methionine, phenylalanine, and tyrosine. It inactivates the membrane function and key enzymes (see reviews 7, 10). As shown in Fig. 1, 3-nitrotyrosine (3-NT) is synthesized by the nitration of tyrosine residues in protein and a marker for the oxidative stress induced by peroxynitrite in vivo (11). 3-Nitrotyrosine containing protein (3-NT protein) was detected in atherosclerosis (12) and neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS) (7), AD, (13,14), and PD (15). Figure 2 shows the immuno-histochemical detection of 3-NT protein in pyramidal hippocampal neurons, using anti-3-NT protein antibody (16). Another oxidation product of tyrosine is dityrosine, which is produced from free and protein-bound tyrosine in the presence of hydrogen peroxide

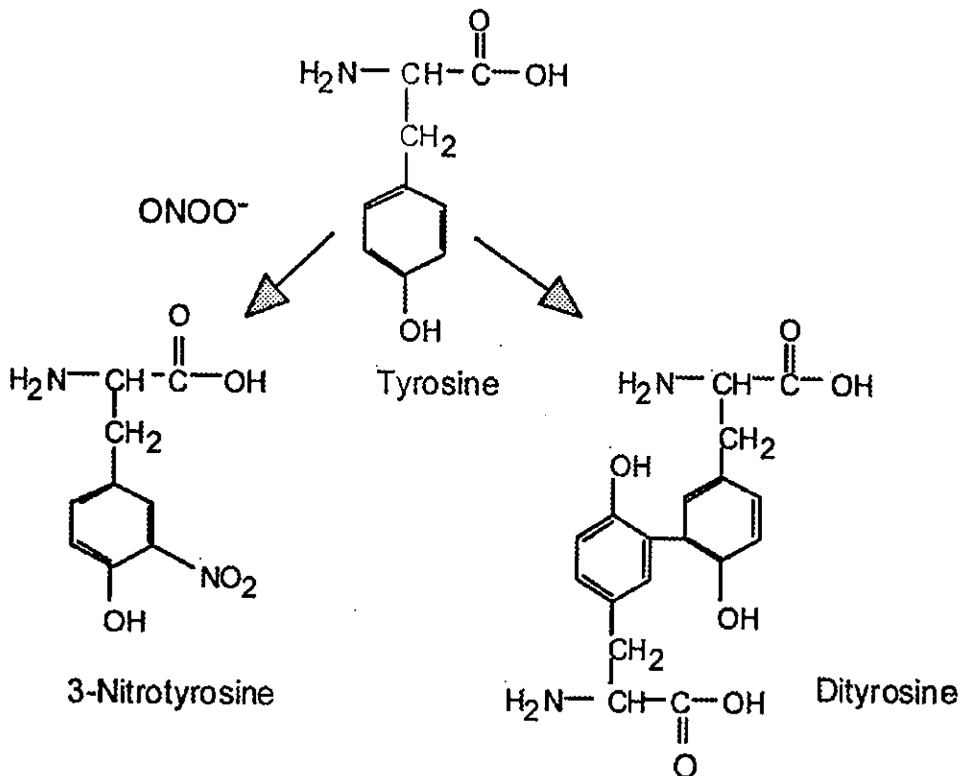


**Figure 1** Modification of tyrosine residue in protein by NOS and RNS. Peroxynitrite modifies tyrosine residues to 3-nitrotyrosine in protein, and hydrogen peroxide and peroxidase, and irradiation produces tyrosyl radicals, yielding dityrosine with tyrosine residues in protein or free tyrosine.

