

Inhibition of Alzheimer β -Fibrillogenesis by Melatonin*

(Received for publication, September 24, 1997, and in revised form, February 2, 1998)

Miguel Pappolla[‡], Peter Bozner[‡], Claudio Soto[§], Haiyan Shao[¶], Nikolaos K. Robakis[¶], Michael Zagorski[¶], Blas Frangione[§], and Jorge Ghiso[§]

From the [‡]University of South Alabama College of Medicine, Mobile, Alabama 36617, [§]New York University, New York, New York 10016, [¶]Case Western Reserve University, Cleveland, Ohio 44106, and [¶]Mount Sinai Medical School, New York, New York 10029

It is generally postulated that the amyloid β protein ($A\beta$) plays a central role in the progressive neurodegeneration observed in Alzheimer's disease. Important pathologic properties of this protein, such as neurotoxicity and resistance to proteolytic degradation, depend on the ability of $A\beta$ to form β -sheet structures or amyloid fibrils. We report that melatonin, a hormone recently found to protect neurons against $A\beta$ toxicity, interacts with $A\beta$ 1–40 and $A\beta$ 1–42 and inhibits the progressive formation of β -sheets and amyloid fibrils. These interactions between melatonin and the amyloid peptides were demonstrated by circular dichroism and electron microscopy for $A\beta$ 1–40 and $A\beta$ 1–42 and by nuclear magnetic resonance spectroscopy for $A\beta$ 1–40. Inhibition of β -sheets and fibrils could not be accomplished in control experiments when a free radical scavenger or a melatonin analog were substituted for melatonin under otherwise identical conditions. In sharp contrast with conventional anti-oxidants and available anti-amyloidogenic compounds, melatonin crosses the blood-brain barrier, is relatively devoid of toxicity, and constitutes a potential new therapeutic agent in Alzheimer's disease.

Most of the recent advances in Alzheimer's disease (AD)¹ stem from the study of a 40–42-amino acid peptide called the amyloid β protein ($A\beta$) as the essential pathologic marker of this disorder (1, 2). In brains afflicted with AD, deposits of $A\beta$ in the form amyloid fibrils are widespread within senile plaques and in cerebral and meningeal blood vessels (3, 4). Interestingly, $A\beta$ is normally produced as a soluble peptide (5–8), and whether this form of $A\beta$ is the immediate precursor of the amyloid deposits is still unknown. Synthetic peptides homologous to $A\beta$ 1–40 and $A\beta$ 1–42, however, undergo spontaneous rearrangements of their initial secondary structure, generating oligomeric and polymeric species with higher content of β -sheets (9–15). Such changes are either promoted or inhibited by numerous factors (9, 14, 16–22).

The secondary structure determines several important prop-

erties of $A\beta$ that may be relevant to the pathogenesis of AD. First, it has been demonstrated that the amyloid peptide is neurotoxic (23–25) and that this characteristic is associated with formation of β -sheets (15, 26–31) or amyloid fibrils (31). Second, the ability of $A\beta$ to form fibrils is directly correlated with the content of β -sheet structures adopted by the peptide (32). In this regard, it has been proposed that peptides with high contents of β -sheets can act as seeds for nucleation and fibril formation (33, 34). Finally, $A\beta$ peptides with high contents of β -sheets become partially resistant to proteolytic degradation, and this may be a crucial mechanism in amyloid deposition (35). Such protease resistance and insolubility features, shared by all known forms of amyloidoses, prevent amyloid removal from tissue deposits. Thus, by preventing the formation of β -sheets one could not only reduce neurotoxicity but also facilitate clearance of $A\beta$ via increased proteolytic degradation.

It has recently been found that melatonin has cytoprotective properties against $A\beta$ toxicity (36). In the process of investigating the mechanisms of action of melatonin, new properties of this hormone were uncovered. As determined by CD, electron microscopy, and ¹H NMR, melatonin interacted with $A\beta$ and had a profound inhibitory effect on the formation of β -sheets and fibrils. Most interestingly, the observed changes in $A\beta$ conformation appear to depend on specific structural characteristics of the hormone rather than on its recently established antioxidant properties (37).

