地域在宅高齢者の栄養状態に及ぼす要因について
―久山町における栄養疫学研究―

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Factor effects on the analysis of the nutritional status of the elderly Hisayama residents

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【目的】

高齢者は生体防御機能作用が低下し，それに伴い老人性疾患，動脈硬化，低栄養状態などが発現する。一般的に高齢者は，加齢に伴って，基礎代謝量の減少と身体活動量の減少などから栄養必要量は低下し，加えて歯牙の欠損による咀嚼機能の低下，味覚・嗅覚の低下などに伴う食欲の低下，消化吸収能の低下など食事摂取上さまざまな問題が起こってくることが考えられる。高齢者が良好な栄養状態を維持するためには，適切な栄養アセスメントやケア・マネジメントを行うことが重要である。

また，高齢社会を迎えたわが国では，高齢者の単独世帯いわゆる一人暮らし世帯が急速に増加しており，2025年には約680万世帯になると予想されている[1]。高齢者にとって食材の調達から炊事，調理の過程を経て喫食に至ることは，加齢に伴い大きな負担となるため，単独世帯の高齢者の栄養状態を複合世帯のそれと比較することは重要であると考えられている[2]。

そこで本研究では，地域在宅高齢者の栄養状態について，栄養摂取に加えて同居者などの世帯構造が及ぼす要因について検討した。

【対象と方法】

対象は福岡県糟屋郡久山町に在住する60歳以上の高齢者で，2002年度の成人健診を受診した1,548名(男性679名，女性869名)である。

健診項目は，身体的計測，血液生化学検査などの医学的検査項目，食習慣調査，身体活動調査，問診などからなり，詳細な検査項目についてはすでに報告している[3][4]。

食習慣調査は，佐々木らの自記式食事歴法調査票(Dietary History Questionnaire; DHQ)[5,6,7]を用い，栄養価等の計算を行った。調査用紙は役場を通じて事前に配布し，健診当日に管理栄養士または栄養士が全員に面接の上，記入項目等の確認や援助を行った。栄養素摂取量および食品群別摂取量は，密度法により1,000kcal当たりに標準化した。

因子分析の主因子法を用いて，食物消費構造の検討を行った。固有値1以上の因子を抽出し，各個人の因子得点を計算した。

対象者の食事摂取量の評価について，エネルギーと各栄養素の摂取適正範囲は，「健康日本21」策定の際に用いられたFAO/WHOによるFood-based Dietary Guidelineに関する指針[8]を参考として作成された厚生労働省案を用いた。

低栄養の判定は，厚生労働省の市町村地域支援事業介護予防事業特定高齢者施策にある判定基準[9]を参考にし，BMIが18.5未満または血清アルブミン値が3.8g/dl未満の者を低栄養群とし，これに該当しない者を正常群とした。

世帯構造の分類については，平成17年国民生活基礎調査の区分に基づき，ひとり暮らし，夫婦のみ，二世代家族，三世代家族，その他に分類した[10]。

解析には，食習慣調査において医師，栄養士等からの指導による食事コントロールを行っていないと回答した者で，かつ世帯構造に関する情報の得られた1,122名(男性495名，女性627名)を最終的な解析対象者とした。

栄養状態低下の関連要因の検討には，低栄養状態

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判定を従属変数とするロジスティク回帰分析を用いて検討した。ロジスティックモデルに投入する変数として，性別，年齢，BMI，適正な食事の有無，世帯構造，第一因子から第三因子の因子得点を選択した。ただしモデルに投入する際に，適正な食事評価のエネルギー摂取については，適正でない者を過剰と不足にカテゴリーを分割した。また因子得点は最も値の低いQ1から最も高いQ5と五分位に分けた上で投入した。

統計解析には，SPSS ver10.0を用い，5%未満を有意水準とした。

【結果】

1. 対象者の栄養状態の判定および身体的特徴

低栄養状態と判定されたものは男性56名(11.3%)，女性58名(9.3%)であった(表1)。正常者との比較では，低栄養の者は男女とも年齢が有意に高く，体重およびBMIは有意に低値であった。また低栄養の者で栄養状態や貧血状態を示す項目で低値を示した。また，結果には示していないが，血清アルブミン値が3.8g/dlを下回った者は16名で全体の1%程度であった。