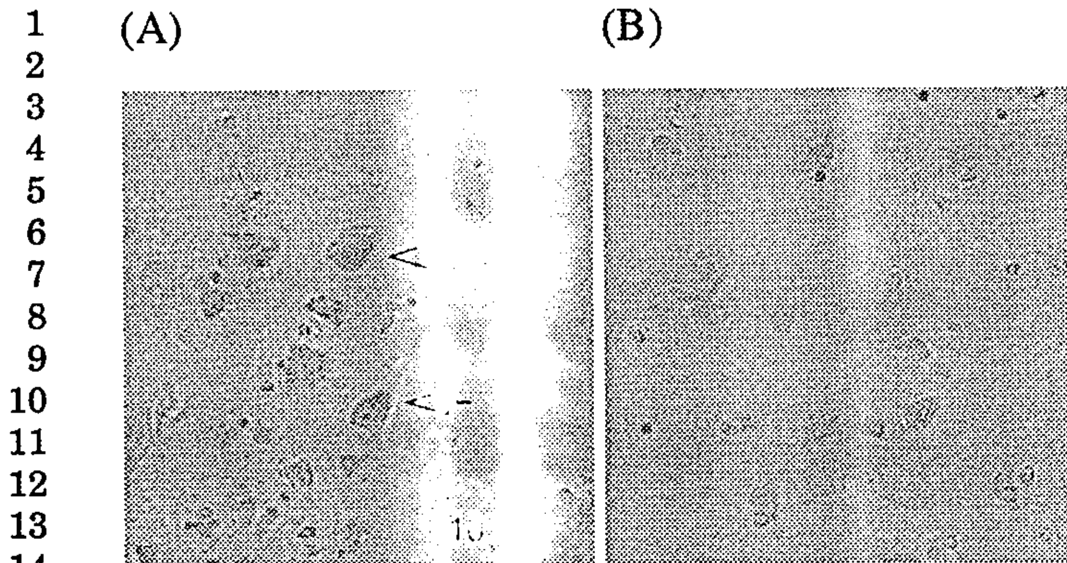


**Figure 2** Immun his emical detection of 3-NT-containing protein in lipofuscin in p midal hippocampal neurons. The brain was obtained from a72-y -old male patient without neurological or psychiatric disorders. e tissue samples were incubated with (A) anti-3-NT protei an ody (diluted 1:200 with bovine serum albumin) or (B) bovine se m albumin alone, followed by the treatment of peroxidase-labele ntirabbit IgG. Lipofuscin stained was observed as brown granu as indicated by arrows.

and myeloperoxidase ( ) (Fig. 1), and is detected in atherosclerotic plaques (18) d lipofuscin pigments in the aged human brain (19).

On the other hand ipid peroxidation generates various reactive aldehydes, incl ling 4-hydroxynonenal (4-HNE) and acrolein as shown in F g. 3 (20). 4-Hydroxynonenal reacts with sulfhydryl and a no groups and leads to inactivation of DNA polymerases, ehydrogenases, and various transporters, and also to ce cycle arrest and apoptosis. Proteins modified with 4-HNE ad malondialdehyde were detected in nigro-striatal dopam ne neurons in PD (21), neurofibral tangles in AD (22,23), nd the spinal cord of ALS patients (24). Acrolein, $CH_2$=C -CHO, is ubiquitously generated in the biological system a is the most reactive $\alpha,\beta$-unsaturated aldehyde product of l id peroxidation. It is incorporated into proteins easily a d accumulates as protein adducts

F3

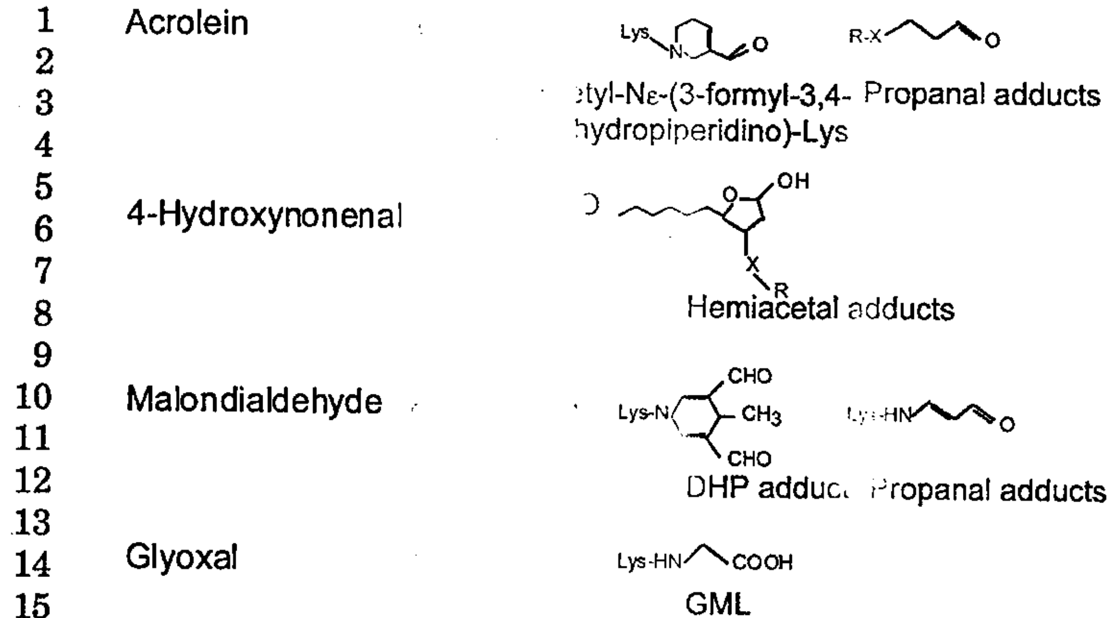


**Figure 3** Modific... ...otein by aldehyde products of lipid peroxidation. Aldeh... ...s of lipid and carbohydrate peroxidation, acrolein, 4-hyd... ...l, malondialdehyde, and glycol, modify lysine residues i...

after reacting wit... ...nd histidine residues by forming Michaelis-type a... ...ino acid complexes (25). Acrolein-modified pro... ...detected in oxidized low-density lipoproteins (26) a... ...ain of patients with AD (27). Figure 4 shows the hi... ...al staining of the substantia nigra in a parkinsonia... ...ith an antibody against 4-HNE-modified protein. ... ...e neurons containing neuromelanin from parkinso... ...ients were stained more markedly than those in no... ...trol and nondopaminergic cells. These results indic... ...t the oxidative stress increases markedly in nigro-s... dopamine neurons of a parkinsonian brain.