MATERIALS AND METHODS

Circular Dichroism Spectroscopy—Peptides $A\beta$ 1–40 and $A\beta$ 1–42 were synthesized in the W. M. Keck Foundation (Yale University, CT), and their purity was evaluated by amino acid sequence and laser desorption mass spectrometry as described (32). Aliquots of $A\beta$ 1–40 and $A\beta$ 1–42 at a concentration of 250 μ M in 5 mM Tris-HCl, pH 7.4, were incubated at room temperature alone or with 100 μ M of either melatonin or the melatonin analog 5-hydroxy-*N*-acetyl-tryptamine (NAT) (Sigma) or *N*-*t*-butyl- α -phenylnitron (PBN) (Sigma), a powerful free radical scavenger structurally unrelated to melatonin. Because of the antioxidant properties of melatonin (37) and because oxidative conditions may promote fibril formation (34, 38), NAT and PBN were specifically selected both as controls for the method and to discount for possible “nonspecific” antioxidant effects of melatonin in the phenomenon described here.

Spectra in the far ultraviolet light (190–250 nm) were recorded at various time intervals with a Jasco-720 spectropolarimeter as described (32) using a cell path of 0.01 cm. Experiments with $A\beta$ 1–42 necessitated shorter incubation times due to the more fibrillogenic properties and faster aggregation exhibited by the longer peptide. 40 scans/experimental condition were obtained at 0.2 nm intervals over the wavelength range 190–250 nm. The data were analyzed by the Lincomb algorithm (39) to obtain the percentages of the different secondary structures motifs.

Electron Microscopy—To determine whether melatonin displayed inhibitory effects on amyloid fibril formation, transmission electron microscopy was performed following a standard method previously described (40) using a Phillips CM100 microscope and Formvar-coated nickel grids. $A\beta$ 1–40 was incubated at the same concentrations as noted for the CD and NMR experiments in the presence or absence of melatonin, and fibril formation was monitored at 0, 12, 24, 36, and 48 h in three independent experiments. Additional controls containing $A\beta$ plus NAT and $A\beta$ plus PBN were incubated in parallel for 48 h. To determine the minimal inhibitory concentration of melatonin on fibril formation, we performed experiments in which several melatonin concentrations (1 nM, 10 nM, 1 μ M, 10 μ M, 100 μ M, and 200 μ M) were added to tubes containing 250 μ M $A\beta$ 1–40, incubated for 48 h, and then examined.

* This work was supported by National Institutes of Health Grants AG11130, AG05891, AR02594, AG08992, and AG14363. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ The abbreviations used are: AD, Alzheimer's disease; $A\beta$, amyloid β protein; NAT, 5-hydroxy-*N*-acetyl-tryptamine; PBN, *N*-*t*-butyl- α -phenylnitron.

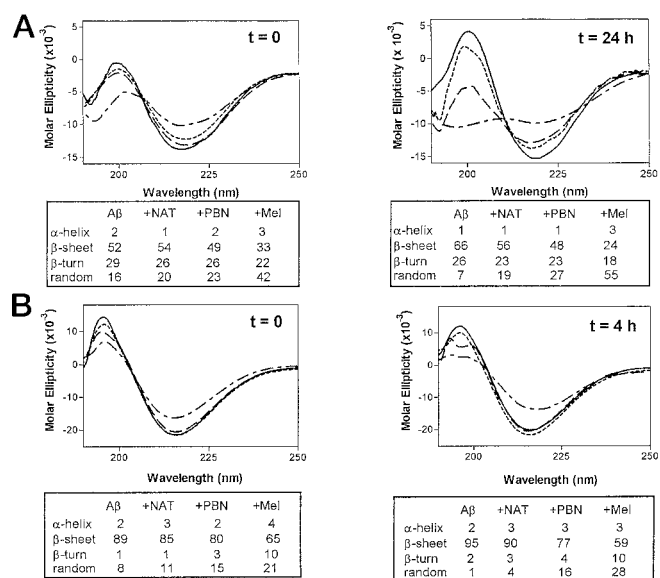


FIG. 1. Circular dichroism studies of A β 1-40 (A) and A β 1-42 (B) alone or in the presence of melatonin. Spectral tracings were generated as described under "Materials and Methods" and expressed in terms of mean residue ellipticity in units of deg cm² dmol⁻¹ after subtraction of buffer base-line spectra (including melatonin, NAT, or PBN when indicated) and smoothed by a computer assisted algorithm provided by Jasco Co. The curves designate the spectra of A β alone (solid line), A β plus NAT (short dashes), A β plus PBN (long dashes), or A β plus melatonin (short and long dashes). Left panels indicate results obtained at time 0; right panels show the values obtained at 24 h for A β 1-40 and 4 h for A β 1-42. The corresponding percentages of the different secondary structure motifs are shown in the tables below each respective tracing. An average of 40 scans/independent experimental condition was obtained. An independent experiment yielded qualitatively similar data.

