Neurosci Bull October 1, 2013, 29(5): 655–660. http://www.neurosci.cn
DOI: 10.1007/s12264-013-1330-2

·Review·

Contribution of β-phenethylamine, a component of chocolate and wine, to dopaminergic neurodegeneration: implications for the pathogenesis of Parkinson's disease

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While the cause of dopaminergic neuronal cell death in Parkinson's disease (PD) is not yet understood, many endogenous molecules have been implicated in its pathogenesis. β-phenethylamine (β-PEA), a component of various food items including chocolate and wine, is an endogenous molecule produced from phenylalanine in the brain. It has been reported recently that long-term administration of β-PEA in rodents causes neurochemical and behavioral alterations similar to that produced by parkinsonian neurotoxins. The toxicity of β-PEA has been linked to the production of hydroxyl radical (·OH) and the generation of oxidative stress in dopaminergic areas of the brain, and this may be mediated by inhibition of mitochondrial complex-I. Another significant observation is that administration of β-PEA to rodents reduces striatal dopamine content and induces movement disorders similar to those of parkinsonian rodents. However, no reports are available on the extent of dopaminergic neuronal cell death after administration of β-PEA. Based on the literature, we set out to establish β-PEA as an endogenous molecule that potentially contributes to the progressive development of PD. The sequence of molecular events that could be responsible for dopaminergic neuronal cell death in PD by consumption of β-PEA-containing foods is proposed here. Thus, long-term over-consumption of food items containing β-PEA could be a neurological risk factor having significant pathological consequences.

Keywords: oxidative stress; hydroxyl radical; mitochondrial complex-I; α-synuclein; Lewy body; ubiquitin-proteasome system

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopamine-containing neurons in the substantia nigra pars compacta (SNc), resulting in four cardinal behavioral abnormalities: tremor, rigidity, akinesia and postural instability[1,2]. While the cause of dopaminergic neurodegeneration in PD is not well understood, excessive production of reactive oxygen species[3] and the resulting mitochondrial complex-I dysfunction[4] are generally regarded as the underlying causes. It is now considered that PD is caused not only by exogenous substances such as rotenone[5] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[5,6], but also by endogenous molecules such as homocysteine[7], 6-hydroxydopamine (6-OHDA)[8-11] and dopamine itself[12,13].

β-Phenethylamine (β-PEA)

β-PEA is a naturally-occurring plant-derived biogenic amine found in cocoa beans[14] and its products[15], and is also an endogenous amine produced by decarboxylation of phenylalanine in the mammalian brain[16,17]. β-PEA is present in trace amounts in various food items such as chocolate[18,15,19], cheese[20] and wine[21,22], with the highest being reported in chocolate[18,19]. Although β-PEA is distributed throughout the mammalian brain, its concentration in dopaminergic areas such as the caudate-putamen is

relatively high[23,24].

Physiological Role of β-PEA in Brain — Is It Similar to Parkinsonian Neurotoxins?

Generation of ·OH Radical

The mechanism of action of parkinsonian neurotoxins has been linked to the production of hydroxyl radical (·OH) and the generation of oxidative stress in dopaminergic areas of the brain, mainly mediated by the inhibition of mitochondrial complex-I[25-27]. It has been reported recently that long-term administration of β-PEA to rodents causes oxidative stress[28-30], similar to that produced by parkinsonian neurotoxins such as MPTP[5], rotenone[5,25] and 6-OHDA[6,8]. β-PEA-induced oxidative stress has been linked to its ability to inhibit mitochondrial complex-I[28], directly leading to the generation of cytotoxic ·OH in a dose-dependent manner[28]. In addition, β-PEA has also been reported to inhibit mitochondrial O_2 consumption, suggesting that the generation of cytotoxic ·OH is the underlying cause[29]. Moreover, β-PEA itself has been reported to generate ·OH *in vitro* and in isolated mitochondrial fractions[30,28]. Thus, these reports suggest that β-PEA generates ·OH either by inhibiting mitochondrial complex-I or by producing ·OH by itself.

Neurochemical and Behavioral Alterations

Another significant observation was that administration of β-PEA in rodents reduces striatal dopamine content and induces disorders such as akinesia, catalepsy and other motor abnormalities[28,31,32], similar to those of parkinsonian rodents[6]. However, no reports are available on the extent of dopaminergic neuronal cell death after administration of β-PEA. In contrast, several reports have suggested that β-PEA acts like a dopaminergic agonist and regulates the activity of nigrostriatal dopaminergic pathways[33,34]. β-PEA, when administered intraventricularly, increases the extracellular dopamine levels in the striatum[35], and acute administration results in increases in locomotor activity and stereotypic behavior in rodents[31,32]. Importantly, only long-term administration or high doses of β-PEA induces loss of dopamine in the nigrostriatum leading to motor disabilities similar to those of PD, whereas acute or sub-acute doses of β-PEA in rodents increase dopamine levels and induce hypermotility[32]. Thus, β-PEA may be comparable with parkinsonian neurotoxins such as MPP^+, which when unilaterally infused into the SNc, initially results in release of dopamine into the striatum causing contralateral rotational bias[36].