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## II. MITOCHOND... ...MPLEX I SUBUNITS ARE NITRATED B... ...O⁻

In the brain, NO h... ...onsidered to be produced in microglia and astrocytes ... ...ransported to neurons, where it

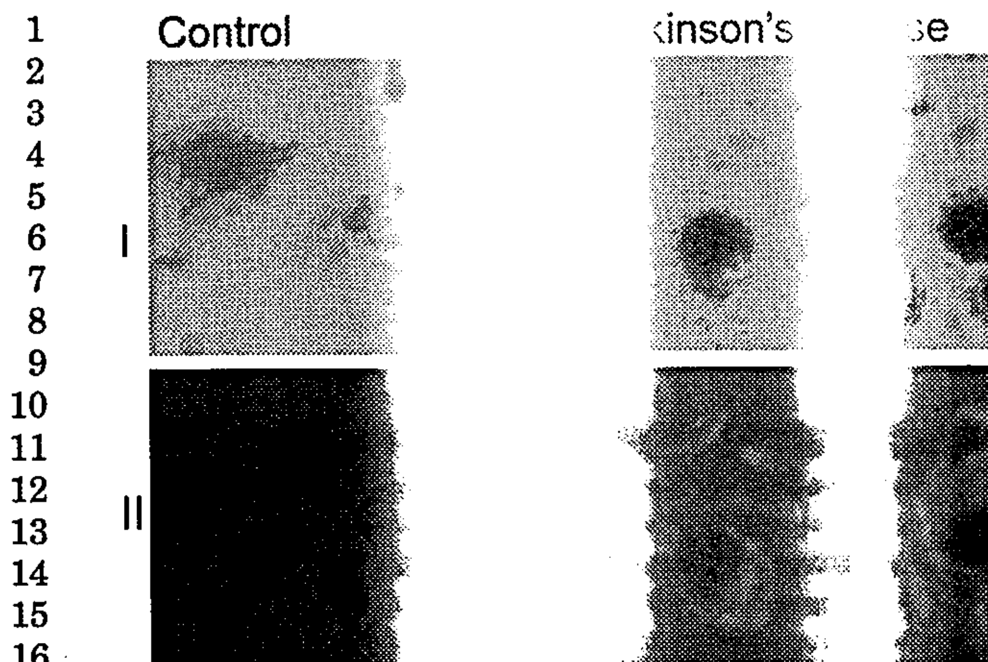


**Figure 4** Occurr... ...E-modified pr... in in dopamine neurons in substan... ...igr... ...brain from th... ...atient with Parkinson's disease. O... ...antia nigra of t... brain from the parkinsonian patie... ...eurons contain...g neuromelanin are positively sta... ...body again... HNE modified protein. In control, ...cells other than ...pamine neurons are not stained wit... ...dy.

reacts with the s... ...roxi... ...lding $ONOO^-$. However, SH-SY5Y cells produ... ...$ONOO^-$ in situ, ...s confirmed by the use of 2′,7′-dicl... ...fluorescein dia... ...te ($H_2DCFDA$) (28) and inhibitors ...ide synthase (N... ...S); $H_2DCFDA$ is cleaved into 2′,7′-... ...orescein by hyd...xyl radical and $ONOO^-$; and NO... ...hib... ..., $N^5$-(l-iminoet...yl) -L-ornithine (L-NIO) and $N^5$-... ...o-L-... ...nine methyl e...ter (L-NAME), reduced DCF to a... ...f.

Using an ant... ...st the 3-NT pro... ...n (16), nitrated proteins were dete... ...human dopaminergic SH-SY5Y cells. The lysate from th... ...el... was subjected to western blot analysis as shown in Fig... ..., a... ...he molecular weight of major 3-NT proteins was esti... ...ted ... be 33, 21, 15, and 11 kDa. The nitrated protein ... ...detected even in control under physiological cond... ...uggesting that the cells were under