For the more amyloidogenic A β 1-42, experiments were preformed at the same peptide concentration (250 μ M) in the presence or absence of melatonin at various concentrations (100 nM, 1 μ M, 10 μ M, 100 μ M, and 200 μ M). The formation of amyloid fibrils was monitored at 0, 2, and 6 h.

Nuclear Magnetic Resonance Spectroscopy—To further explore structural changes of A β by melatonin we performed one-dimensional ¹H NMR spectroscopic studies on A β 1-40. The NMR approach has the distinct advantage of being able to specifically locate the amino acid side chains that bind to a particular ligand (41). The solution conditions for the NMR and CD studies were similar, except that deuterated water (D₂O) in phosphate buffer was used in the NMR study. All ¹H NMR spectra were obtained at 600 MHz using a Varian UnityPlus-600 spectrometer, and the data were processed using the FELIX program (version 95.0, Biosym, Inc.). The NMR solutions were prepared in D₂O (0.6 ml) with sodium phosphate buffer (5 mM, pH 7.5), perdeuterated Na₂EDTA (0.5 mM), NaN₃ (0.05 mM), and 3-(trimethylsilyl) propionate-2,2,3,3-d₄ (0.05 mM), the last of which serves as an internal chemical shift reference at 0 ppm. The NMR measurements were performed at 10 °C and the residual protium absorption of D₂O was suppressed by low power irradiation during the recycle delay. For all spectra, 128 scans were required with a total recycle delay of 4.2 s, which included an acquisition time and recycle delay of 2.2 and 2.0 s, respectively. The digital resolution of the acquired data was 0.24 Hz/pt, which was reduced to 0.12 Hz/pt by zero-filling the data once before processing. To further improve the resolution, before Fourier transformation spectra were multiplied by a Lorentzian-to-Gaussian weighting factor. This experiment was duplicated on two different days.

RESULTS

Circular Dichroism Studies—As expected, the content in β -sheet conformation of A β 1-40 incubated alone increased over time from 52% at time 0 to 66% after 24 h at 37 °C (Fig. 1A). These results are in qualitative agreement with previous work (42). The relative proportion of the structures was dramatically changed by addition of melatonin to sister tubes. At time 0, there was an immediate increase of the random conformation, whereas the original β -sheet content markedly dimin-

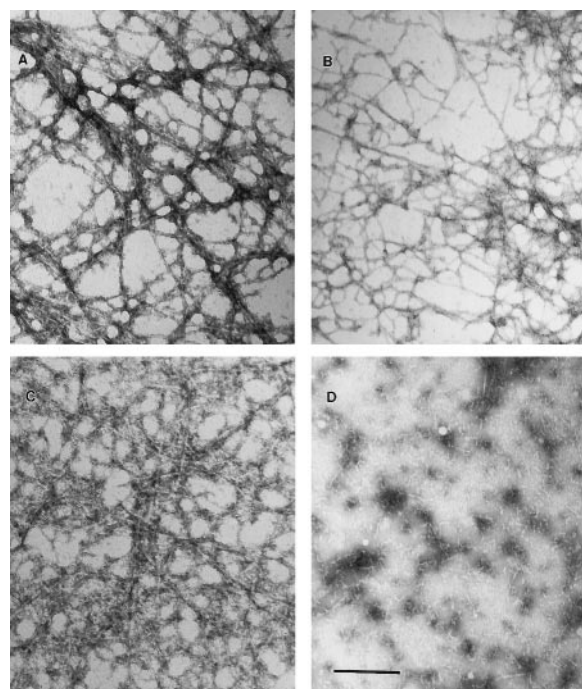


FIG. 2. A β 1-40 fibril formation in the presence or the absence of melatonin. A β 1-40 incubated for 48 h either alone (A) or with NAT (B), PBN (C), or melatonin (D). Bar, 200 nm. Well formed amyloid fibrils are easily recognized in A, B, and C. Fibrils were not formed in D. EM grids were extensively and carefully examined, and a negative result was only documented when fibrils were totally absent from the grids. These results were reproduced in three independent experiments.

