Mechanisms of Suppression of α-Synuclein Neurotoxicity by Geldanamycin in Drosophila

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Parkinson’s disease is a common neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of the protein α-synuclein into aggregates called Lewy bodies and Lewy neurites. Parkinson’s disease can be modeled in Drosophila where directed expression of α-synuclein induces compromise of dopaminergic neurons and the formation of Lewy body-like aggregates. The molecular chaperone Hsp70 protects cells from the deleterious effects of α-synuclein, indicating a potential therapeutic approach to enhance neuron survival in Parkinson’s disease. We have now investigated the molecular mechanisms by which the drug geldanamycin protects neurons against α-synuclein toxicity. Our studies show that geldanamycin sensitizes the stress response within normal physiological parameters to enhance chaperone activation, offering protection against α-synuclein neurotoxicity. Further, geldanamycin uncouples neuronal toxicity from Lewy body and Lewy neurite formation such that dopaminergic neurons and the formation of Lewy body-like aggregates. These studies indicate that compounds that modulate the stress response are a promising approach to treat Parkinson’s disease.

1% of the population over the age of 65 is afflicted by Parkinson’s disease (PD) (1). Pathologically, PD is typified by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the formation of Lewy bodies (LBs) and Lewy neurites (LNs), which are electron dense, eosinophilic accumulations of proteins in the cell bodies and neuritic processes of affected neurons. The loss of dopaminergic neurons is primarily responsible for the bradykinetic movements, cogwheel rigidity, and tremors that characterize this disease.

Although PD is typically sporadic, rare hereditary forms have yielded new etiologic insights. α-Synuclein, the first gene linked to hereditary PD (2, 3), is also a major component of the LBs and LNs found in patients with sporadic PD (4, 5), suggesting shared pathologic mechanisms for familial and sporadic PD. Transgenic mouse models have demonstrated α-synuclein-dependent inclusion formation and degeneration of dopaminergic nerve terminals (6) or motor axons (7, 8). Expression of both wild-type and mutant α-synuclein in Drosophila has consistently shown both inclusion formation and age-dependant degeneration of dopaminergic neurons (9, 10). Progressive loss of neuronal integrity is preventable in flies genetically through the directed expression of Hsp70 (9), a molecular chaperone involved in nascent chain folding and refolding of misfolded proteins (11). Further, up-regulation of Hsp70 mitigates toxic properties of α-synuclein in transgenic mouse models (12). α-Synuclein toxicity in Drosophila can also be prevented pharmacologically with geldanamycin (GA) (13), an ansamycin antibiotic currently in clinical trials as an anticancer agent (14). Although existing pharmacological therapies for PD help to relieve patient symptoms, they fail to address the underlying cause, the loss of dopaminergic cells. Therefore GA represents a new class of cytoprotective drugs for the treatment of this disease.

GA has been pursued as a therapeutic agent for cancers associated with abnormally elevated levels of receptor tyrosine kinase activity (15). Subsequent studies have shown that GA acts by binding to the ATP-binding domain of Hsp90 and inhibiting its ATP-dependent activities (16). Hsp90 is a ubiquitous chaperone implicated in a number of signaling cascades (15) as well as the stabilization of nuclear hormone receptors (17). Furthermore, in vitro studies have shown that Hsp90 negatively regulates stress pathways by binding to and inhibiting activation of its central mediator, heat shock transcription factor (HSF) (18, 19). However, despite these studies elucidating actions of GA and its promise for therapeutics, little has been done to address its activity and targets in vivo.

Invertebrates have been used successfully to identify pathways involved in diverse processes ranging from neurodegenerative disease to aging (20, 21). Here, we use our Drosophila model for PD to identify the pathways required for neuroprotection by GA in vivo. We demonstrate that GA modulates the stress response thereby affecting α-synuclein pathology and solubility. These studies emphasize the importance of the molecular chaperones to neuronal integrity in PD and suggest a role for chaperones in the promotion of protective α-synuclein inclusions.

EXPERIMENTAL PROCEDURES

Fly Stocks—Drosophila were raised on standard media or instant media reconstituted with placebo (0.3% Me₂SO) or GA (3 µg/ml in 0.3% Me₂SO).
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Results

GA Enhances the Stress Response—Previous studies have described selective toxicity of α-synuclein toward the dorsomedial (DM) dopaminergic neuronal cluster in the Drosophila brain. In 20-day-old flies, loss of TH staining is observed in ~50% of the DM neurons by paraffin sectioning (9). A similar decrease in TH staining is seen only in the DM clusters by whole mount immunofluorescence of the fly brain; other dopaminergic neuronal clusters appear resistant to α-synuclein expression (see supplemental Fig. S1).