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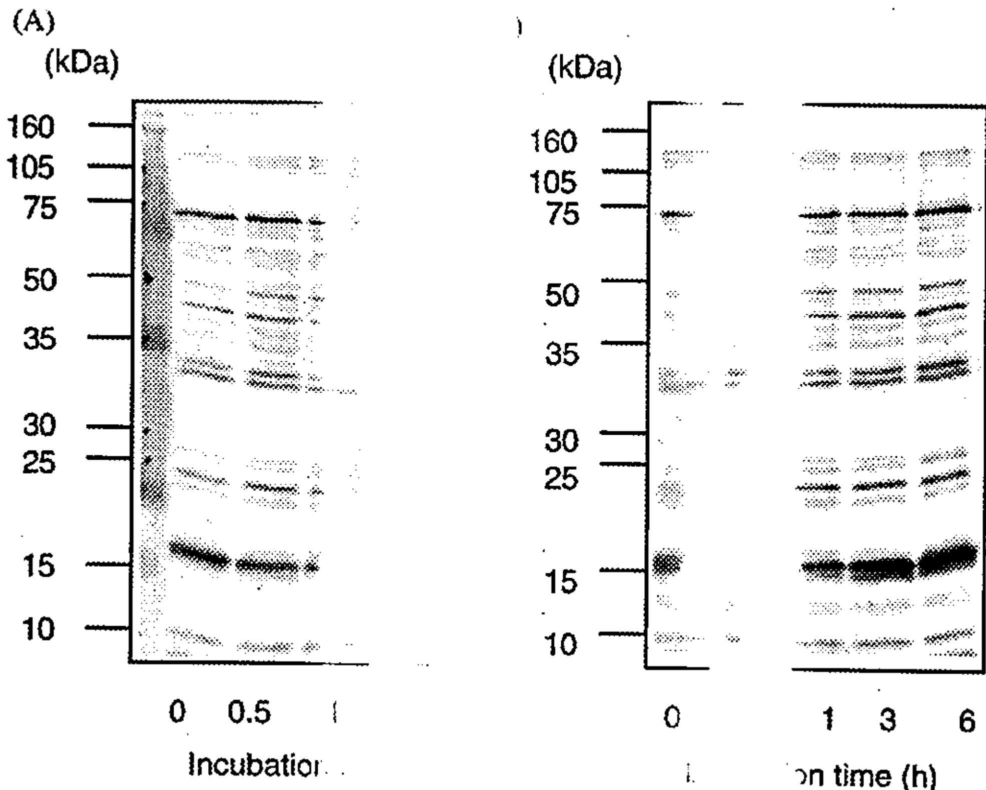


20 **Figure 5** Formatio... ...tein in SI... cells and the
21 effects of peroxynitri... SIN-1 and a pr... ...asome inhibi-
22 tor, PSI. (A) Cells were t... ...h 250 μM of ..., then applied
23 to the immunoblotting w... ...dy against ... ...roteins. After
24 the treatment with SIN-1 ...nsity of 3-N... ...ins increased,
25 but the number did ... ...arkedly. A... ...ft lane in A,
26 the molecular marke... (B) The cel... ...treated with
27 SIN-1 (250 μM) in the ...oteasome in...ib... PSI (10 μM).
28 3-Nitrotyrosine prote... ...d in amount ...rding to the
29 incubation time.

30
31

32 constant oxidative ... ...ever, the ... ...re intact in
33 growth and prolife... ...esting the ... ...oning of an
34 active mechanism t... ...in ...odified prot... ...rom the cells.
35 The mitochondrial frac... ...e SH-SY5Y ... was the one
36 most intensively ...ta... ...h the a... ...T antibody,
37 and wassubjected t... ...lot analysi... ...g antibodies
38 against 3-NT protei... ...st mitocho... ...complex I, II,
39 III, and IV (29). Son... ...rated protei... ...ere identified

