

## HYPOTHESIS

**Chronic polysystemic candidiasis as a possible contributor to onset of idiopathic Parkinson's disease**

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**Abstract**

**The underlying cause of Parkinson's disease is still enigma. Several mechanisms have been implicated in the etiopathogenesis of PD including oxidative damage, environmental toxins, genetic predisposition, and accelerated aging. Recent research suggests that salsolinol, a derivate of dopamine, is an important contributing factor. In the presence of acetaldehyde dopamine is converted into salsolinol, a neurotoxin involved in apoptosis of dopaminergic neurons. Increased production of acetaldehyde is associated with chronic polysystemic candidiasis (CPC). Chronically elevated levels of acetaldehyde in patients with CPC might participate in the formation of salsolinol and its metabolites in the brain contributing to the destruction of dopaminergic cells in substantia nigra. Clinical mental symptoms of PD often correspond with the mental manifestations of CPC. This hypothesis may constitute basis for further scientific and clinical research of PD etiopathogenesis (Fig. 1, Ref. 29).**

**Key words: acetaldehyde, candidiasis, dopamine, Parkinson's disease, salsolinol.**

Despite an extensive research, the etiopathogenesis of Parkinson's disease remains elusive. Several studies indicate that dopamine metabolites exhibit significant toxic effects. Published data suggest that a derivate of dopamine, salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline), and its metabolites have a selective toxic effect on dopaminergic neurons (1, 2). Salsolinol can be synthesized from dopamine and acetaldehyde (3).

Patients with chronic polysystemic candidiasis exhibit significantly elevated levels of acetaldehyde in the gastrointestinal (GI) tract. This phenomenon is a direct result of the metabolic processes of the invading organism – *Candida albicans*. Chronic polysystemic candidiasis is a condition first described as an intestinal disbiosis caused by yeast overgrowth in the intestines and mucous membranes (4). Predisposing factors include long term use of broad spectrum antibiotics, corticosteroids, oral contraceptives and a diet rich in simple carbohydrates and sugars. Once the yeast begins to proliferate excessively in the GI tract, the normal bacterial gut flora becomes replaced by the invading organism, a process that results in a wide array of physiological and mental symptoms. *C. albicans* utilizes carbohydrates available in the GI tract to produce acetaldehyde both aerobically and anaerobically (4). Upon entering the bloodstream, acetaldehyde

is distributed to the central nervous system, where it expresses a high affinity to tissues (5). The concept of chronic polysystemic candidiasis is not widely accepted in the mainstream medical community, mostly due to the lack of large-scale clinical research. However, clinical data collected by Truss (4) strongly supports the hypothesis of *C. albicans*-mediated acetaldehyde formation. Truss (5) also suggested that an increased plasma concentration of acetaldehyde is responsible for metabolic disturbances, which are clinically interpreted as the symptoms of chronic polysystemic candidiasis. Truss (5) also postulated the involvement of acetaldehyde produced by *C. albicans* in the formation of salsolinol.

In light of the above data, the question arises: can the acetylaldehyde produced by *C. albicans* in patients with CPC result in chronically elevated levels of salsolinol in the brain,

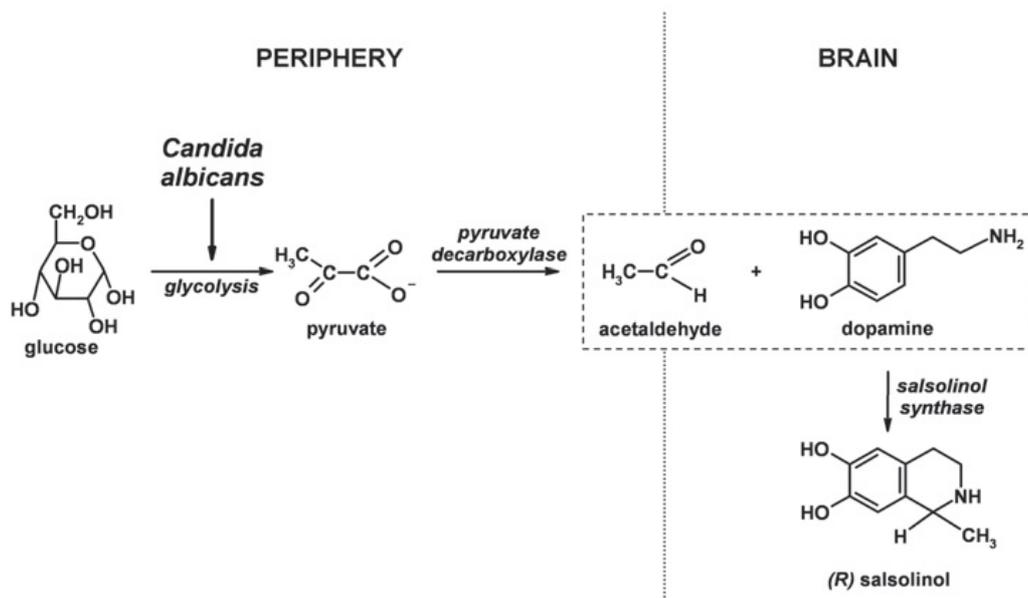
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### Hypothetical mechanism of (R) salsolinol formation in the brain through the *Candida albicans* mediated pathway