2. 適正な食事をしている者の割合

判定基準に基づき，適正範囲にある者の割合を表2に示す。基準を満たしている者の割合が最も高かったものは食塩摂取量で，次いでビタミンC，脂肪摂取量の順で，最も基準を満たしている者が少なかった項目はエネルギー摂取量であった。また，すべての項目が適正であった者は男性157名(31.7%)，女性252名(40.2%)で，全体では36.5%の者が適正な食事を摂取していた。

3. 世帯構造別にみた栄養状態

世帯構造別にみた栄養状態の判定を表3に示す。世帯構造別では，男女とも夫婦のみの世帯が対象者全体の約3分の1と最も多く，次いで三世代家族，二世代家族で，ひとり暮らしの高齢者は，男女それぞれ7.3%，8.3%と全体の10%未満であった。低栄養と判定された者は，男性56名(11.3%)，女性58名(9.3%)で，世帯構造間では，男性は三世代，夫婦のみに，女性ではひとり暮らし，三世代，夫婦のみに低栄養の者が多かった。尚，その他の分類の世帯構造は，主に兄弟(姉妹)のみの構造，老夫婦とその孫の構造や二世代，三世代家族に同居人がいる等の構造であった。

表1　対象者の栄養状態の判定および身体的特徴

	男性			女性		
	正常 (n=439)	低栄養 (n=56)		正常 (n=569)	低栄養 (n=58)	
年齢（歳）	69.0 ± 7.0	73.5 ± 7.2	*	69.5 ± 6.8	73.5 ± 8.5	*
身長（cm）	161.7 ± 6.3	161.8 ± 6.0		148.3 ± 5.8	148.8 ± 5.8	
体重（kg）	61.4 ± 8.7	50.0 ± 9.3	*	51.6 ± 7.5	42.5 ± 8.4	*
BMI (kg/m^2)	23.5 ± 2.6	19.0 ± 3.0	*	23.5 ± 2.9	19.2 ± 3.9	*
ｱﾙﾌﾞﾐﾝ(g/dl)	4.3 ± 0.2	4.0 ± 0.4	*	4.3 ± 0.2	4.1 ± 0.4	*
血清鉄(ug/dl)	107.9 ± 39.5	110.0 ± 68.3		95.5 ± 31.7	87.3 ± 43.4	
総ｺﾚｽﾃﾛｰﾙ(mg/dl)	192.9 ± 30.0	175.2 ± 34.1	*	213.0 ± 31.4	204.9 ± 33.0	
HDLｺﾚｽﾃﾛｰﾙ(mg/dl)	57.1 ± 14.4	61.9 ± 16.7	*	64.6 ± 14.6	72.6 ± 18.8	*
LDLｺﾚｽﾃﾛｰﾙ(mg/dl)	118.2 ± 27.9	100.6 ± 32.9	*	132.5 ± 28.7	118.3 ± 28.6	*
中性脂肪(mg/dl)	126.4 ± 83.1	96.4 ± 58.6	*	108.2 ± 54.1	103.4 ± 57.6	
赤血球数(万/ul)	448.2 ± 41.5	399.9 ± 57.3	*	414.8 ± 33.4	394.3 ± 36.2	*
血色素量(ug/dl)	14.5 ± 1.3	12.9 ± 1.8	*	13.0 ± 1.0	12.4 ± 1.1	*
ﾍﾏﾄｸﾘｯﾄ値(%)	43.0 ± 3.5	38.7 ± 5.2	*	38.6 ± 2.8	37.0 ± 3.1	*

* $p<0.05$（正常と比較）
平均値±標準偏差

表2 適正な食事をしている者の割合

	エネルギー	脂肪	カルシウム	ビタミンC	食物繊維	食塩	すべて適正
男性	358	461	352	457	277	487	157
	(72.3%)	(93.1%)	(71.1%)	(92.3%)	(56.0%)	(98.4%)	(31.7%)
女性	378	523	560	618	508	611	252
	(60.3%)	(83.4%)	(89.3%)	(98.6%)	(81.0%)	(97.4%)	(40.2%)
合計	736	984	912	1075	785	1098	409
	(65.6%)	(87.7%)	(81.3%)	(95.8%)	(70.0%)	(97.9%)	(36.5%)

上段: 人数　　下段: %

判定基準:
エネルギー: 70 < %RDA ≦ 130
カルシウム摂取密度: ≧ 200mg/1,000kcal
食物繊維摂取密度: ≧ 6g/1,000kcal
総脂肪摂取密度: ≦ 33 g/1,000kcal
ビタミンC摂取密度: ≧ 30 mg/1,000kcal
食塩摂取密度: ≦ 7.5g/1,000kcal