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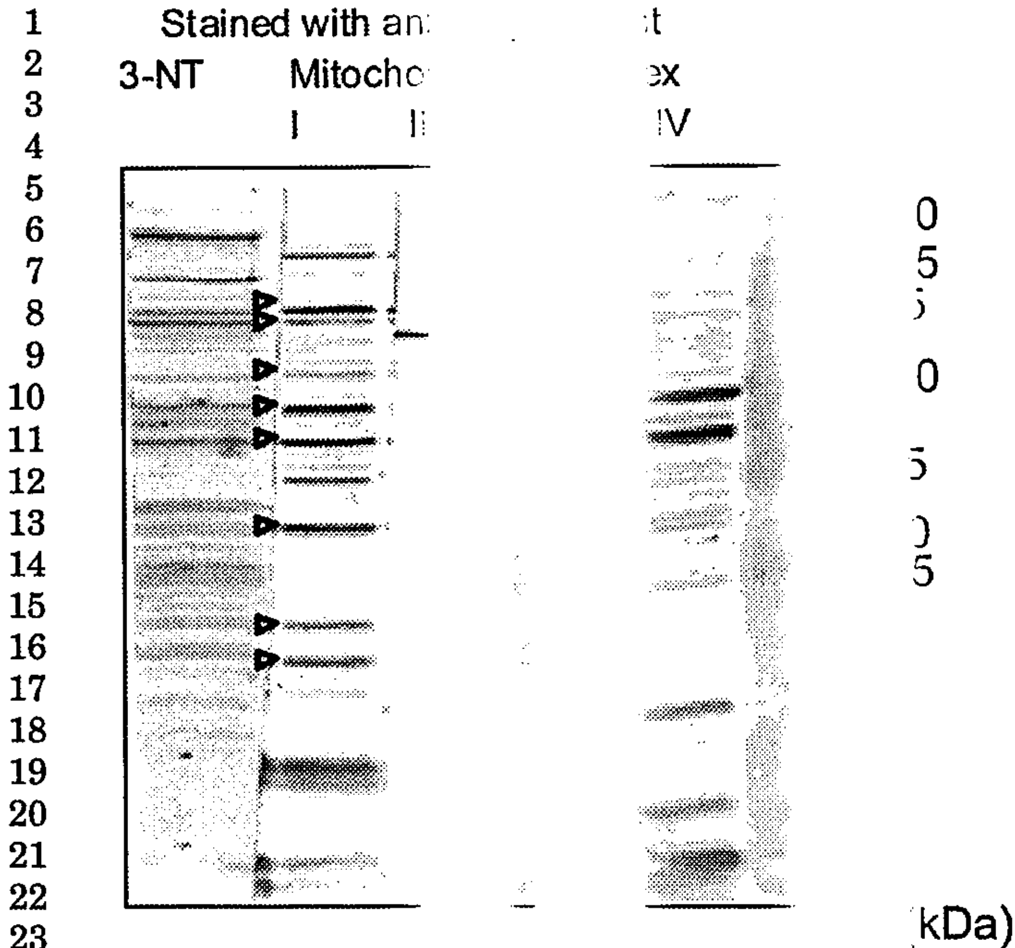


24 25 26 27 28 29 30 31 32

**Figure 6** Detectio teins in dria complex I–IV subunits. The ted with 2 IN-1 for 1 hr, and P2 fraction was samples w ected to SDS-PAGE and detected oblot ass the antibody against 3-NT (samp x I (I), co (II), complex III (III), and comple ectively. M markers are shown in the right s show th n bands positively stained with an anticomple body.

33 34 35 36 37 38 39

to be the subunits s assigne on the staining with anticompl an (Fig. 6). esults clearly show that the pre ration of x I subunits may contribute to n l dysfunct erved in the nigro-striatum of pa brain (30,3

Treatment of O rating *N*-r lino sydnonimine (SIN-1) induc in the SH ells (32–35).

F6

A step-wise activ otic cas as observed: decline in $\Delta\Psi$m, a pase 3, sphorylation of p38 mitogen-a okinase ) (33). Nitric oxide and $ONOO^-$ to induc osis by nitration of tyrosine resi e cytochr 36), or of cytochrome *c* itself (37). mitochoı TP synthesis was inhibited marke N $O^-$, as sh Fig. 7, which may be due to its ng to cy ne oxidase or inactivation of co and ATP 5–41).

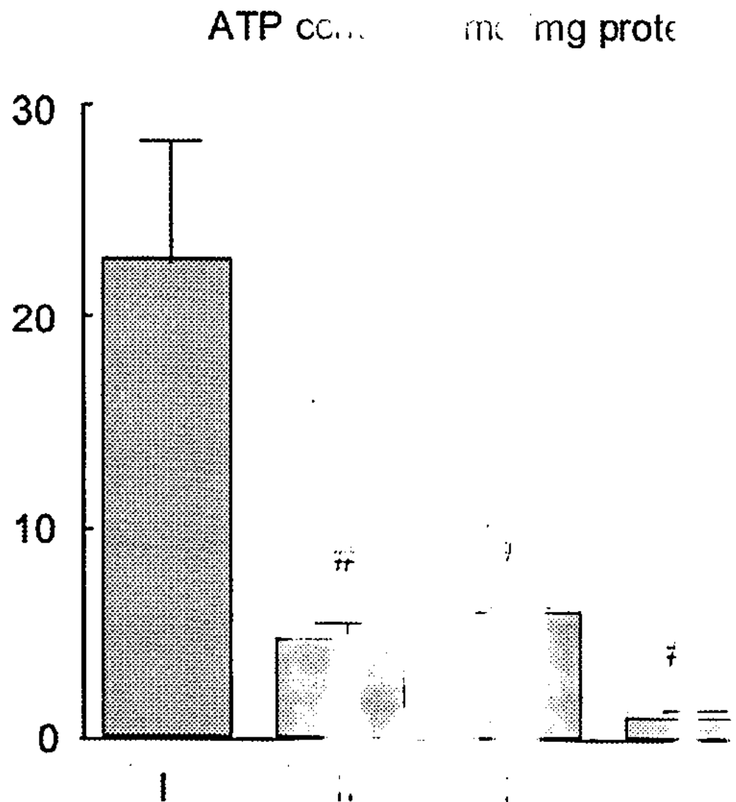


**Figure 7** Effect of SIN P on the A s in SH-SY5Y cells. The cells were hout or μM SIN-1 in the absence and presence of PSI for ATP content was measured by the lumino metric method e column and bar represent the mea riplicate nents of three independent experimen nt. l cells; II, ated with PSI alone; III, SIN-1 alone; V, N-1 and fference from control (I) is statistical t ($p < 0.$ ). fference from SIN-1 alone (III) is st nificant (