ished (Fig. 1A, left panel). This effect was not observed with NAT or PBN. The amount of β -sheet structures for A β 1-40 plus melatonin decreased over time, reaching 24% after 24 h of incubation (Fig. 1A, right panel). At 24 h, no structural changes were again detected in control experiments with the melatonin analog NAT, and only small effects were observed with PBN. Experiments with the more amyloidogenic A β 1-42 showed qualitatively similar results (Fig. 1B). Melatonin caused an immediate reduction in the amount of β -sheet structures at time 0 from 89 to 65% (Fig. 1B, left panel). This percentage continued to decrease to 59% after 4 h of incubation (Fig. 1B, right panel). As observed with A β 1-40, such striking structural changes were not elicited in parallel control preparations containing A β 1-42 plus NAT or PBN.

Electron Microscopy Studies—Results of the ultrastructural studies reflected the conformational changes and supported the hypothesis that formation of β -sheet structures precede fibrillogenesis (32, 33). In three independent experiments, fibrils were abundant in the tubes containing A β 1-40 alone incubated for 36 h. In contrast, no fibrils were detected for solutions of A β 1-40 plus melatonin up to 48 h (Fig. 2). Notably, fibrils were abundant and easily identifiable in the tubes incubated for 48 h containing A β alone, A β plus NAT, or A β plus PBN but not in the tubes containing A β plus melatonin. Such a contrasting finding suggests that the methoxy group at position 5 of the indolamine nucleus of melatonin confers relative structural specificity to the observed phenomena.

Fibril formation was inhibited in all tubes containing A β 1-40 plus melatonin at concentrations above 10 μ M. To substantiate the negative results obtained with PBN, three different concentrations of this scavenger (10, 100, and 200 μ M) were added to tubes containing A β 1-40, incubated for 48 h, and then examined. Fibrils were abundant in all these tubes. In contrast, only amorphous material was again identified in

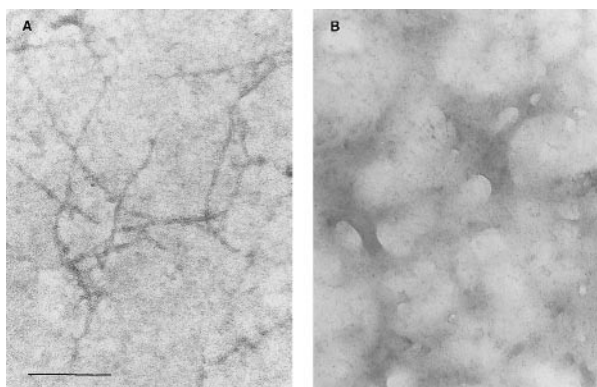


FIG. 3. A β 1-42 fibril formation in the presence or the absence of melatonin. A β 1-42 was either incubated alone (A) or with melatonin (B) as described under "Materials and Methods." Fibrils were only found in the tubes containing A β 1-42 alone after 2 h of incubation (not shown) and after 6 h of incubation (A). Only amorphous material was seen in the tubes containing A β 1-42 alone immediately after dissolution (time 0, not shown) or containing A β 1-42 plus melatonin at the indicated time points and with a range of melatonin concentrations. In (B), amorphous material as seen at one of the concentrations of melatonin used is representatively illustrated (in this picture, melatonin concentration was 100 μ M and incubation time was 6 h). Bar, 200 nm.

control sister tubes containing 250 μ M A β 1-40 plus 100 μ M melatonin.

In the experiments with A β 1-42, fibrils were identified in the tubes containing the peptide alone incubated after 2 and 6 h (no fibrils were seen at time 0). In contrast, only amorphous material was identified in the tubes containing A β 1-42 plus melatonin at these time points (Fig. 3). All the concentrations of melatonin used in the experiments with A β 1-42 (see "Materials and Methods") were effective to inhibit fibril formation.

Nuclear Magnetic Resonance Spectroscopy—Shown in Fig. 4 are the downfield spectral regions for the A β 1-40 peptide, melatonin (Fig. 4E) and the A β 1-40 with 0.4, 0.8, and 1.2 molar equivalents of melatonin (Fig. 4, B–D). The three well resolved His-2H and His-4H signals are consistent with the A β 1-40 peptide being partly folded into an ordered structure, which according to the CD studies should be β -sheet and random coil. If only random coil structure were present, then degenerate signals should be present for His⁶, His¹³, and His¹⁴ (43).

