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Chapter 3

NEUROLOGICAL ACTIVITIES OF LINALOOL AND OTHER FRAGRANT COMPOUNDS

Yasue Yamada*, PhD
Department of Biotechnology and Chemistry, Faculty of Engineering,
Kindai University, Higashi-Hiroshima, Japan

ABSTRACT

Fragrant compounds from plants have been used in perfumes, cosmetics, food processing and recently in aromatherapy products. Linalool is one of the most widely used fragrant compounds. Essential oils have functions of self-defense, sterilization, and antibiosis in plants. The effects of fragrant compounds to the G-protein-coupled olfactory receptor have been examined, and relationships between odors and neural activity have been shown. When volatile organic compounds enter the blood through the skin or lungs, there is the possibility that they will pass through the blood-brain barrier (BBB) and affect the central nervous system (CNS). However direct effects of those compounds on neural functions and their toxicities are still unclear.

N-methyl-D-aspartate-type glutamate receptors (NMDA receptors) and γ-amino butyric acid type A receptors ($GABA_A$ receptors) are widely distributed in the central nervous system. NMDA receptors play critical roles in synaptic plasticity. $GABA_A$ receptors can mediate inhibitory

* Tel: +81-082-434-7000. E-mail address: y-yamada@hiro.kindai.ac.jp.

neurotransmission by hyperpolarizing the membranes of postsynaptic neurons, resulting in an inhibitory postsynaptic potential that decreases the probability of firing. Potentiation of the receptors response causes anxiolytic, sedative, and anesthetic activities in the brain. We will introduce recent reports on the effects of linalool and another fragrant compounds on NMDA receptors, $GABA_A$ receptor and neural cells. The present review attempts to give an overview of neurological studies on linalool and other fragrant compounds.

Keywords: fragrant compounds, N-methyl-D-aspartate-type glutamate receptors (NMDA receptors), γ-amino butyric acid type A receptors ($GABA_A$ receptors), neural cells, linalool

INTRODUCTION

Essential oils extracted from various parts of plants contain 200~300 aromatic chemical substances (Berger, 2007; Burt, 2004). Essential oils in plants have the functions of self-defense, sterilization, and incentives for antibacterial insects. These compounds have a long history for use in perfumes and in aromatherapy. Lavender has been used in aromatherapy as a relaxant. Linalool, one of the primary components of lavender oil, is known to decrease anxiety, to have anti-nociceptive effects, and to alter the behavior of patients suffering from dementia. Sedative effects of inhaled linalool have been shown in both animal and human studies. (Woronuk et al., 2011; Holmes et al., 2002; Bowles et al., 2002). When aromatic compounds enter blood vessels through the skin or lungs, there is the possibility that they pass through the blood-brain barrier (BBB) and affect the central nervous system (CNS) (Linck et al., 2010; Woronuk et al., 2011; Sakurada et al., 2011). Recently, several studies have shown that lavender oil altered the behavior of patients suffering from dementia (Holmes et al., 2002; Bowles et al., 2002; Holmes and Ballard 2004). Studies using a combination of massage therapy and inhalation of lavender oil have shown that exposure to lavender aromatics significantly decreased excessive motor behavior in subjects diagnosed with dementia. These results support the hypothesis that absorption of lavender essential oils through the nose to the lungs and through the skin promote mental health. These results also suggest that other fragrant compounds used in aromatherapy, decorative cosmetics, fine fragrances, shampoos, toilet soaps, and other toiletries as well as fragrant compounds used in non-cosmetic products such as household

cleaners and detergents are absorbed through the lungs and skin and influence brain function.