We have reported that treating flies with GA protects against α-synuclein neurotoxicity (13). To understand mechanisms of action of GA, we first examined the effects of GA on the stress response, detected by levels of the stress-induced form of Hsp70. In Drosophila, GA induces Hsp70 protein synthesis in a concentration-dependent manner (13). Specifically, a small increase in Hsp70 levels is detectable in flies fed 12 μg/ml GA with a 2–3-fold increase above baseline in flies fed higher concentrations (96 μg/ml). However, flies fed 3 μg/ml GA (a concentration sufficient to protect neurons against α-synuclein toxicity) do not exhibit elevated levels of Hsp70 above baseline (13). Therefore we hypothesized that GA might be enhancing the endogenous stress response rather than directly inducing heat shock protein synthesis.

Stress response proteins are rapidly induced in response to changes in temperature. In Drosophila, Hsp70 mRNA and protein levels are maximally induced at 37 °C (27). Upon heat shock, mRNA levels begin to rise within 4 min, and an increase in newly synthesized Hsp70 is detected within 8–12 min with a plateau in protein synthesis occurring after 30–45 min of continuous heat shock (27). We focused our analysis on the early phase of Hsp70 induction. Newly eclosed control flies

kinetics of Hsp70 induction upon 37 °C heat shock for 15 min. D, upon 32 °C heat shock for 15 min, Hsp70 levels rise earlier and reach higher levels of expression in GA-treated flies. E, Hsp70 levels increase earlier and reach higher levels in GA-treated flies (squares) than in placebo-treated flies (diamonds) (data from four independent experiments; *, p < 0.05). Genotype B–E, w^{1118}.

Fig. 1. GA enhances Hsp70 induction at submaximal heat shock temperatures. Flies were fed placebo or 3 μg/ml GA for 3 days prior to heat shock. A, neither treatment with GA (−, no GA; +, with GA) nor expression of α-synuclein (lane 4; lanes 1–3 are controls) alters Hsp70 induction upon 37 °C heat shock. Genotypes: (lane 1) elav^{GAL4}, (lane 2) w^{118}, (lane 3) w^{1118};UAS-α-syn / +, and (lane 4) elav^{GAL4};UAS-α-syn / +. B, treatment with GA augments Hsp70 induction upon heat shock at submaximal temperatures (30–33 °C). Shown is an immunoblot for stress-induced Hsp70. C, GA treatment does not alter the
(w^{118}, driver line alone (elav^{C115}), and transgene insert alone (w^{118}; UAS-α-syn)) and flies expressing α-synuclein throughout the nervous system (elav^{C115}; UAS-α-syn / +) were fed placebo or 3 μg/ml GA for 48 h prior to heat shock for 15 min at 37 °C. Flies were then flash-frozen, and induced Hsp70 levels were examined by immunoblot of fly heads. Our analysis revealed that GA treatment did not enhance maximal levels of Hsp70 induction compared with placebo-fed flies (Fig. 1A). Given that the maximum stress response appeared unaffected by GA, we therefore examined GA treatment at submaximal stress-inducing temperatures.

Newly eclosed w^{118} flies were fed placebo or GA for 3 days, heat shocked for 15 min at temperature increments between 25 °C (no heat stress) and 37 °C (maximal heat stress), and then analyzed for elevation of stress-induced Hsp70 levels. As above, the maximal heat shock response at 37 °C was unaltered by GA treatment. However, treatment with 3 μg/ml GA consistently enhanced Hsp70 protein levels in flies heat stressed between 30 °C and 33 °C (n = 5, Fig. 1B). At 31 °C, GA treatment resulted in a 50% of maximum induction of Hsp70. In contrast, placebo-treated flies increased Hsp70 levels by only 10% of maximum. These results reveal that GA treatment reduces the temperature threshold for induction of the heat shock response, facilitating Hsp70 expression.