thereby inducing the apoptosis of dopaminergic neurons – a prerequisite to the onset of PD symptoms?

#### Acetaldehyde formation by *Candida albicans*

It has been suggested that *C. albicans* produces up to 50 known toxins, among those the most significant being acetaldehyde. This compound is also produced by other bacterial and fungal organisms colonizing the intestinal environment, blood, liver or other tissues (6–8). *C. albicans* is capable of producing acetaldehyde in the GI tract through the fermentation of sugar.

The main aldehyde degradation mechanism in the body is oxidation by the enzyme aldehyde dehydrogenase. This process takes place primarily in the liver, although other tissues participate in this process to some extent as well. Because of the efficiency of acetaldehyde oxidation, the compound accumulates in the bloodstream only when its formation is prolonged and significantly greater than the oxidation capacity, as may be the case in CPC patients. Although oxidation accounts for the majority of the acetaldehyde removal from the bloodstream, its high tissue affinity represents the second mechanism of dissipation. Binding of acetaldehyde to tissue effectively protects it from the oxidation pathway (5, 9). This protective binding most likely eliminates most of the active acetaldehyde, the removal of remaining acetaldehyde is determined by the oxidizing capacity of the liver. Once this capacity is exceeded, the acetaldehyde is distributed in the peripheral blood throughout the tissues. It was concluded that, when generated chronically, acetaldehyde binding to the amine groups is cumulative as is the case with CPC patients (5).

#### Role of salsolinol in etiopathogenesis of Parkinson's disease

Salsolinol is an endogenously synthesized catechol isoquinoline that has been detected in rat and human brain tissue samples (10, 11). Salsolinol can be synthesized from dopamine and acetaldehyde by an enzyme i.e. salsolinol synthase (3, 12). Salsolinol and its metabolites can be detected in many areas of the brain including the substantia nigra (12, 13). The compound is metabolized by N-methyltransferase to N-methyl-salsolinol and subsequently by amine oxidase to 1,2-dimethyl-6,7-dihydroxyisoquinolinium ion (12, 14). It has been established that the elevation in brain salsolinol is a direct result of the increase in brain acetaldehyde concentrations (15). Additionally, it is thought that the metabolites of salsolinol are involved in the etiopathogenesis of Parkinson's disease (2).

The neurotoxic properties of salsolinol have been intensively studied. Salsolinol has a molecular structure similar to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPPT) and 6-hydroxydopamine (6-OHDA), which are known to induce a loss of catecholaminergic cells. Salsolinol and/or its methylated derivatives have been suggested to act as endogenous dopaminergic neurotoxins, inducing selective neuronal cell death and eliciting symptoms almost identical to idiopathic Parkinson's disease (2, 16). The data suggest that N-methylated derivatives of salsolinol, N-methyl (R) salsolinol and its metabolite products play a major role in the etiopathogenesis of PD (17). It has also been demonstrated that patients with PD have an increased activity of N-methyltransferase, which catalyzes the synthesis of N-methyl (R) salsolinol from salsolinol in lymphocytes (2, 12, 14, 18). It has

also been observed that levels of endogenously synthesized salsolinol and its derivatives (e.g. norsalsolinol, N-methyl-norsalsolinol, N-methyl-salsolinol) are increased in the cerebrospinal fluid (19) and the urine (20) of patients with idiopathic PD. Because norsalsolinol derivatives are found in low or undetected concentrations in healthy subjects (21), its use as a biological marker for PD has been proposed (1). However, recent data indicates that the observed increase of systemic levels of norsalsolinol derivatives can be induced by levodopa treatment and may not represent an accurate biological marker of PD (22).