Green odor, a mixture of *cis*-3-hexen-1-ol and trans-2-hexanal, has been shown to attenuate the response and anxiety caused by psychological stress in rodents (Nikaido et al., 2011). Phenethyl alcohol was found to be major constituent of rose absolute and was reported to have antibacterial activity (Ulusoy et al., 2009; Fraud et al., 2003). n-Propyl alcohol is contained in fruits and fermented products and is used as a food additive. Sousa et al. showed by animal experiments (elevated plus maze test, light/dark test or open field test) of many researchers that 25 fragrant compounds in essential oils have anxiolytic effects (de Sousa et al., 2015). However, no common chemical characteristics except for low molecular weight were found. They reported that 6 compounds (carvacrol, 1,8-cineole, (E)-methyl isoeugenol, (+)-limonene epoxide, thymol, and vanillin that were orally administered to rodents showed anxiolytic effects (Melo et al., 2010; Gomes et al., 2010, Fajemiroye et al., 2014; de Almeida et al., 2014; Labaque et al., 2013; Bhagwat et al., 2013) and that 11 compounds (carvacyl acetate, (R)-(-)-carvone, nerol, isopulegol, myrtenol, phytol, pulegone, linalool, phenetylalcohol, n-propylalcohol, and citronellol that were intraperitoneally administered to mice or rats showed anxiolytic effects (Melo et al., 2010; Hatano et al., 2012; Marques et al., 2013; Silva et al., 2007; Moreira et al., 2014; Costa et al., 2014; da Silveira et al., 2014; Yamada et al., 2015a). A direct effect of these compounds in essential oil on $GABA_A$ receptor is still unclear. Many volatile organic compounds are used in daily life, and it is therefore important to elucidate the mechanisms of their effects on neuronal receptors and human neural cells (Jager et al., 1992).

To elucidate the mechanisms of the effects of fragrant compounds on the CNS, it is necessary to determine whether these compounds have direct effects on $GABA_A$ receptors and NMDA receptors. NMDA receptors are related to brain plasticity and various mental disorders such as dementia and schizophrenia (Javitt,1992). $GABA_A$ receptor is related to anxiety and depression. Here we introduce recent reports about direct effects on NMDA receptors, $GABA_A$ receptor, and neural cells for understanding the effects of fragrant compounds.

NMDA RECEPTORS AND FRAGRANT COMPOUNDS

NMDA receptors are widely distributed in the central nervous system and play a critical role in synaptic plasticity (Dingledine et al., 1999). NMDA receptors are assembled from two GluN1 subunits and two GluN2 subunits and are activated by simultaneous binding of glycine and glutamate to the GluN1 and GluN2 subunits, respectively (Schorge and Colquhoun, 2003). NMDA receptors are implicated in multiple brain disorders, including ddepression, ischemic stroke, Alzheimer's disease and schizophrenia (Javitt, 2004). Phencyclidine one of antagonists of the receptor, is known to cause schizophrenia like symptoms (Olney et al., 1999). A partial antagonist of NMDA receptors (memantine), has been approved as an anti-dementia medicine for more than 10 years in Europe and has recently been permitted in the USA and Japan (Chen and Lipton, 2006). Partial agonists of NMDA receptors have the possibility of becoming therapeutic agents for psychological illnesses. Many synthesized agents that have agonist or antagonist activity toward the receptors have been examined the possibility for the therapeutic agents (Kussius and Popescu, 2009; Clausen et al., 2008). Identification of naturally derived and subunit-specific NMDA receptor agonists, antagonists and modulators might lead to the development of valuable pharmacological tools as well as new therapeutic agents. Batista et al. reported that linalool produced marked antinociception against pain induced by glutamate, NMDA, AMPA, and kinate in mice (Batista et al., 2008). Brum et al. suggested that at least a part of linalool's anticonvulsant action might be mediated via direct interaction with NMDA receptor complexes (Brum et al., 2001). Inhibitory effects of ethanol on NMDA receptor activity were reported, and the position of the alcohol binding site was also reported. In order to understand the effects of fragrant compounds on neural activity, the effects of 13 fragrant constituents in sake and shochu that are traditional Japanese liquors on activities of GluN1/GluN2A and GluN1/GluN2B subtype NMDA receptors were examined using a *Xenopus* oocytes expression system (Yamada et al., 2015a). Twelve fragrant compounds (linalool, terpinen-4-ol, cis-hexen-1-ol, 1-octen-3-ol, phenetylalchol, isoamyl alcohol, furfural, n-propyl alcohol, nerol, citronellol, geraniol, and α-terpineol) inhibited channel activity of GluN1/GluN2A and GluN1/GluN2B receptors at concentrations of 2.5 mM. In that study, the effects of ethanol as a control at 100 mM, a concentration that is known to inhibit these receptors were examined. Ethanol is well known to inhibit NMDA receptors and to have anxiolytic activity (Wirkner et al., 1999; Eckardt et al., 1998). After intraperitoneal (*i.p.*) injection of fragrant