Next we examined whether GA might also prolong the stress response. Newly eclosed w^{118} flies were fed GA or placebo for 48 h and then heat stressed for 15 min at 37 °C or 32 °C. After heat shock, the flies were allowed to recover at 25 °C for up to 4.5 h. Stress-induced Hsp70 levels were measured at 30-min intervals. Upon 37 °C heat shock, we found that GA did not alter the kinetics of the stress response; Hsp70 levels rose and fell comparably in both GA- and placebo-treated flies (Fig. 1C). However, upon heat shock at 32 °C, Hsp70 levels in GA-fed flies increased earlier and rose to higher levels when compared with placebo-fed flies (Fig. 1D). Data pooled from four independent experiments revealed a consistent 2-fold amplification of Hsp70 levels in the early induction phase of the stress response at 32 °C over controls at 30 min (Fig. 1E). Thus, GA treatment enhances the stress response and facilitates the early induction of heat shock protein synthesis at submaximal levels of stress.

Neuroprotection by GA Requires HSF—In Drosophila, the stress response (including activation of Hsp70) is primarily regulated by HSF. Homozygous disruption of hsf gene activity results in developmental arrest (26). However, a temperature-sensitive allele, hsf^{p}, which abrogates HSF activity at elevated (non-permissive) temperatures (≥28 °C) but is functional at permissive temperatures (25 °C, Ref. 26), allowed us to examine whether GA mitigation of α-synuclein toxicity requires hsf function. We confirmed that abolishing HSF activity with the hsf^{p} allele reduces induction of Hsp70 when flies are oxygen-deprived for 5 min (Fig. 2A and Ref. 26). We then generated flies expressing an α-synuclein that were homzygous for the hsf^{p} mutant allele (hsf^{p}/α-syn flies) and asked whether GA was still effective at protecting neurons against α-synuclein toxicity. hsf^{p}/α-syn flies as well as normal α-synuclein-expressing (α-syn) flies were allowed to develop at permissive temperatures on normal medium. Upon eclosion, adult flies were transferred to vials containing GA or placebo and aged 1, 10, and 20 days at non-permissive temperatures for HSF activity, TH immunoreactivity of dopaminergic neurons was then quantified.

In α-syn flies aged at non-permissive temperatures (28 °C), TH immunostaining in the DM clusters progressively degenerated from 18.5 ± 0.5 cells at 1 day to 5.7 ± 0.9 cells at 20 days (Fig. 2B). This result is consistent with previous experiments performed at 25 °C (9, 13). Degeneration at higher temperatures was also suppressed by GA treatment; neuron numbers in the presence of GA were now maintained at 16.0 ± 1.5 cells at 20 days (Fig. 2B). We then performed the same experiment but in the hsf^{p} mutant background. Loss of TH immunoreactivity in placebo-fed hsf^{p}/α-syn flies did not differ statistically from that of α-syn flies. Neuron numbers in the DM clusters decreased from 17.5 ± 2.5 cells at 1 day to 7.3 ± 1.3 cells at 20 days (Fig. 2C). However, in contrast to α-syn flies, GA treatment of hsf^{p}/α-syn flies no longer prevented α-synuclein toxicity (Fig. 2C); rather, neurons continued to degenerate over 20 days to 6.7 ± 0.3 cells. Thus GA requires HSF activity for neuroprotection.

![Fig. 2. GA treatment requires HSF activity for neuroprotection. A, induction of Hsp70 upon O2 deprivation for 5 min in placebo (−) and GA-treated (+) flies. Anoxia induces a stress response in control flies (α-syn), which is considerably decreased in flies bearing the hsf^{p} allele (hsf^{p}/α-syn and Ref. 26). Hemizygous reduction in HSF with the hsf^{p} null allele (hsf^{p}/α-syn) decreased Hsp70 induction in placebo-fed flies, which was compensated by GA treatment. GA treatment did not alter Hsp70 induction in control flies. Genotypes: (α-syn) w^{118}; Ddc-GAL4, UAS-α-syn / +, (hsf^{p}/α-syn) w^{118}; hsf^{p}/Ddc-GAL4, UAS-α-syn / +, and (hsf^{p}/α-syn) w^{118}; hsf^{p}/Ddc-GAL4, UAS-α-syn / +. B, placebo-fed (blue) α-syn flies aged at 28 °C (control for experiments in C) exhibit dopaminergic neuron loss in the DM clusters (percent mean ± S.E.). Neuron loss is prevented by GA treatment (red) (*, p = 0.0013, Student’s t test). Genotype: w^{118}; Ddc-GAL4, UAS-α-syn / +. C, GA treatment fails to protect against α-synuclein toxicity in flies lacking functional HSF. hsf^{p}/α-syn flies were aged at 28 °C, which abrogates HSF activity in the hsf^{p} homzygous mutants (26). Neuron loss in GA-treated hsf^{p}/α-syn flies (red) was not significantly different from that of placebo-fed flies (blue) (p = 0.85, Student’s t test). Genotype: w^{118}; hsf^{p}/Ddc-GAL4, UAS-α-syn / +.]