## Conclusions

The development of PD is thought to be triggered by a variety of factors including infectious and immunological abnormalities, the effects of ageing, toxins (endogenous as well as exogenous), genetic factors and numerous environmental factors (23–25). Some data suggest a correlation between gastrointestinal infection by *Helicobacter pylori* and the onset of PD (26, 27). However, the published data do not indicate any research conducted to investigate a possible association between PD and chronic polysystemic infection by *C. albicans*. Here, we suggest that increased levels of acetaldehyde in patients with CPC may increase the formation of salsolinol in the brain, which may, in turn, participate in the destruction of dopaminergic cells in the substantia nigra. A correlation between fungal infection and PD is also supported by findings that seborrheic dermatitis is particularly common in patients with PD (28). This finding corroborates the hypothesis of the absence of an effective immunologic response to the fungal infections in CPC patients (29). *We hypothesize that an increased level of acetaldehyde in CPC patients is a factor suggesting a correlation between C. albicans infection and PD. We speculate that the combination of an increased production of acetaldehyde possibly combined with the presence of other exogenous neurotoxins represents the set of factors sufficient for an onset of idiopathic PD symptoms.*

## References

- Moser A, Scholz J, Nobbe F, Vieregge P, Bohme V, Bamberg H. Presence of N-methyl-norsalsolinol in the CSF: correlations with dopamine metabolites of patients with Parkinson's disease. *J Neurol Sci* 1995; 131 (2): 183–189.
- Maruyama W, Naoi M. Cell death in Parkinson's disease. *J Neurol* 2002; 249 (Suppl 2): 6–10.
- Naoi M, Maruyama W, Dostert P, Kohda K, Kaiya T. A novel enzyme enantio-selectively synthesizes (R)salsolinol, a precursor of a dopaminergic neurotoxin, N-methyl(R)salsolinol. *Neurosci Lett* 1996; 212 (3): 183–186.
- Truss CO. Tissue injury induced by *Candida albicans*. Mental and neurologic manifestations. *J Orthomolec Psych* 1978; 7 (1): 17–37.
- Truss CO. Metabolic abnormalities in patients with chronic candidiasis: the acetaldehyde hypothesis. *J Orthomolec Psych* 1984; 13 (2): 66–93.
- Jokelainen K, Roine RP, Vaananen H, Farkkila M, Salaspuro M. In vitro acetaldehyde formation by human colonic bacteria. *Gut* 1994; 35 (9): 1271–1274.
- Jokelainen K, Siitonen A, Jousimies-Somer H, Nosova T, Heine R, Salaspuro M. In vitro alcohol dehydrogenase-mediated acetaldehyde production by aerobic bacteria representing the normal colonic flora in man. *Alcohol Clin Exp Res* 1996; 20 (6): 967–972.
- Salaspuro MP. Acetaldehyde, microbes, and cancer of the digestive tract. *Crit Rev Clin Lab Sci* 2003; 40 (2): 183–208.
- Umulis DM, Gurmen NM, Singh P, Fogler HS. A physiologically based model for ethanol and acetaldehyde metabolism in human beings. *Alcohol* 2005; 35 (1): 3–12.
- Sandler M, Carter SB, Hunter KR, Stern GM. Tetrahydroisoquinoline alkaloids: in vivo metabolites of L-dopa in man. *Nature* 1973; 241 (5390): 439–443.
- Collins MA, Bigdeli MG. Tetrahydroisoquinolines in vivo. I. Rat brain formation of salsolinol, a condensation product of dopamine and acetaldehyde, under certain conditions during ethanol intoxication. *Life Sci* 1975; 16 (4): 585–601.
- Naoi M, Maruyama W, Akao Y, Yi H. Dopamine-derived endogenous N-methyl-(R)-salsolinol: its role in Parkinson's disease. *Neurotoxicol Teratol* 2002; 24 (5): 579–591.
- Musshoff F, Schmidt P, Dettmeyer R, Priemer F, Wittig H, Maeda B. A systematic regional study of dopamine and dopamine-derived salsolinol and norsalsolinol levels in human brain areas. *Forensic Sci Int* 1999; 105 (1): 1–11.
- Naoi M, Maruyama W, Nagy GM. Dopamine-derived salsolinol derivatives as endogenous monoamine oxidase inhibitors: occurrence, metabolism and function in human brains. *Neurotoxicology* 2004; 25 (1–2): 193–204.
- Jamal M, Ameno K, Kubota T, Ameno S, Zhang X, Kumihashi M, Ijiri I. In vivo formation of salsolinol induced by high acetaldehyde concentration in rat striatum employing microdialysis. *Alcohol Alcohol* 2003; 38 (3): 197–201.
- Martinez-Alvarado P, Dagnino-Subiabre A, Paris I, Metodiewa D, Welch CJ, Olea-Azar C, Caviedes P, Caviedes R, Segura-Aguilar J. Possible role of salsolinol quinone methide in the decrease of RCSN-3 cell survival. *Biochem Biophys Res Commun* 2001; 283 (5): 1069–1076.
- Maruyama W, Sobue G, Matsubara K, Hashizume Y, Dostert P, Naoi M. A dopaminergic neurotoxin, 1(R), 2(N)-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, N-methyl(R)salsolinol, and its oxidation product, 1,2(N)-dimethyl-6,7-dihydroxyisoquinolinium ion, accumulate in the nigro-striatal system of the human brain. *Neurosci Lett* 1997; 223 (1): 61–64.
- Naoi M, Maruyama W. Cell death of dopamine neurons in aging and Parkinson's disease. *Mech Ageing Dev* 1999; 111 (2–3): 175–188.
- Maruyama W, Abe T, Tohgi H, Dostert P, Naoi M. A dopaminergic neurotoxin, (R)-N-methylsalsolinol, increases in Parkinsonian cerebrospinal fluid. *Ann Neurol* 1996; 40 (1): 119–122.
- Moser A, Siebecker F, Vieregge P, Jaskowski P, Kompf D. Salsolinol, catecholamine metabolites, and visual hallucinations in L-DOPA treated patients with Parkinson's disease. *J Neural Transm* 1996; 103 (4): 421–432.