The NMR spectra of the mixtures of melatonin and A β 1-40 show changes in chemical shifts indicative of binding and local conformational changes. The His-2H and His-4H signals shift downfield 0.05 and 0.02 ppm, respectively, whereas the aromatic peaks of melatonin also shift downfield (Fig. 4). In addition, careful analysis of the upfield spectral region (spectra not shown) revealed downfield shifts for the Asp β CH₂ groups (Table I). Control NMR experiments with NAT showed only minor chemical shift perturbations (\pm 0.01 ppm), suggesting a specificity for the interaction of melatonin with A β . The lack of any line broadening or separate peaks for the bound and free states indicates that the binding is in the fast exchange limit (41). The downfield shifts can be interpreted in terms of ring-current shift contributions, with the shifted hydrogens becoming located in the planes of the melatonin and His aromatic ring (44). A remarkable feature is the identical shift seen for each of the three His residues. This result together with the observed non-linearity of the shifts with varied melatonin concentrations suggests that the binding is not localized to a particular His site on A β . Instead, the chemical shift changes are consistent with a residue-specific interaction between melatonin and any of the three His and Asp residues of A β .

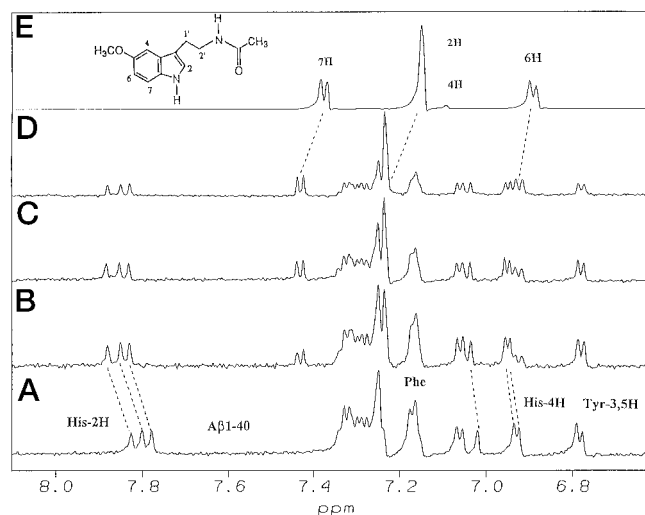


FIG. 4. Downfield ¹H NMR spectral region (600 MHz) of 0.25 mM A β 1-40 peptide (A) and 5.0 mM melatonin (E), with the chemical structure of melatonin provided above the upper plot. The spectra in B, C, and D contain 0.25 mM A β 1-40 plus 0.1, 0.2, and 0.3 mM melatonin, respectively. Assignments for the aromatic signals of melatonin and the A β 1-40 peptide are shown, and those resonances exhibiting changes in shifts are connected by dotted lines. A duplicate independent experiment showed virtually identical results.

TABLE I

Titration studies of A β (1-40) peptide with melatonin

All solutions contained 5 mM sodium phosphate buffer in D₂O, pH 7.5, at 10 °C with the chemical shifts referenced to internal 3-(trimethylsilyl) propionate-2,2,3,3-d₄.

	Chemical shift	Bound chemical shift ^a
	<i>cpm</i>	
Melatonin ^b		
2H	7.15	0.09
4H	7.15	0.09
6H	6.89	0.03
7H	7.38	0.05
1'-CH ₂	2.92	0.04
2'-CH ₂	3.48	0.01
CH ₃ -N-acetyl	1.91	-0.01
CH ₃ -methoxyl	3.87	0.03
A β (1-40) ^c		
His-4H	6.92	0.02
	6.94	0.02
	7.01	0.02
His-2H	7.78	0.05
	7.80	0.05
	7.83	0.05
Asp- β CH ₂	2.84-2.77	2.87-2.80
	2.70-2.67	2.72-2.69

^a Obtained by subtracting the chemical shift of melatonin and the A β (1-40) peptide with the present data, we are unable to assign the 2H and 4H signals specifically to His⁶, His¹³, and His¹⁴.

^b Assignments for 5 mM melatonin.

^c Because the β CH₂s for Asp¹, Asp⁷, and Asp²³ are not resolvable by ¹H NMR, chemical shift ranges are presented.

