4-Hydroxy-2-Nonenal, a Reactive Product of Lipid Peroxidation, and Neurodegenerative Diseases: A Toxic Combination Illuminated by Redox Proteomics Studies

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Abstract

Significance: A

. A , 4- , -2- ( ) ,

. Recent Advances:

. Critical Issues:

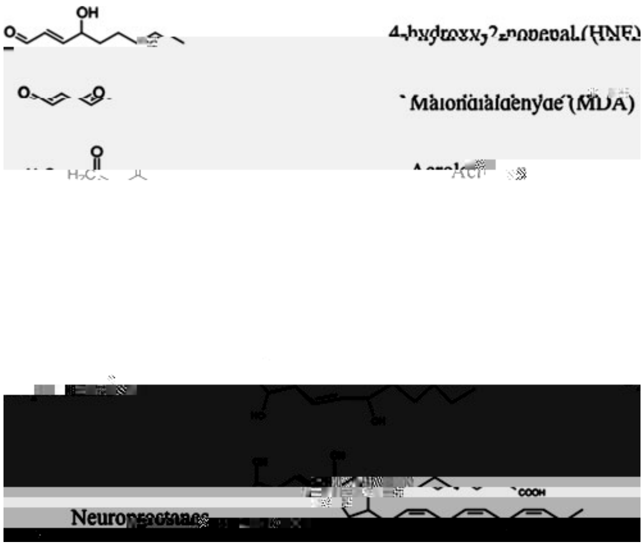

FIG. 1. Products of lipid peroxidation. A, ; , 4- , -2- - ; ; 13- , 3- , -9 ,11 - ; $_2$-

$_4$- ($_4$-) (A). , $_2$- $_4$- (170). A , A . A A , (AA) A . , C (-C $_2$-) (86, 155). (9, 213). (71). (32, 72, 194). C

(32).

Lipid Peroxidation: vlog and Products

(. 2). 1 ($_2$ $_2$ $_2$ $_2$$^-$) A , 2, 3, A, A (69). 4, 5, B C (21, 56). (α-) 1, α- (5) C ( ) ( ). C et al. (40) 1983 -1,

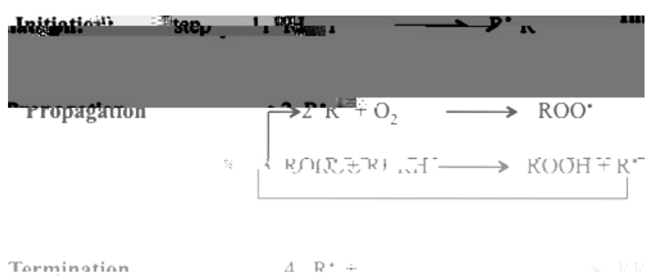

FIG. 2. Mechanism of lipid peroxidation (five steps).

(189, 204).

(2, 164).

HNE

α,β-
ω-6 A
AA (. 3). A

(161).

AA
A - (68).

A .
A
(182).
β-
A .
. A
C 9-
.
C ,
(195,
202).

(70).
10 μ 5

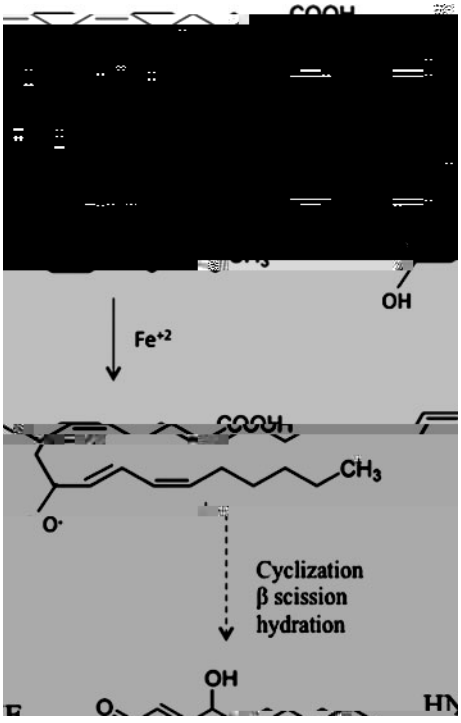

FIG. 3. Formation of HNE by arachidonic acid (AA).

B (-κB) (211). -κB

C 2+, +/ +A
(70).

(146).
/

(129).