As shown i ... treat ... reased 3-NT protein only in ... ds, ... g the preference of some pr ... modi ... In addition, increase in the a ... in w ... significant.

## III. PROTEASO... ACCUMULA... D PR...

Insoluble intrac... ggreg... ch as Lewy body in PD and ... compo... β-amyloid in AD, are hallmark... ration. ... h it remains unclear whether ... tes ca... tly neuronal cell death or are ... eterior... llular homeostasis in dying ... lysis of ... nstituents of inclusion bodies ... molecu... hanism leading their formation ... gation ... nifestation of disturbed cellular ... homeo... aintained by the ubiquitin–prot... In LB, ... uitin, and proteasome, subunits ... components (...,43), in addition to α-synuclein, P... ubiquitin C-t... al hydrolase-L1 (UCH-1) (41–4 ... modified ... ROS–RNS as nitrated synuclein ... osine (4...

To clarify ... among ... idative stress, dysfunction of the proteasome system, and formation of the inclusion body, the effects of a proteasome inhibitor, carbobenzoxy-L-isoleu... butyl-L-alanyl-L-... al (PSI) were examined on the ... odified ... s and the cell vulnerability (34,... SI ... ased th... amount of 3-NT proteins in the SH-... cells, but the number of 3-NT protein bands was almost the same as in the control (Fig. 5B). The functional deterioration of mitochondria was also enhanced by PSI, as shown by the se... reduction of ATP synthesis (Fig. 7). In addition, the numb... po... cells inc... d significantly by PSI, whereas that of necrotic cells remained almost the same (Fig. 8A). At the same time, the acrolein-modified protein increased significantly in subcellular fractions of the SH-SY5Y cells after being treated with PSI (Fig. 8B). These results clearly demonstrat... that the inhibition of proteasome activity

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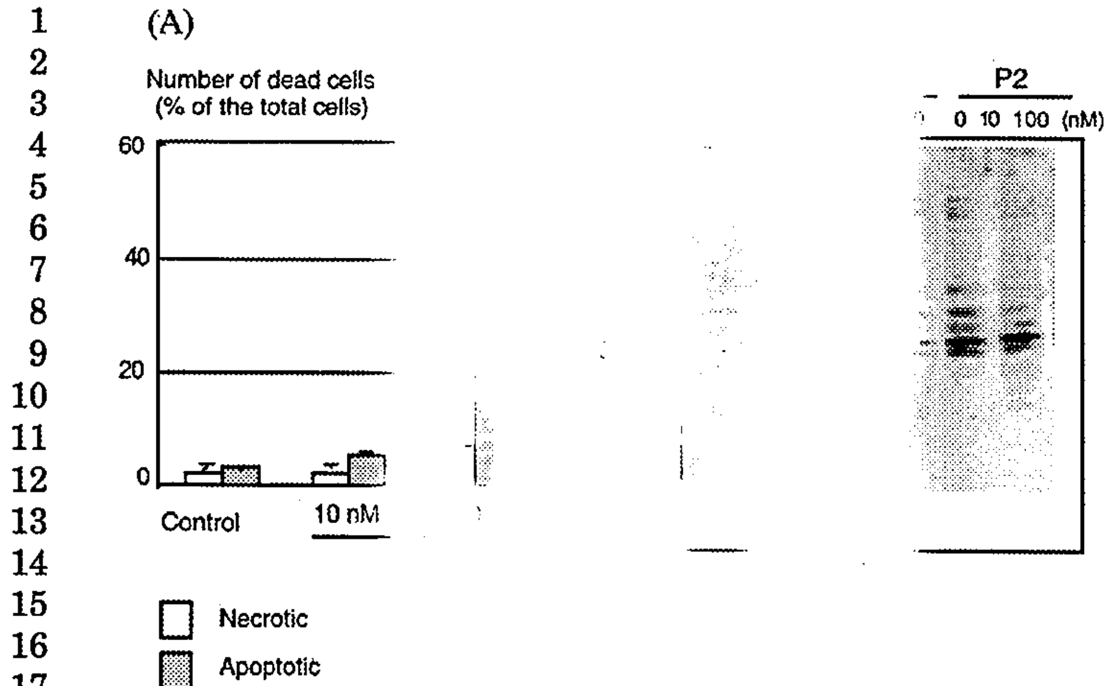


