HEALTH RESEARCH ABSTRACT SUBMISSIONS #33

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Title of Research *	OXIDATION OF 3,4-DIHYDROXYPHENYLACETALDEHYDE ENHANCES PROTEIN AND NUCLEOPHILE REACTIVITY
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Introduction & Purpose *

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by loss of dopaminergic neurons in the brain, intraneuronal protein aggregates, and motor and cognitive deficits. Our research focuses on determining the chemical mechanisms involved in PD. The dopamine metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL) is an endogenous neurotoxin cytotoxic to dopaminergic neurons both in vivo and in vitro. To explain the high levels of toxicity associated with DOPAL, we hypothesized that DOPAL may be capable of undergoing auto-oxidation to a quinone, resulting in enhanced reactivity with cellular nucleophiles and proteins.

Experimental Design *

Model systems known to oxidize dopamine to a quinone (NaIO4, tyrosinase, prostaglandin H synthase) were quantitatively assessed (via HPLC) for their ability to also oxidize DOPAL. Unique color changes associated with these oxidations were analyzed spectrophotometrically. Resultant oxidized species were reacted with various model nucleophiles such as amino acids. Colorimetric and spectrophotometric changes were used to measure reactivity. Oxidized and non-oxidized DOPAL were then incubated with a model protein (glyceraldehyde 3-phosphate dehydrogenase), in order to determine if oxidation enhances DOPAL induced protein cross-linking as shown by SDS-PAGE and densitometry.

Results *

Quantitative HPLC measurements indicate that DOPAL is susceptible to oxidation by the tested methods. Spectrophotometric analysis also shows the formation of unique chromophores, likely corresponding to the quinone (λmax = 520 nm) and a stably rearranged species (λmax = 400 nm). Oxidized species are selectively reactive toward free thiols such as glutathione, and are sensitive to ascorbate, a known quinone reducing agent. Oxidation also enhances DOPALs ability to induce protein cross-linking by 20-35% as compared to controls.

Conclusions *

These experiments indicate that DOPAL is capable of undergoing an oxidation resulting in the formation of unique species that demonstrate enhanced reactivity with cellular-type nucleophiles and proteins. This is highly relevant because protein cross-linking is an important mechanism of toxicity. Also, DOPAL was shown to be a substrate for prostaglandin H

synthase, an enzyme with known implications in Parkinson's disease. These experiments highlight the potential of DOPAL to exert toxicity in biological systems in a fashion similar to dopamine, i.e. auto-oxidation and protein reactivity.

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