Reaction of HNE with proteins: biological consequences

(156).
C=C C
3.
4 (. 4).
3 1
(155). B
. A
(195). A 1
(50)
(195).
(46).
C
(46).
A
(39).
1% 8%
(101, 119).
C (. 5).
( ) (2)
A
C
C > .
C

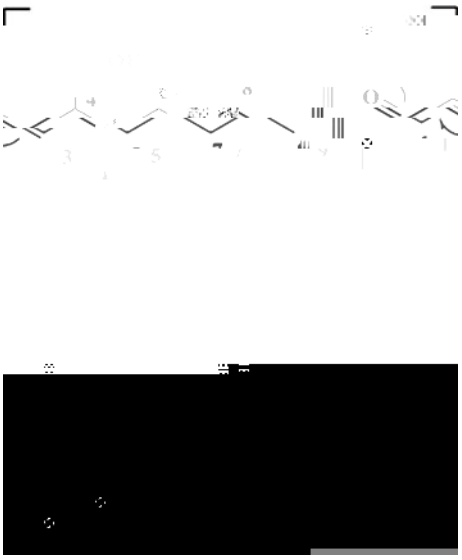

FIG. 4. The first step of Michael addition. C-3 C-4 -
(‡). A
C-3 C-2
C-3.
C-3

(60).
; -
; -
; ; ;
(152, 155).
-
-

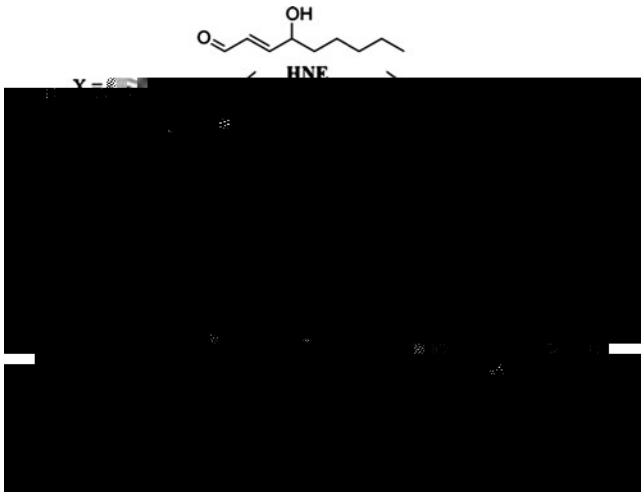

FIG. 5. Michael addition reaction between HNE and Lys, Hys, and Cys.

. B ,
-
-
/
(156).
-
(A*β*), ( ),
. , A*β* -
.
A*β*(1 40) 1,4- A*β*
A*β* (187). , A
A*β*, -1,
(144).
C
C .
A - ( ), -
(-1).
-
(*β*- -)
(84).
; (3) -
.

Lipid Peroxidation and Neurodegenerative Disorders: A Redox Proteomics Overview

-
(32, 168).
A
-
(130),
-
A ,
A .
(32, 168).
. B
-
.

A ,

/ -

Redox proteomics

1995 (209),

B

(44, 50),

( ) (50).

, 3-

(50).

B

Amyotrophic Lateral Sclerosis

(49). C

2 5

( ), 5% 10%

( ) C /

(1),

. A

. C

100 1

(7)

1 85 , 1 37 , 1 93A. 1-

1 (73). 1

(49, 203),

C / (20),

( )

(20, 115).

1 (165).

1

93A

(116, 117).

1

93A- 1

(158).

1

(24),

1.

1, , C /

1

1

1 (24). A

post mortem

(17).

(183)

(72) 3-

1

(1).

(184). A

(190) C

A (8, 72,

73, 117).

, 93A- 1 ,

-2 (C -2),

( )70, α- (1)

(148). C -2

( ) , - (82). C -2 - ( ) A , C -2 (214). C -2 , , , C -2 , . - C -2 93A- 1 , - , Å (87). (157), 1 70, 40, α- (186). , , (41). 1- , Å , - C70 (207). , , , 70 , - 93A- 1 , (29). , -Å , (105), , 70 1 . 1 , 70, . , - , , , , 1.

Alzheimer Disease

A , , (, , ,) (, , ,) (162). A A post mortem - : , - . Aβ, 40 42 , , (A) - - - . , , , , (64, 83).