compounds, an elevated plus maze test was carried out. The anxiolytic activities of fragrant compounds showing inhibition of NMDA receptors were tested with the elevated plus-maze test in mice. Linalool significantly increased the percentages of entry at a dose of 89 mg/kg body weight (bw). Citronellol significantly increased the percentages of entry as well as the time spent in the open arms after *i.p.* injection at a dose of 16 mg/kg bw. Phenetylalchol and n-propyl alcohol also significantly increased the percentages of entry after *i.p.* administration at a dose of 70 mg/kg and 35 mg/kg bw, respectively. These findings suggest that linalool, citronellol and n-propyl alcohol exhibit anxiolytic activity at concentration lower than that of ethanol (51 mg/kg bw). These results indicate that fragrant compounds that inhibit the NMDA receptor might be useful in therapy for mental disorders such as dementia and depression by administration through skin or lungs. However, further experiments are needed to determine their usefulness.

$GABA_A$ Receptor and Fragrant Compounds

$GABA_A$ receptors are heteromeric protein complexes comprising five subunits arranged around a chloride channel. Various isoforms of $GABA_A$ receptors have been identified. These comprise the $\alpha_{1–6}$, $\beta_{1–3}$, $\gamma_{1–3}$, δ, ε, π, θ, and $\rho_{1–3}$ subunits in mammals (Rudolph & Knoflach, 2011; D'Hulst et al., 2009). The major receptor isoforms of the $GABA_A$ receptors in the brain comprises the α_1, β_2, and γ_2 subunits. $GABA_A$ receptors can be activated by GABA or various agonists mediating inhibitory neurotransmission in the central nervous system. $GABA_A$ receptors are the major targets of mood-modulating compounds, such as ethanol, that can pass through BBB (Kumar et al., 2009). Potentiation of the receptor response causes anxiolytic, sedative, and anesthetic activities in the brain. $GABA_A$ receptors can mediate inhibitory neurotransmission by hyperpolarizing the membranes of postsynaptic neurons, resulting in an inhibitory postsynaptic potential that decreases the probability of firing. The chloride channels can be opened by GABA and are targets for a variety of important drugs such as benzodiazepine, barbiturate, neuroactive steroids, anti-convulsants and anaesthetics. Fragrant compounds in various liquors and herbal essential oils are known to have significant effects on human brain function, altering moods and relaxing consciousness.

These have been several studies showing that the receptor was activated by fragrant compounds in tea, whisky, sake and shochu. Hossain et al. reported that linalool, geraniol, phenylethyl alcohol, and (3Z)-hexen-1-ol (leaf alcohol)

in tea activated the $GABA_A$ receptor (Hossain et al., 2002a). Of tested fragrances in oolong tea, *cis*-jasmone, jasmine lactone, linalool oxide and methyl jasmine significantly potentiated the response of the receptor (Hossain et al., 2004). 1,1-Diethoxypropane, 1,1-diethoxyheptane, ethyl phenylpropanoate, 1,1-diethoxy-3-methybutane, 1,1-diethoxy-2-methylpropane, quercus lactone b, damascenone, lactone derivatives (butyrolactone, dodecalactone, deconolactone, and nonalactone), and phenol derivatives (5-methyl-2-acetylpheno, 2, 6-dimethylphenol, 2-methoxy-4-methylphenol, 2-acetylphenol, 4-ethylguaiacol, and 4-ethylphenol) contained in whisky potentiated the $GABA_A$ receptor expressed in *Xenopus* oocytes (Hossain et al.,2002b). It was reported that phenethylalcohol, nerol, and geraniol activated the $GABA_A$ receptor but that isoamylalcohol, citronellol, and linalool did not (Yamada et al., 2015). In an elevated plus-maze test, significant anxiolytic effects were observed in the presence of phenethylalcohol, n-propyl alcohol, and citronellol. Citronellol (16 mg/kg bw) showed almost the same effects as that of memantine (20 mg/kg bw). These results suggest that many fragrant compounds other than ethanol play an important role in inhibiting NMDA receptor channels and potentiating the $GABA_A$ receptor-mediated response.