β-PEA as a Specific Dopaminergic Neurotoxin

Although the distribution of β-PEA in the mammalian brain is heterogeneous, the highest concentrations are reported to occur in dopaminergic regions e.g., in mesolimbic and caudate-putamen regions[23,24]. The rates of synthesis and turnover of β-PEA in brain are also similar to that of dopamine[23,24], which has been reported to cause neurotoxicity because of its ability to produce endogenous toxins such as 6-OHDA[9-12]. As the concentration of β-PEA in dopamine-rich region is relatively high, it may be proposed here that these regions are particularly vulnerable to toxic insult from β-PEA. Thus, consumption of β-PEA-containing food items over a long time would cause preferential dopaminergic neurodegeneration like other endogenous parkinsonian neurotoxins[7,8,10-12] and may contribute to the development of PD in humans.

Probable Molecular Mechanism of Action of β-PEA in Brain

Mitochondrial dysfunction has been implicated to play a central role in PD pathogenesis[37-39]. Mitochondrial dysfunction and the resulting oxidative stress have been reported to promote α-synuclein aggregation or Lewy body formation[40-42] that culminates in the loss of dopaminergic neurons through impairment of the ubiquitin-proteasome system (UPS)[43]. The aggregated α-synuclein has been shown to inhibit the UPS system by interacting with the proteasomal subunits[44,45]. Moreover, a decrease in cellular energy or ATP generation as a consequence of mitochondrial complex-I inhibition results in α-synuclein aggregation[40-42,46,47]. Rotenone, a parkinsonian neurotoxin and a specific mitochondrial complex-I inhibitor[48], has been implicated in the formation of Lewy bodies[49] and UPS dysfunction in rodents[50]. Likewise, other parkinsonian neurotoxins such as Paraquat and MPTP also contribute to α-synuclein aggregation and UPS dysfunction[51,52]. Thus, a molecule that causes mitochondrial oxidative stress may cause α-synuclein aggregation and UPS dysfunction in the brain. On the other hand, UPS dysfunction alone has

the potential to cause α-synucleinopathies[53,54] and can also reciprocally inhibit mitochondrial functions[55]. Most importantly, aggregated α-synuclein through its ability to impair UPS and mitochondrial dysfunctions may contribute to dopaminergic neurodegeneration[56]. Meanwhile, dopaminergic neurodegeneration by the apoptotic mode of cell death as a consequence of mitochondrial dysfunction[57] and α-synucleinopathies has been implicated in the pathogenesis of PD.

Similar to other parkinsonian neurotoxins, β-PEA inhibits mitochondrial complex-I, causes oxidative stress, and induces parkinsonian symptoms in rodents[28]. Thus, β-PEA-induced mitochondrial dysfunctions and the resulting oxidative stress may promote α-synuclein aggregation or Lewy body formation in dopaminergic areas that may cause proteasome dysfunction, resulting in dopaminergic neurodegeneration[56] by apoptosis[57]. The sequence of molecular events that could be responsible for dopaminergic neuronal death and the behavioral abnormalities, as a result of consumption of β-PEA-