21. Niwa T, Takeda N, Yoshizumi H, Tatematsu A, Yoshida M, Dostert P, Naoi M, Nagatsu T. Presence of 2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and 1,2-dimethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, novel endogenous amines, in parkinsonian and normal human brains. *Biochem Biophys Res Commun* 1991; 177 (2): 603–609.
22. Scholz J, Klingemann I, Moser A. Increased systemic levels of norsalsolinol derivatives are induced by levodopa treatment and do not represent biological markers of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2004; 75 (4): 634–636.
23. O'Neill CJ, Richardson MD, Charlett A, McHugh L, Bowes SG, Purkiss AG, Weller C, Dobbs SM, Dobbs RJ. Could seborrhoeic dermatitis be implicated in the pathogenesis of parkinsonism? *Acta Neurol Scand* 1994; 89 (4): 252–257.
24. Stoessl AJ. Etiology of Parkinson's disease. *Can J Neurol Sci* 1999; 26 (Suppl 2): 5–12.
25. Logroscino G. The role of early life environmental risk factors in Parkinson disease: what is the evidence? *Environ Health Perspect* 2005; 113 (9): 1234–1238.
26. Dobbs SM, Dobbs RJ, Weller C, Charlett A. Link between *Helicobacter pylori* infection and idiopathic parkinsonism. *Med Hypotheses* 2000; 55 (2): 93–98.
27. Weller C, Oxlade N, Dobbs SM, Dobbs RJ, Charlett A, Bjarnason IT. Role of inflammation in gastrointestinal tract in aetiology and pathogenesis of idiopathic parkinsonism. *FEMS Immunol Med Microbiol* 2005; 44 (2): 129–135.
28. Gupta AK, Bluhm R. Seborrheic dermatitis. *J Eur Acad Dermatol Venereol* 2004; 18 (1): 13–26.
29. Truss CO. Restoration of immunologic competence to *Candida albicans*. *J Orthomolec Psych* 1980; 9 (4): 287–301.

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