DISCUSSION

Melatonin has a proposed role in the aging process (45, 46). Decreased secretion of this hormone during aging is well documented (47, 48), and more profound reductions are reported in populations with dementia (49, 50). The reported lack of toxicity of melatonin and the ease and rapidity with which this molecule crosses the blood-brain barrier following oral administration (51) makes it a prime candidate for experimental testing in humans. This hormone has been administered to human subjects at very high doses (*i.e.* 1 g/day) without any clinically significant toxicity (52). Our data clearly indicate that under the conditions tested, melatonin modifies the sec-

ondary structure of the A β peptide and inhibits the formation of amyloid fibrils.

These newly found anti-amyloidogenic properties of melatonin are very rare for endogenous substances. Because of the relationship between oxidative stress and AD and the recently established antioxidant properties of this hormone, it was initially thought that the neuroprotective actions of melatonin were mostly due to its intracellular antioxidant effects (36). However, the results presented here suggest that the anti-amyloidogenic properties are dependant on structural interactions of the hormone with A β rather than on antioxidant properties exclusively. The His and Asp residues play important roles in β -amyloid fibril production and stability. Many physiological constituents such as transthyretin and zinc can prevent or promote aggregation by their affinities for the His residues of A β (53, 54). Additionally, imidazole-carboxylate salt bridges between the side chains of the His⁺ and the Asp⁻ residues are critical to the formation of the amyloid β -sheet structures (12, 55–57). More significantly, disruption of these salt bridges promotes fibril dissolution (58). One possibility is that melatonin promotes the β -sheet \rightarrow random coil conversion by disruption of the His⁺-Asp⁻ salt bridges. Alternatively, the described effects may result from a unique combination of structural and antioxidant features of this molecule. More experiments are necessary to clarify this interpretation and dissect the relationship between cytoprotection, changes in peptide structure, and antioxidant characteristics. The antioxidant properties of melatonin may provide additional cytoprotection at the intracellular level (36).

The ratio melatonin:A β used in these studies is within physiologic range, because the concentration of both substances in the brain are normally around 1:1 during youth (both substances are at comparable picomolar concentrations in brain tissue during the dark phase of the cycle (59, 60)). However, limitations of the methods employed required concentrations of melatonin and A β that deviate from actual physiological conditions.

At this time, no information is available about the possible therapeutic or preventive values of melatonin or of its potential efficacy at physiologic or pharmacologic dosages. It would be premature to conclude that a subgroup of AD is caused by an age-related deficiency of this hormone, although such a possibility is nonetheless intriguing. The results reported here suggest that melatonin can provide a combination of antioxidant and anti-amyloidogenic features that can be explored either as a preventive or therapeutic treatment for AD or as a model for development of anti-amyloidogenic indole analogs.

Acknowledgment—Jan Moore provided editorial assistance.