EFFECTS ON NEURAL CELLS

There is limited information about the mechanisms underlying the actions of fragrant compounds on neuronal cells. For use in aromatherapy as medical treatment, the mechanisms of their effect should be elucidated. We will introduce several reports about effects of fragrant compound on enzymes, channels, transcription factors, oxidative stress, and neurotoxicity in neuronal cells. It was known that lavender oil inhibits voltage-dependent calcium channels (VOCCs) in synaptosomes, primary hippocampal neurons and stably overexpressing cell lines as highly selective drug targets for anxiety (Schuwald et al., 2013). It was also indicated that linalool and β-pinene contained in lavender oil produced an antidepressant-like effect through interaction with the monoaminergic system using antagonists related to the depression process such as 5-HT(Guzman-Gutierrez et al., 2015). β-pinene myrcene, nerol, geraniol, 1,8-cineol, linalool, borneol, α-terpioneol, terpinen-4-ol, linalyl acetate and β-caryophyllene inhibited acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) and exhibited anti-oxidant activity in

experiments using rat brain homogenates (Oboh et al., 2014). In an Alzheimer's disease condition, the amounts of acetylcholine in the brain is decreased. The major medicine for t Alzheimer's disease is an AChE inhibitor. Some seeweeds, citrus juices, vegetables and herbs have been shown to inhibit the AChE (Ademosun and Oboh, 2012; Yoon et al., 2008; Ferreira et al., 2006; Mukherjee et al., 2007). Salvia oils containing α–pinene, β–pinene, sabinene, 1, 8-cineol, borneol, carvacrol, and β–caryophyllene protected PC12 cells from H_2O_2-induced apoptosis by attenuating the Bax/Bcl-2 ratio (Bax: pro-apoptotic effector, Bcl-2: ant-apoptotic effector) and decreasing cytochrome c release (initiator of a cascade of caspase activation that brings about known features of apoptotic cell death) to the cytoplasm (Alamdary et al., 2012; Paknejadi et al., 2012). Bergamot essential oil (BEO) containing limonene, α-pinene, β-pinene, myrcene, γ-terpinene, terpinolene, sabinene, β–bisabolene, linalool, neral, geranial, linalyl acetate, neryl acetate, and geranyl acetate reduced the death of SH-SY5Y human neuroblastoma cells caused by 1 mM NMDA. In addition to preventing reactive oxygen species (ROS) accumulation and activation calpain I, BEO deactivated Akt activation and activated glycogen synthase kinase-3β (GSK-3β) reduction induced by NMDA (Corasaniti et al., 2007). The serine/threonine kinase Akt functions as a major downstream target of phosphatidylinositol 3 kinase (PI3K) and, after being phosphorylated, it promotes cell survival by phosphorylating and inhibiting several proteins including GSK-3β (Corasaniti et al., 2007; Brazil and Hemmings, 2001). Activation of calpain I has been implicated in excitotoxic neuronal death (Corasaniti et al., 1996; Lankiewiczet et al., 2000). Anise oil (*Pimpinella anisum*) containing mainly t*rans*-anethole showed that the anticonvulsant and neuroprotective effects *in vivo* and *in vitro* in the rat brain (Karimzadeh et al., 2012; Orav et al., 2088). Lemongrass (*Cymbopogon citrus*) containing citral, myrcene, citronella, citronellol and geraniol showed neuroprotective effects on glutamate-induced neurotoxicity and antiapoptotic activity in cerebellar granule neurons (Tayeboon et al., 2013). These results indicate that some compounds might be related to signaling pathways in neuronal cells and down streams of neural receptors.

Slowly progressive neuronal loss is a common feature of neurodegenerative diseases (Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis). ROS may directly cause oxidative injury to cellular constituents such as proteins, DNA and lipids. Mechanisms of the action of antioxidants in plants include scavenging ROS, chelation of transition metal expression of antioxidants and inhibition of the activity of

ROS-generating enzymes. Chen et al. reported that *trans*-cinnamaldehyde, an essential oil in cinnamon powder, has a potential neuroprotective effect against ischemic stroke, which may be via the inhibition of neuro-inflammation through attenuating iNOS, COX-2 expression and the NF-κB signaling pathway (Chen et al., 2016). Limonene contained in orange oil induced neurite outgrowth of PC12 mutant cells *via* the p38 MAPK pathway, which is required for memory formation in the rat hippocampus (Shinomiya et al., 2012; Alonso et al., 2003).