The Stress Response Modifies α-Synuclein-related Pathology and Solubility—Next we examined placebo- and GA-treated flies for changes in α-synuclein-related pathology. Expression of wild-type or mutant α-synuclein leads to age-dependent accumulation of α-synuclein in LB- and LN-like inclusions (9, 10). Treatment with GA, like transgenic expression of Hsp70 (9), protects neurons despite the continued presence of LB-like inclusions. Between two and four inclusions per fly brain were detectable in both treated and untreated α-SYN flies aged to 20 days (data not shown). Similarly, GA treatment did not alter LN-like deposition in the neuropil adjacent to the DM region of the fly brain (Fig. 3, A and B). However, GA treatment increased LN-like neuritic pathology evident in the optic neuropil (Fig. 3, E and F).

We also examined α-synuclein pathology in hsfsyn/α-SYN flies. Disruption of HSF activity decreased the amount of LN-like pathology in both the DM and optic neuropil (Fig. 3, C and D). Quantification by counting the number of punctate deposits in the DM neuropil revealed an approximate 30% decrease in LN-like pathology in hsfsyn/α-SYN flies. The formation of LB-like inclusions, however, was not affected; 2–4 inclusions were still evident in 20-day-old hsfsyn/α-SYN flies. In contrast, treatment with GA did not increase LN-like pathology in hsfsyn/α-SYN flies (Fig. 3, G and H).

To further examine α-synuclein aggregation, we adopted a serial extraction approach used for study of α-synuclein solubility in human disease (28, 29). In control human brain tissue α-synuclein is normally soluble in high salt buffer, whereas in humans with PD or dementia with Lewy bodies α-synuclein is recovered in high salt/Triton X-100-insoluble fractions (28, 29). Similarly, in mice expressing A53T, α-synuclein accumulates in detergent-insoluble fractions to a greater degree than healthier wild-type α-synuclein mice (7). In light of these findings, we examined whether α-synuclein also accumulates in detergent-insoluble fractions when expressed in the Drosophila brain.

The heads of 20-day-old flies expressing α-synuclein in the brain with the elav<sup>C153</sup> driver were homogenized in high salt buffer, sequentially extracted through buffers of increasing detergent strength by high speed ultracentrifugation, and examined by Western blot. The majority of α-synuclein was found to be high salt or high salt/Triton X-100 soluble with only a trace amount of protein recoverable in the SDS- and urea-soluble fractions (Fig. 4A).

Next we examined whether GA had an effect on the solubility properties of α-synuclein. Flies expressing α-synuclein throughout the brain (with both elav<sup>C153</sup> and Ddc-gal4 drivers) were aged to 20 days at 28 °C on placebo- or GA-treated media and were then subjected to serial extraction. Strikingly, we found an increase in the amount of α-synuclein calcitrant to solubilization in GA-treated flies (Fig. 4A). A similar increase in insoluble α-synuclein was found in flies expressing Hsp70 together with α-synuclein (Fig. 4C). Coexpression of β-galactosidase, which does not suppress α-synuclein toxicity (9), did not alter α-synuclein solubility (Fig. 4D). Intriguingly, abrogation of HSF activity with the hsfsyn<sup>w</sup> allele only partially prevented GA from increasing the amount of insoluble α-synuclein present; in these flies, insoluble α-synuclein accumulated to a slightly lesser degree than in HSF intact flies (Fig. 4B) although changes in LN-like pathology were minimal (Fig. 3, D and H). Taken together, these data demonstrate a dissociation between α-synuclein aggregation and neurotoxicity, whereby conditions that protect cells from α-synuclein toxicity are associated with an increase in insoluble α-synuclein. These data are consistent with the idea that inclusions may play a protective role.

Other Pathways Augmented by GA Do Not Significantly Alter α-Synuclein Toxicity—Our studies demonstrate that GA acts through modulation of the stress response to protect neurons in Drosophila; however it remained possible that additional pathways regulated by Hsp90 might also modify the toxicity of α-synuclein. GA (through its inhibitory activity on Hsp90) may decrease the activity of Ras and ecdysone pathways (15). Given the importance of Ras signaling and steroid hormone receptors in the regulation of cell survival, we examined whether GA may also protect neurons through inhibition of these pathways.

