further studies are warranted to confirm the application of essential oils delivered via inhalation for anxiety-related states.

In summary, many have explored and inferred anxiety-reducing effects via bio-behavioural animal studies, a few have alluded to compounds in the essential oils that interact with GABAergic transmission, and few have conducted elegant neuropharmacology studies to show a direct binding of the compound to the GABA receptor. Further studies are warranted to confirm that aromas, essential oils, and their constituents directly interact with the GABAA receptor complex.

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