表3 世帯構造別にみた栄養状態の判定

		ひとり暮らし	夫婦のみ	二世代	三世代	その他	合計
男性	正常	33	144	109	129	24	439
		(91.7%)	(88.9%)	(90.8%)	(87.2%)	(82.8%)	(88.7%)
	低栄養	3	18	11	19	5	56
		(8.3%)	(11.1%)	(9.2%)	(12.8%)	(17.2%)	(11.3%)
	合計	36	162	120	148	29	495
		(100%)	(100%)	(100%)	(100%)	(100%)	(100%)
女性	正常	46	192	136	162	33	569
		(88.5%)	(90.6%)	(91.9%)	(90.5%)	(91.7%)	(90.7%)
	低栄養	6	20	12	17	3	58
		(11.5%)	(9.4%)	(8.1%)	(9.5%)	(8.3%)	(9.3%)
	合計	52	212	148	179	36	627
		(100%)	(100%)	(100%)	(100%)	(100%)	(100%)

上段: 人数
下段: %

4. 栄養状態別にみた栄養素等摂取量 (1,000kcal 当たり)

栄養状態別にみた 1,000kcal 当たりの栄養素等摂取量を表 4 に示す。すべての項目に有意差はみられなかった。

5. 栄養状態別にみた食品群別摂取量 (1,000kcal 当たり)

栄養状態別にみた 1,000kcal 当たりの食品群別摂取量を表 5 に示す。種実類摂取量にのみ有意差がみられた。

6. 食物消費パタン (バリマックス回転後の因子負荷量 (表 6))

食物消費パタンの分析を行うために，1,000kcal 当たりの食品群別摂取量 (25 食品群) を変量として主因子法による因子分析を行った。その結果，第一因子の正方向には「その他の野菜」「緑黄色野菜」「藻類」「いも類」「きのこ類」「豆類」などの『副菜因子』，負方向には『アルコール因子』が抽出された。第二因子は，正方向に「パン類」「洋菓子類」「砂糖類」「嗜好飲料」「油脂類」「和菓子類」などの『間食因子』，負方向は「米類」「豆類」「みそ類」「塩・しょうゆ」

などの『和風食品因子』が抽出された。第三因子の正方向は「塩・しょうゆ」「肉類」「魚介類」「油脂類」の『主菜因子』が，負方向には「米類」の『米食因子』が抽出された。

7. 低栄養状態に関連する要因分析（オッズ比；OR）

表7にロジスティック回帰分析の結果を示す。低栄養状態と有意な関連を示したものは，年齢（OR=1.07，CI: 1.03-1.10），BMI(OR=0.51，CI: 0.45-0.58），エネルギーの不足（OR=4.38，CI: 1.06-18.10）であった。因子得点や世帯構造との関連はみられなかった。

表4 栄養状態別にみた栄養素等摂取量（1,000kcal当たり）

	正常 (n=1,008)		低栄養 (n=114)	
エネルギー (kcal)	1841 ±	503	1769 ±	444
たんぱく質 (g)	36.3 ±	6.3	35.7 ±	6.0
動物性たんぱく質 (g)	19.4 ±	6.6	19.6 ±	6.4
脂質 (g)	25.2 ±	6.9	25.1 ±	7.0
動物性脂質 (g)	15.3 ±	6.2	16.0 ±	6.5
脂肪酸 (g)	21.2 ±	6.1	21.3 ±	6.1
SFA (g)	6.85 ±	2.28	7.09 ±	2.40
MUFA (g)	8.38 ±	2.76	8.38 ±	2.78
PUFA (g)	6.01 ±	1.81	5.81 ±	1.90
炭水化物 (g)	146.5 ±	19.7	147.7 ±	18.7
ナトリウム (mg)	1812.1 ±	498.2	1819.3 ±	490.2
カリウム (mg)	1390.8 ±	331.7	1362.1 ±	312.7
カルシウム (mg)	285.6 ±	93.8	286.0 ±	93.9
マグネシウム (mg)	146.3 ±	29.0	141.0 ±	26.7
リン (mg)	566.8 ±	106.1	558.9 ±	101.3
鉄 (mg)	4.18 ±	0.93	4.09 ±	0.91
ビタミンA (μgRE)	476.0 ±	250.6	493.2 ±	260.6
ビタミンD (μg)	8.8 ±	4.1	8.7 ±	4.0
ビタミンB1 (mg)	0.47 ±	0.12	0.46 ±	0.12
ビタミンB2 (mg)	0.79 ±	0.19	0.78 ±	0.19
ビタミンC (mg)	70.4 ±	29.2	68.7 ±	27.5
食物繊維総量 (g)	7.4 ±	2.2	6.9 ±	2.2
水溶性 (g)	1.8 ±	0.8	1.7 ±	0.7
不溶性 (g)	5.5 ±	1.5	5.2 ±	1.5
アルコール (g)	4.9 ±	9.4	4.4 ±	10.4