18 **Figure 8** Effect ... ath ... ls of acrolein-
19 modified protein. ( ) ... ecrot ... h after treat-
20 ment with 10 and ... antii ... ing the cells
21 with 10 nM Hoech ... represent the
22 mean and SD of t ... ells, ... as the percen-
23 tage of the total. T ... ed c ... esent necrotic
24 and apoptotic dead ... The from the con-
25 trol cells is signific ... (p ... NOVA ... effects of PSI
26 on the level of acrolei ... ins w ... ned by immu-
27 noblot with antiacrole ... y. ... e cyto ... yt) P1 and P2
28 fractions of the ce ... ea ... ith ... and ... PSI for 24 hr
29 were prepared by c ... ifu ... 0 g a ... , respectively.

30 may play a key ro ... a t ... iation ... ion-modified
31 protein and neuron ... d
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34 IV. MITOCHONDRIAL ... TION
35 INHIBITS TH ... RO ... SYSTE
36 BY OXIDATI ... MC ... N
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38 Systemic reduction ... x the ... rial electron
39 transfer chains was ... ep ... in ... e nigr ... m of patients

with PD (30,3l inhi lex I, rote-
none, was rep ki dents, and
fibrillar cytop con uitin and
α-synuclein we he dministra-
tion (52). The c rial on the pro-
teasome syste the enone at a
concentration t in t Y cells (50).
ATP levels red d a induced in
the cells after wi The oxida-
tive modificati follo use of anti-
body against t d pr he levels of
the acrolein-m ase by rotenone
treatment (Fig. F9
The ubiq syste jor site to
remove damag ins latory pro-
teins controllin signa ion. In the
nigro-striatum n bra eased activ-
ity of the prot ted, its involve-
ment in the pa (53 zed protein
is preferentiall ro by some in an
ATP-independ teason sed of four
rings to make cture, ing is made
of seven α and β 4). No -heptameric
rings form each rings ytic β-hepta-
mers form the t indin latory subu-
nit named 19S e, PA7 ends of the
20S cylinder pr easome er catalytic
activity than th me. Th easome can
degrade polyubi eins an decarboxy-
lase in an ATP- s.
In the SH-S one tre eased ROS–
RNS levels on y and whereas the
oxidized protein progre gesting that
degradation of eins ma nly involved
inthe deposition. c activ easome mea-
sured with an a ent sul bobenzoxy-L-
leucyl-L-leucyl-L- -(4-met yl-7-amide)
(Z-Leu-Leu-Glu- in a ti e-dependent
way, and virtual cted afte atment with

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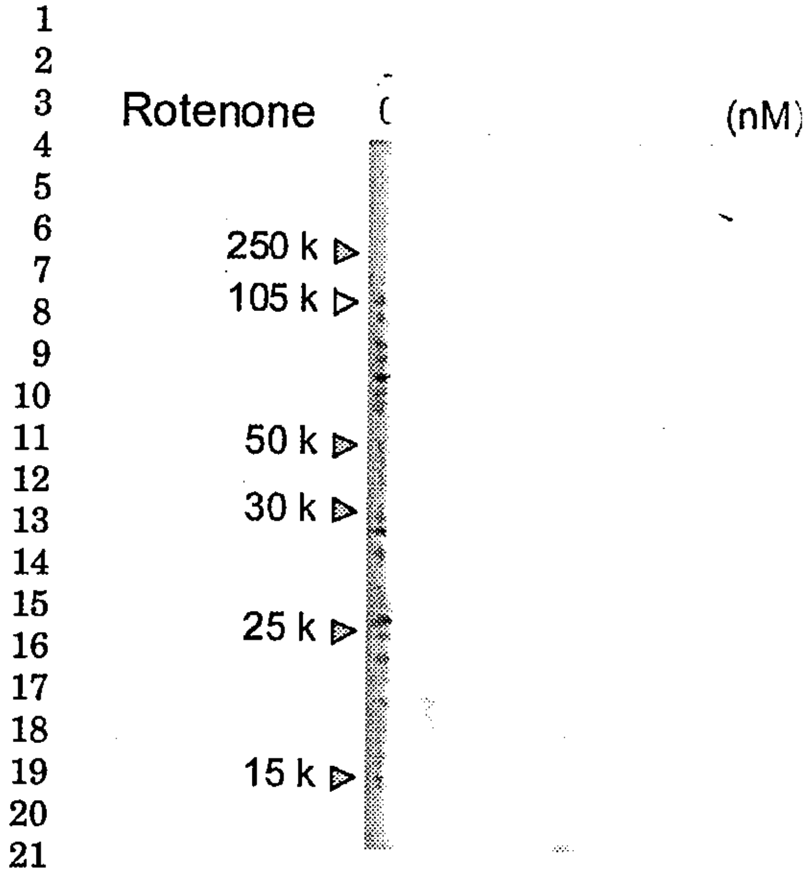