A : (C), - A (A), - A (A). , , , -

1. - 93A- 1

Protein	Function
A	/
C , -2	
α-	

C , , A (CA). A , , - . B ( ) ; B (, A). CA A , (208). B post mortem (208). CA , , , . , - CA (4) CA C , , C , CA (5). C , - , A . C - A , A , C . C C ( ) - , ( ) , ( ) . C (-) C C (65, 153). B C , , . , C , , , , ( ) (54), A , (61). C A 10% 15% , (173); , C (153). A , C A , , , . B . A , , A , . A C (126), - , - , CA , A . A , , , , , . B , , - , , , . A - , , , Aβ , , - (179). A , , , , - . , , , , ,

A

.

A

.

Protein-bound HNE: from MCI to late stage AD

C
(38, 103, 210).

2− 4−

(159). A A

. B

A -

-

Aβ

(125). ,

A

(120). B -

C A (210).

- C , A ,

A , -

CA .

C A ;

( ) ( ).

A .

-

A

.

B

A

.

(C , A , A) ; ,

(A A); -

. B

C

" ; i.e.,

, A -

.

A .

et al. (132),

A .

A 2 -

A : A α-

. , 2 C -2

- A A .

Energy dysfunction: ATP synthase and α-enolase

A 5%

, 30%

A

. ,

;

(91, 131).

A (94, 166).

A .

A : A

α- .

A

. A

-

(α, β) , A .

A

-

(197). A -

(C) , A , , -

-

A (200). A

C

A (12). , -

α- 2-, , -

, 10- , -

A . α- -

A A (36).

-

C (167), A (169),

A (150). A

. B

, ,

-

A . A

,

(Aβ)

/ - (36).

α-

-

A

Aβ

.

-

A A : (2)

C -2.

;

.

C /

(1), (2), . 2 -

. B ,

2

2. -

AD Stage	HNE-modified proteins in HP	Function	HNE-modified proteins in IPL	Function
C	3 C A 1 70 A / α- A .A.		β- A / α - 2 α- A / C -2	C A A
A	A A α- α-	A C	A 1 C -2	A A

A .
A A (150, 167, 169). A , A ; A , A ; ,
; , , ; , ; A , - A ; C , ; ,
; A, .

(113). , C -2 ,
A . 2 A ,
A (169) C , - . B C -2
, , Aβ ,
, C -2
A . 2 (93).
, , (6, 53, 75, 123). - , A : Aβ,
, 2 Aβ , , . , -
Aβ , , - C -2 ,

A (63).
C -2 , - /, , , ,
, A . A , - , , , -
C -2 , - (93). C , -
, , C -2 - A
. C -2 - A ,
, , , .
(82). , , C -2 A ,
- , , ,
(11, 97). C -2 - ″ -
, , - ( )1, ( ),
, - , , C 2+ - ( ) - C ,
, , ( ) A ,
(93). (A 1) A . -
A
A , , , .
(10). , 1,3- , , -
C (181), - 3- , .
. , C -2
, , , A 1,3- , A , -
C 5 3β , , A . , .

(62). -1 A (198). A , A . (CA) - A . A - . A (167). A . A + -3-, 1,3- . (104). C (167), . A 1 1,6- -3- 1,6- (206). A 1 A CA C. C - . A 1 A (22) (81). (22) 1,6- , A . CA ( ) A A - . - A + CA . A A (C) - A . A , - (107). A (30, 141), - A . A CA . A - , - . -, -, A- , - (114, 188). A , - (150). CA ; , (178, 212). A , A - - , A (180). - C , (C 1), (-), 1 (-α), - 3 (3), 70. A - , , (18). , , . , - , . , , . , A (128, 180). C 1 - , . - A (92) C (167), - , . C (59, 142). C A (15). (48). C , 1 (112); , - A , 21, (77, 106). A A - 21 (154) . C C , , Aβ . - -α . - - . - A - A . A , - - (143). , A - , (205).

-α, - A
- , (151),
. , -α
, , .
B -α
, , -
, , , , -
(201). -α ,
, (27, 151), -α
. , - -α
- , , ,
, , -
, . -
, A (58, 74, 176).
, , ,
, , -
- -α, ,
, , ,
, -
, -
, A .
3 ,
. (51, 140).
- - , (A) ,
, A
, (99). A ,
, -
(51, 52, 172). , -
A ,
, (78). 3
C , ,
A (33). 3 , , -
, , (B), , -
, , , ,
. A , ,
, B , , , -
. A, , -
.
B
, , , -
, , B
, , (191). B
, ,
A C A (13, 14,
80) , . B
A , ,
2576
A (80). A / , -
, -κB. A
, 3
, , , -
.