In this review, we focused on the biological activity and toxicity of linalool and other fragrant compounds on neural receptors and neural cells. Various fragrant compounds including linalool have been shown to work directly on neural systems such as receptor activity, protection against neurotoxicity and cellular signaling pathways related to neural differentiation or apoptosis. These findings indicate that fragrant compounds have therapeutic value for the prevention and treatment of neurodegenerative diseases.

TOXICITY OF FRAGRANT COMPOUNDS

Chemical compounds from plants have been used as food additives, in medicines and in aromatherapy. About 1700 substances have been found to be emitted from plants (Dudareva and Pichersky;, 2006). However, their toxicity against neurons is not clear. The neuronal toxicities of synthetic volatile organic compounds and naturally derived volatile organic compounds used as fragrances and flavors were compared (Yamada et al., 2015). Several clinical and pathological studies have shown that chronic abuse of volatile organic compounds (VOCs) from petroleum, mainly toluene, causes several neuropsychiatric disorders (Pascual and Bustamante, 2011; Chouanière et al., 2002; Filley et al., 2004; Rumchev et al., 2004). However, little is known about the mechanisms of neurotoxicity of the solvents. n-Octanal, nonanal, and 2-ethyl-1-hexanol, which are used as catalyzers or intermediates of chemical reactions, are released into the environment. However, the direct effects of VOCs on neural function and their toxicities are still unclear. The toxicities of n-octanal, nonanal and 2-ethyl-1-hexanol were compared with those of five naturally derived fragrant organic compounds (FOCs), linalool, *cis*-3-hexen-1-ol, isoamyl alcohol, n-propyl alcohol and n-phenethyl alcohol. MTT assays of human neuroblastoma SK-N-SH cells showed that the IC_{50} values of linalool, *cis*-3-hexen-1-ol, isoamyl alcohol, n-propyl alcohol and phenethyl alcohol were 1.33, 2.3, >5, >5 and 2.39 mM, respectively, and that

the IC_{50} values of toluene, n-octanal, nonanal and 2-ethyl-1-hexanol were 850, 37.2, 8.31 and 15.1 μM, respectively. Natural fragrant compounds (FOCs) showed lower toxicities than those of VOCs (Yamada et al., 2015b). These data indicate that experiments about toxicities of fragrant compounds against the neural cells are very important to use the compounds for aromatherapy and therapeutics for neural disorders.

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BIOGRAPHICAL SKETCH

Yasue Yamada, PhD

Affiliation: Department of Biotechnology and Chemistry, Faculty of Engineering, Kindai University

Education:

1979 B. S. Agriculture, Yamaguchi University
1980 M. S. Agriculture, Yamaguchi University
1996 Ph. D. Biochemistry, Yamaguchi University

Business Address:

1 Umenobe, Takaya, Higashi-Hiroshima, Hiroshima 739-2116 Japan; Tel: +81-082-434-7000. E-mail address: y-yamada@hiro.kindai.ac.jp

Research and Professional Experience:

1990~ a member, The Japanese Biochemical Society
1992~ a councilor, The Japanese pharmacological Society
2003~ a member, American society for neuroscience
2010~ a director, The Japanese society of food engineering

Professional Appointments:

2007- Professor, Department of Biotechnology and Chemistry, Faculty of Engineering, Kindai University
2004-2007 Assistant professor, Department of Pharmacology, Yamaguchi University Faculty of Medicine and Health Sciences
1992-2004 Research associate, Department of Pharmacology, Yamaguchi University Faculty of Medicine and Health Sciences
1990-1992 Research associate, Department of Biochemistry, Yamaguchi University Faculty of Medicine and Health Sciences
1983-1985 Research associate, Biochemistry and Microbiology, Yamaguchi University Faculty of Medicine and Health Sciences.

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1. Izu H,; Shigemori K; Eguchi M; Kawane S; Fujii S; KitamuraY; Aoshima H; YamadaY. Direct activation of GABAA receptors by substances in the organic acid fraction of Japanese sake. *Food Chemistry* (2017) **214,** 354–359.Available online 8 July 2016.
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