22 **Figure 9** Effect d pro in SH-SY5Y
23 cells. The cells we with otenone for
24 5 days. The cells the ic (Cyt), P1
25 and P2 fractions, sul mmunoblot-
26 ting, using antibo ifie . The aggre-
27 gated proteins we king P1 fraction
28 (arrow).
29

30 rotenone, as sho uc enzymatic T2
31 activity was neit n eduction of
32 the protein leve hon activity of
33 proteasome decr t. Ir 20S β sub-
34 unit protein was as s mmunopre-
35 cipitation with a by ot analysis
36 with the antiacr in cipitant co-
37 precipitated witl d p munoreac-
38 tive to antiacrol cte ells treated
39 with rotenone, s th olei ated protein

**Table 2** Effects c ... an ... ıtic Activity of Proteasome in S

| Rotenone (25 nM) | ATI | ... som... tre... nol... | SH-SY5Y ... tenone ... tein) ... er 96 hr |
|---|---|---|---|
| Control | – | ı1* | 19 ± 0.47 |
| | + | )2 | .21 ± 0.11 |
| Sample | – | .2 | .96 ± 0.04 |
| | + | .02 | 30 0.13 |

Proteasome activity i ... of th ... d with 25 nM rotenone was measur ... ence ... of exogenously added ATP (2 mM).
*Mean ± SD of four e...

may be a substrat ... 20S ... . How ... ther studies are required to c ... acrol ... ied protein can directly inhi ... ity, ... case of the 4-HNE proteins ( ... n ac ... ducts after rotenone treatm ... le w ... observed in the presence of P... as de ... ier.

## V. CONCLUSIO...

The results of th... udy ... t mit ... al dysfunction may induce d... gener ... pamir ... ns through modification and ... prot ... system and subsequent aggr ... zed p ... The precise mechanism behi ... duce ... ative stress requires further ... it ma ... te relevant to consider that the inac ... prot ... may play a critical role in the activa ... ptotic ... In neurodegenerative disor ... th ... e ... ental ... etic factors may induce a n ... a ... ween ... it ... ndrial dysfunction, increas ... , and ... activity of proteasome in neu..., ... the ... pathological

X:



1 characteristics, c ... sion body.
2 Our recent studi ... system in
3 the substantia nig ... er support
4 to our hypothesis. ... 0S $\beta$ subu-
5 nit precipitated w ... dified with
6 acrolein, whereas ... ied. Future
7 studies may give ... n of neuro-
8 nal cell death in a ... d may give
9 us clues for a ne ... ct neurons
10 from apoptosis.
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13 **ACKNOWLEDGE**
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15 This work was s ... Scientific
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17 Promotion of Scie ... l Research
18 for Evidence Bas ... from the
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# Neuroprotection by Rasagiline and Related Propargylamines is Mediated by Suppression of Mitochondrial Death Signal and Induction of Antiapoptotic Genes

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## ABSTRACT

In neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases, apoptosis is a major type of neuronal cell death, and the apoptotic cascade has been proposed to be a target of "neuroprotection" through preventing and delaying cell death. A series of propargylamine derivatives have been confirmed to protect neurons against cell death induced by various insults. The mechanism underlying the neuroprotection has been clarified by use of rasagiline [*N*-propargyl-1(*R*) aminoindan], the most potent propargylamine, and human dopaminergic neuroblastoma SH-SY5Y cells. Rasagiline stabilizes the mitochondrial membrane potential, $\Delta\Psi_m$, prevents permeability transition, and suppresses the activation of following apoptotic signal transduction; release of cytochrome *c*, activation of caspase 3, nuclear translocation of glyceraldehydes-3-phosphate dehydrogenase (GAPDH) and fragmentation of nuclear DNA. In addition, rasagiline induces antiapoptotic Bcl-2 and glial cell-line-derived neurotrophic factor (GDNF) in SH-SY5Y cells. In this review, we summarize our recent advances in understanding the mechanism behind the neuroprotection by rasagiline. Rasagiline was found to activate NF-$\kappa$B, a nuclear transcription factor playing a critical role in determining cell death/survival pathway. Rasagiline activated I$\kappa$B kinase, and active NF-$\kappa$B p65 subunit was translocated into nuclei. In addition, gene array analysis revealed that rasagiline increased the expression of the genes coding mitochondrial energy synthesis, apoptosis, transcription, kinases, and ubiquitin–proteasome system, the involvement of which has been proposed in neuronal cell death and accumulation of inclusion bodies in various neurodegenerative disorders. These results are discussed in concern to possibility of neuroprotection by propargylamines in Parkinson's and Alzheimer's diseases.