A , , , -
, , , , .
. 70 , , A
(45).
A (45) (67),
90 60, , -
, 27 32, C (57).
, , , ,
, ,
A (102). Aβ- , -
(25),
, Aβ , , , -
A (110) , , , -
. , -
, -
A
A α- , ( ), , , -
, (,) (150).
α- β-
, , -
. , (i.e.,
)
vice versa. , α- -
, , , (79). -
,
(136, 137).
, A
(109).
, , , .
1-C , , ,
. , , ,
C 2+- , , , A_2
(177), , -
(47). ,
, , , A_2
. , , A_2 1,
, -
- A
C (37, 196, 197).
,
(66).
, , , .
C , , -
, , , -
, .
.
.
.
,
, , , , ,
(35). , -
A (92) -
, .

Down Syndrome

21.

(89).

(171).

(16). (40)

A (124).
A Aβ .

(95). A

(43, 100, 145, 215),

. C

(95, 138, 193).

21

. 1

: 1

2 2,

1

. A , B (31)

A et al. (85)

1 ,

21

A .

Aβ(1 42),

(34, 42, 98, 160), post mortem Aβ(1 42) (90).

(139). ,

(8,12-iso- 2α)

(160).

et al. (98)

1C .

(98). A 1

, α-

3- -9 ,11 -

(13-).

α,

, 1, -

(3). ,

A ,

. , ,

α- , , 1,

- A C (32, 150, 167),

.

A

,

A

. A ,

C

. ,

. B ,

(147).

Parkinson Disease

-

, -

, -

.” , α-

, -

(23), .

. α- -

-

(175). A -

α-

(96). α-

C ,

(108, 192) (122). -

A

(217).

-

(55).

A

(216). -

(76).

, -

-

-

3. 1C
( ) 3- -9 ,
11 -

Protein	Function
C	
C	
A	
1	
13-	
-	
α-	
A	

13- , 3- , -9 , 11 - .

(135).

B

Huntington Disease

( )
CA ( ) . CA
11 35
35
(174). A

(88).
(1872)

. A
10

50%
A

. A

(19).

(28). A

(19).

A

(26). A

A
(28, 111).

6/2 . A
(A)

6/2 . A

A
(111). A

(149).

Concluding Remarks

A ,
, A .

. A

. B

. A 6, α- A
A , , A .

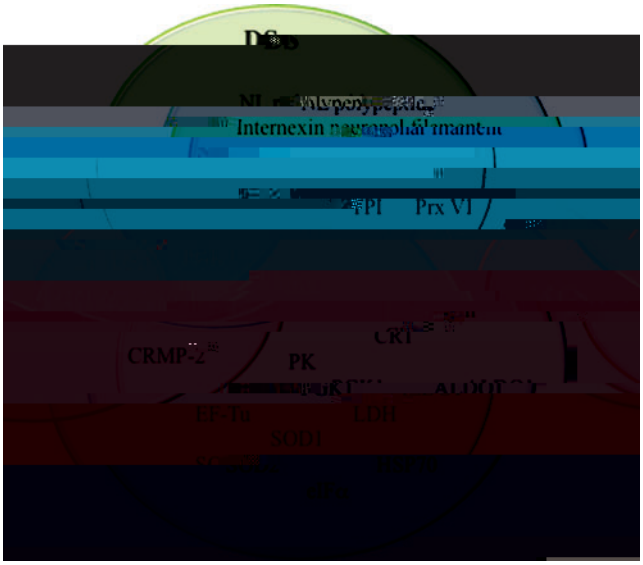

FIG. 6. Venn diagram of HNE modified proteins identified in ALS, AD, and Down syndrome (DS). Á 1, - ; C 1, 1; C -2, , -2; - , ; -α, 1 ; 70, 70; , ; 3, 3; , , ; 1, 1; , ; , , , ; 1, C / ; 2, ; , , . (. . / .)

Acknowledgments

.A.B. A -05119; A -029839 . . , B .

Disclosure Statement

, .

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A C , 14, 2011;
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, , 23, 2011.

Abbreviations used

13- =3- , , -9 ,11 -
A = -, ,
AA =
A =A
A 1 =
A =
A =
C 1 = 1
C -2 = , , , -2
A =
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A = A
- =
-α = 1 ,
C =
2- = 2 ,
4- = 4-
A =
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-1 = , -1
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A =
-κB = - , , B
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3 = , , , 3
A = - - ,
2 = ,
CA = , A ,
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B = , ,
1 = , , 1
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A =,
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