REFERENCES

- Glenner, G. G., and Wong, C. W. (1994) *Biochem. Biophys. Res. Commun.* **120**, 885–890
- Masters, C. L., Simms, G., Weinman, N. A., Multhaup, G., McDonald, B. L., et al. (1985) *Proc. Natl. Acad. Sci. U. S. A.* **82**, 4245–4249
- Pappolla, M. A., and Robakis, N. K. (1995) in *Chronic Diseases* (Stein, M., and Baum, M., eds) pp. 3–20, Academic Press, San Diego, CA
- Tomlinson, B. E., and Corsellis, J. A. N. (1984) in *Greenfield's Neuropathology* (Adams, J. H., and Corsellis, J. A. N., eds) pp. 951–1025, John Wiley & Sons, New York
- Gravina, S. A., Ho, L., Eckman, C. B., Long, K. E., Otvos, L., Jr., Younkin, L. H., Suzuki, N., and Younkin, S. G. (1995) *J. Biol. Chem.* **270**, 7013–7016
- Haas, C., Schlossmacher, M. G., Hung, A. Y., Vigo-Pelfrey, C., and Mellon, A. (1992) *Nature* **359**, 322–324
- Shoji, M., Golde, T. E., Ghiso, J., Cheung, T. T., Estus, S., et al. (1992) *Science* **258**, 126–129
- Seubert, P., Vigo-Pelfrey, C., Esch, F., Lee, M., Dovey, H., et al., (1992) *Nature* **359**, 325–327
- Barrow, C. J., and Zagorski, M. G. (1991) *Science* **253**, 179–182
- Barrow, C. J., Yasuda, A., Kenny, P. T. M., and Zagorski, M. G. (1992) *J. Mol. Biol.* **225**, 1075–1093
- Hilbich, C., Kisters-Woide, B., Reed, J., Masters, C. L., and Beyreuther, C. L. K. (1991) *J. Mol. Biol.* **218**, 149–163
- Kirchner, D. A., Inouye, H., Duffy, L. K., Sinclair, A., Lind, M., et al. (1987) *Proc. Natl. Acad. Sci. U. S. A.* **84**, 6953–6957
- Gorévic, P. D., Castano, E. M., Sarma, R., and Frangione, B. (1987) *Biochem. Biophys. Res. Commun.* **147**, 854–862
- Shen, C.-L., and Murphy, R. M. (1995) *Biophys. J.* **69**, 640–651
- Salomon, A. R., Marciniowski, K. J., Friedland, R. P., and Zagorski, M. G. (1996) *Biochemistry* **35**, 13568–13578
- Naiki, H., Gejyo, F., and Nakakuki, K. (1997) *Biochemistry* **36**, 6243–6250
- Pike, C. J., Burdick, D., Walencewicz, A. J., Glabe, C. G., and Cotman, C. W. (1993) *J. Neurosci.* **13**, 1676–1687
- Hilbich, C., Kisters-Woike, B., Reed, J., Masters, C. L., and Beyreuther, K. (1991) *J. Mol. Biol.* **218**, 149–163
- Burdick, D., Soregan, B., Kwon, M., Kosmoski, J., Knauer, M., Henneschen, A., Yates, J., Cotman, C., and Glabe, C. (1992) *J. Biol. Chem.* **267**, 546–554
- Naiki, H., and Nakakuki, K. (1996) *Lab. Invest.* **74**, 374–383
- Eriksson, S., Janciauskiene, S., and Lannfelt, L. (1995) *Proc. Natl. Acad. Sci. U. S. A.* **92**, 2313–2317
- Matzubara, E., Soto, C., Governale, S., Frangione, B., and Ghiso, J. (1996) *Biochem. J.* **316**, 671–679
- Yankner, D. A., Duffy, L. K., and Kirchner, D. A. (1990) *Science* **250**, 279–282
- Behl, C., Davis, J. B., Lesley, R., and Schubert, D. (1994) *Cell* **77**, 817–827
- Harris, M. E., Hensley, K., Butterfield, D. A., Leedle, R. A., and Carney, J. M. (1995) *Exp. Neurol.* **131**, 193–202
- Buchet, R., Tavitian, E., Ristig, D., Swoboda, R., Stauss, U., et al. (1996) *Biochim. Biophys. Acta* **1315**, 40–46
- Simmons, L. K., May, P. C., Tomaselli, K. J., Rydel, R. E., and Fuson, K. S. (1994) *Mol. Pharmacol.* **45**, 373–379
- Greenfield, N. J., and Fasman, G. D. (1969) *Biochemistry* **8**, 4108–4116
- Tomski, S., and Murphy, R. M. (1992) *Arch. Biochem. Biophys.* **294**, 630–638
- Pike, C. J., Walencewicz-Wasserman, A. J., Kosmoski, J., Cribbs, D. H., Glabe, C. G., et al. (1995) *J. Neurochem.* **64**, 253–265
- Lorenzo, A., and Yankner, B. A. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91**, 12243–12247
- Soto, C., Castaño, E. M., Kumar, R. A., Beavis, R. C., and Frangione, B. (1995) *Neurosci. Lett.* **200**, 105–108