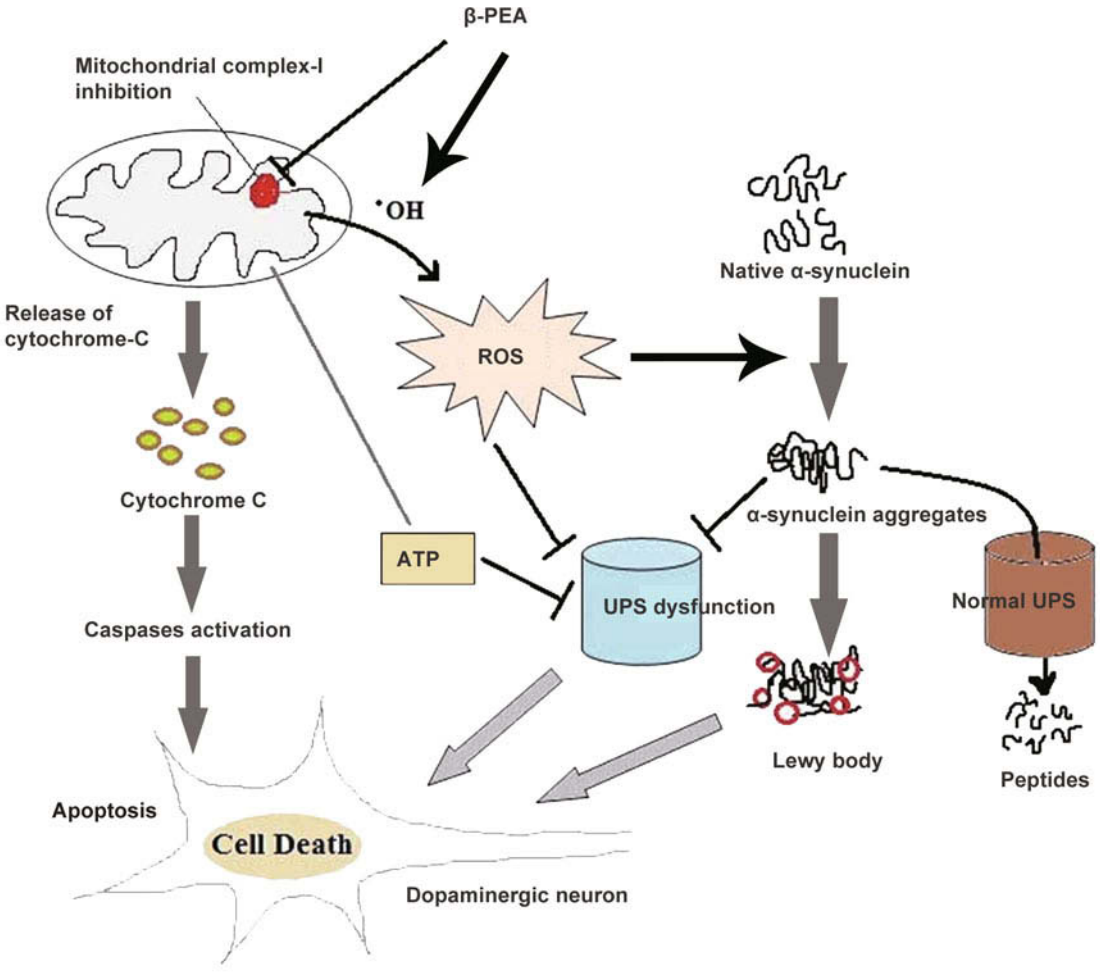

Fig. 1. Molecular mechanisms underlying β-phenethylamine (β-PEA)-induced dopaminergic neurodegeneration. High levels of β-PEA generate hydroxyl radicals (·OH) either by inhibiting mitochondrial complex I or by producing ·OH itself and contribute to oxidative stress. Mitochondrial complex-I inhibition and the resulting oxidative stress promote α-synuclein aggregation or Lewy-body formation which inhibits the ubiquitin proteasome system (UPS) by interacting with the proteasomal subunits. Decreased cellular energy or ATP generation as a consequence of mitochondrial complex-I inhibition also inhibits the UPS. Alterations or diminution of UPS functions enhances α-synuclein aggregation and reciprocally inhibits mitochondrial functions. The mitochondrial dysfunctions and the resulting oxidative stress that trigger the accumulation of α-synuclein aggregates together with UPS dysfunction to culminate in dopaminergic neurodegeneration by apoptosis.

containing food items, is proposed in Fig. 1.

Is Consumption of Chocolate Sufficient to Cause PD in Humans?

If a person takes 100 g of chocolate per day, the total β-PEA intake would be 0.36–0.83 mg/day depending on the type of chocolate[58]. Since β-PEA is an integral component of many food items, a "chocolate addict" would be exposed to a much higher dose. It has recently been demonstrated that acute (one day) and chronic (7 days) intraperitoneal administration of β-PEA, both at doses of 0.63 mg/day and 1.25 mg/day, are sufficient to cause parkinsonian symptoms in adult mice[28]. These results suggest that the amount of chocolate that a person takes normally might be toxic to dopaminergic neurons.

However, chocolate and wine also contain various antioxidants such as polyphenols[59], which have been reported to be protective against many diseases including PD[60,61]. The polyphenol constituents of cocoa, such as epicatechin and catechin, have been reported to attenuate MPTP-induced dopaminergic neurodegeneration in rodent models of PD[60,61]. Few reports are available on their adverse effects[62,63]. Although the reports on the neuroprotective effect of polyphenols are promising, adverse effects of polyphenols on human health have yet to be ascertained. Thus, it may be suggested that the toxic effect of β-PEA on dopaminergic neurons may be attenuated by polyphenols like cathechins or other antioxidants. Moreover, the attenuation of β-PEA-induced neurotoxicity may depend on the quality and/or quantity of polyphenols present in the chocolate or wine consumed.

Conclusion

To date, the cause of PD in humans is a mystery. Although β-PEA has mood-enhancing effects, long-term over-consumption of foods containing β-PEA could be a neurological risk factor having significant pathological consequences such as PD. The proposed mechanism tries to explain the molecular events that might lead to dopaminergic neuronal loss in PD by consumption of β-PEA-containing food items. The neurotoxic potential of β-PEA in the development of PD has been discussed and limited consumption of these foods is recommended. As consumption of some β-PEA-enriched food items has become an addiction in modern life, our proposed mechanism is of enormous significance and impact. Although reports on the neurotoxic effects of β-PEA and the neuroprotective effects of polyphenols are promising, their roles in human health need further investigation.

Received date: 2012-09-01; Accepted date: 2012-11-21

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