We coexpressed a number of transgenes altering different aspects of the Ras and ecdysone pathways and found that neither inhibition of Ras activity nor a decrease in hormone signaling leads to significant suppression of α-synuclein toxic-
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Although our studies demonstrated that GA acts through the stress response to protect neurons, it remained possible that additional pathways regulated by Hsp90 (and therefore affected by GA treatment) might also modify α-synuclein toxicity. Our experiments here demonstrate that neither decreased Ras activity nor decreased ecysdine (steroid hormone) signaling contributes toward cell survival, although we did find that increased Ras activity protects against α-synuclein toxicity, which is opposite of the known effects of GA on the Ras pathway. Although GA-mediated changes in Ras activity likely do not contribute toward the neuroprotective activity of GA, our studies suggest that manipulation of the Raf/mitogen-activated protein kinase pathway modifies α-synuclein toxicity, consistent with evidence suggesting that α-synuclein may be phosphorylated (30, 31).

That GA-mediated enhancement of chaperone activity and Hsp70 overexpression both suppress α-synuclein neurotoxicity suggests that elevated chaperone levels may be associated with alteration of α-synuclein solubility. α-Synuclein has been shown to polymerize and form β-pleated sheet amyloid conformations under disease-related conditions (32, 33) and to deposit in LBs, LNs, and glial cytoplasmic inclusions in disease brains (4, 5). Flies similarly develop LB- and LN-like inclusions (9, 10). However, we found that these LB-like inclusions persist under conditions that elevate Hsp70 levels, and LN-like pathology even increases in response to GA treatment. In contrast, inhibition of HSF activity reduces the LN-like pathologic burden found in the brains of aged α-synuclein-expressing flies. Using a serial extraction protein solubility assay, we found that treatment with GA and Hsp70 overexpression are both associated with increased amounts of insoluble α-synuclein. In effect, we found a discordance between α-synuclein solubility and toxicity; under chaperone-associated neuroprotection, dopaminergic neurons are unaffected by α-synuclein toxicity despite the continued presence of LB- and LN-like deposits and an overall increase the insoluble α-synuclein component. We previously noted that LB-like aggregates form preferentially in the DL-1 and DL-2 neuronal clusters (9), which are resistant to α-synuclein toxicity. These data are inconsistent with hypotheses that the large protein aggregates are toxic, and rather support the idea that in PD and other LB-related diseases protein inclusions may be unrelated or protective with Hsp70 acting to shuttle toxic forms of α-synuclein into inclusions. Recent cell culture data from studies on toxic polyglutamine protein of Huntington’s disease lend support to our results in that neurons that developed disease-related inclusion bodies exhibited enhanced survival compared with those neurons which did not form inclusions (34). Moreover, Hsp70 transiently associates with such inclusion bodies in cells in culture, potentially assisting their formation (35). In a cell culture α-synuclein model, GA pretreatment decreases the formation of α-synuclein inclusions (36) and decreases basal levels of α-synuclein suggesting that in this in vitro model GA neither decreases the expression of α-synuclein or increases its turnover through enhanced degradation. Although we see no gross changes in α-synuclein levels, we cannot discount the possibility that GA and Hsp70 may also be affecting precursor protofibrillar or other forms of α-synuclein through the mobilization of the ubiquitin proteasome (37, 38) or lysosomal (39) degradation pathways. Indeed, the multipotent ability of chaperones to decrease levels of toxic α-synuclein species, shuttle and maintain the protein into inclusion bodies, and/or maintain the protein in non-toxic conformations should all have the same outcome of preventing neurodegeneration.
The importance of chaperone pathways in PD has recently come under careful scrutiny with the following observations: elevated chaperone activity suppresses toxic effects of α-synuclein in Drosophila (9, 13) and transgenic mice (12), chaperones colocalize to LBs in PD and other related human neurodegenerative diseases (9, 40), proteomic studies in PD have shown significant alterations in chaperone activity and a direct interaction between Hsp70 and α-synuclein (41), and polymorphisms that compromise activation of Hsp70 are more frequent in PD patients than in normal controls (42). Here, we have used an in vivo model for PD to study the neuroprotective activity of GA. Our findings demonstrate that GA is a potent enhancer of the stress response, elevating Hsp70 levels only in the presence of exogenous stressors. GA and other similar agents hold promise as a novel therapeutic, neuroprotective agent for PD and related disorders.

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