- Jarrett, J. T., Berger, E. P., and Lansbury, P. T., Jr. (1993) *Biochemistry* **32**, 4693–4697
- Snyder, S. W., Lador, U. S., Wade, W. S., Wang, G. T., Barrett, G. T. (1994) *Biophys. J.* **67**, 1216–1228
- Soto, C., and Castaño, E. M. (1996) *Biochem. J.* **314**, 701–707
- Pappolla, M. A., Sos, M., Omar, A. R., Bick, R. J., Hickson-Bick, D. L. M., et al. (1997) *J. Neurosci.* **17**, 1683–1690
- Reiter, R. J., Poeggeler, B., Tan, D.-X., Chen, L.-D., and Manchester, L. C. (1993) *Neuroendocr. Lett.* **15**, 103–116
- Dyrks, T., Dyrks, E., Hartmann, T., Masters, C., and Beyreuther, K. (1992) *J. Biol. Chem.* **267**, 18210–18217
- Percezel, A., Park, K., and Fasman, G. D. (1992) *Anal. Biochem.* **203**, 83–93
- Pappolla, M. A., Alzofon, J., McMahon, J., and Theodoropoulos, T. J. (1990) *Eur. Arch. Psych. Neurol. Sci.* **239**, 314–319
- Wemmer, D. E., and Williams, P. G. (1994) in *Nuclear Magnetic Resonance* (James, T. L., and Oppenheimer, N. J., eds) Vol. 239, pp. 739–767, Academic Press, New York
- Terzi, E., Holzemann, G., and Seelig, J. (1995) *J. Mol. Biol.* **252**, 633–642
- Zagorski, M. G., and Barrow, C. J. (1992) *Biochemistry* **31**, 5621–5631
- Perkins, S. J. (1982) *Biological Magnetic Resonance* (Berlier, L. J., and Reuben, J., eds) Plenum Press, New York
- Pierpaoli, W., Dall'Ara, A., Pedrinis, E., and Regelson, W. (1991) *Ann. N. Y. Acad. Sci.* **621**, 291–313
- Pierpaoli, W. (1991) *Aging (Milano)* **3**, 99–101
- Iguchi, H., Kato, K., and Ibayashi, H. (1982) *J. Clin. Endocrinol. Metabol.* **55**, 27–29
- Dori, D., Casale, G., Solerte, S. B., Fioravanti, M., et al. (1994) *Chronobiology* **21**, 121–126
- Souetre, E., Salvati, E., Krebs, B., Belugou, J. L., and Darcourt, G. (1989) *Am. J. Psychiatry* **146**, 1037–1040
- Mishima, K., Okawa, M., Hishikawa, Y., Hozumi, S., et al. (1994) *Acta Psychiatr. Scand.* **89**, 1–7
- Tan, D. X., Chen, L.-D., Poeggeler, B., Manchester, L. C., and Reiter, R. J. (1993) *Endocrinol. J.* **1**, 57–60
- Nordlund, J. J., and Lerner, A. B. (1977) *J. Clin. Endocrinol. Metab.* **45**, 768–774
- Bush, A. L., Pettingell, W. H., Paradis, M. D., and Tanzi, R. E. (1994) *J. Biol. Chem.* **269**, 12152–12158
- Schwarzman, A. L., Gregori, L., Vitek, M. P., Lyubski, S., Strittmatter, W. J., et al. (1994) *Proc. Natl. Acad. Sci. U. S. A.* **91**, 8368–8372
- Fraser, P. E., McLachlan, D. R., Surewicz, W. K., Mizzen, C. A., Snow, A. D., et al. (1994) *J. Mol. Biol.* **244**, 64–73
- Fraser, P. E., Nguyen, J. T., Surewicz, W. K., and Kirchner, D. A. (1991) *Biophys. J.* **60**, 1190–1201
- Huang, T. J. H., Fraser, P. E., Chakrabartty, A., et al. (1997) *J. Mol. Biol.* **269**, 214–224
- Lee, J. P., Stimson, E. R., Ghilardi, J. R., Mantyh, P. W., Lu, Y.-A., et al. (1995) *Biochemistry* **34**, 5191–5200
- Johnson-Wood, K., Lee, M., Motter, R., Hu, K., Gordon, G., Barbour, R., et al. (1997) *Proc. Natl. Acad. Sci. U. S. A.* **94**, 1550–1555
- Pang, S. F., Ralph, C. L., and Reilly, P. (1974) *Gen. Comp. Endocrinol.* **22**, 499–506

Inhibition of Alzheimer β -Fibrillogenesis by Melatonin

Miguel Pappolla, Peter Bozner, Claudio Soto, Haiyan Shao, Nickolaos K. Robakis,
Michael Zagorski, Blas Frangione and Jorge Ghiso

J. Biol. Chem. 1998, 273:7185-7188.

doi: 10.1074/jbc.273.13.7185

Access the most updated version of this article at <http://www.jbc.org/content/273/13/7185>

Alerts:

- [When this article is cited](#)
- [When a correction for this article is posted](#)

[Click here](#) to choose from all of JBC's e-mail alerts

This article cites 57 references, 18 of which can be accessed free at
<http://www.jbc.org/content/273/13/7185.full.html#ref-list-1>