平均値±標準偏差

表5 栄養状態別にみた食品群別摂取量（1,000kcal当たり）

	正常 (n=1,008)		低栄養 (n=114)		
米類 (g)	209.7 ±	74.5	210.4 ±	75.3	
パン類 (g)	21.1 ±	27.8	17.6 ±	25.6	
めん類 (g)	19.8 ±	27.6	17.2 ±	21.5	
種実類 (g)	1.3 ±	2.7	0.7 ±	1.4	*
いも類 (g)	15.4 ±	12.7	16.2 ±	14.8	
砂糖類 (g)	4.2 ±	3.8	5.1 ±	5.2	
和菓子類 (g)	5.6 ±	6.4	6.2 ±	5.7	
洋菓子類 (g)	5.2 ±	5.9	5.7 ±	6.0	
油脂類 (g)	8.6 ±	6.2	8.4 ±	6.5	
大豆製品 (g)	32.8 ±	18.0	29.6 ±	21.7	
みそ (g)	4.6 ±	3.6	4.3 ±	3.6	
果物 (g)	69.0 ±	56.9	71.8 ±	57.0	
緑黄色野菜 (g)	64.5 ±	44.4	61.9 ±	37.7	
漬物 (g)	19.5 ±	18.1	21.0 ±	20.2	
その他の野菜 (g)	78.1 ±	42.6	76.7 ±	41.0	
きのこ (g)	5.7 ±	5.6	4.9 ±	5.1	
海藻類 (g)	9.6 ±	7.9	10.0 ±	8.9	
酒類 (g)	62.4 ±	103.4	52.7 ±	110.0	
嗜好飲料 (g)	92.0 ±	107.6	93.9 ±	110.5	
魚介類 (g)	40.1 ±	22.0	37.9 ±	21.9	
肉類 (g)	25.9 ±	16.3	27.7 ±	17.8	
卵類 (g)	13.4 ±	10.2	15.3 ±	11.6	
乳・乳製品 (g)	76.8 ±	62.0	74.6 ±	64.6	
塩・しょうゆ (g)	3.9 ±	1.6	3.9 ±	1.7	
その他の調味料 (g)	0.05 ±	0.07	0.05 ±	0.05	

* $p<0.05$（正常と比較）
平均値±標準偏差

表6　食物消費パタン（バリマックス回転後の因子負荷量）

	第一因子	第二因子	第三因子
米類	−0.168	−0.795	−0.486
パン類	−0.115	0.456	−0.109
めん類	−0.027	0.045	−0.029
種実類	0.148	0.052	0.038
いも類	0.423	0.012	0.118
砂糖類	0.074	0.310	0.036
和菓子類	0.228	0.234	−0.040
洋菓子類	0.204	0.334	−0.008
油脂類	0.087	0.257	0.316
豆類	0.331	−0.221	0.162
みそ	0.044	−0.219	−0.003
果実類	0.309	0.232	−0.023
緑黄色野菜	0.498	−0.051	0.070
その他の野菜	0.525	−0.053	0.153
漬物類	0.144	−0.139	−0.007
きのこ類	0.403	−0.047	0.128
藻類	0.437	−0.187	0.073
酒類	−0.434	−0.133	0.038
嗜好飲料	−0.102	0.275	−0.061
魚介類	0.160	−0.082	0.341
肉類	−0.013	0.062	0.403
卵類	0.019	−0.072	0.175
乳類	0.152	0.202	−0.064
塩・しょうゆ	0.047	−0.204	0.737
その他の調味料	0.069	0.040	0.097
寄与率（%）	6.835	6.319	5.259
累積寄与率（%）			18.413

表7　栄養状態判定を説明するためのロジスティック回帰分析
（オッズ比（OR）および95%信頼区間）

		OR	95%信頼区間			p値
年齢		1.07	1.03	—	1.10	0.00
BMI		0.51	0.45	—	0.58	0.00
性別	男性	1.00				
	女性	0.81	0.47	—	1.37	0.426
適正（エネルギー）	適正でない（低値）	4.38	1.06	—	18.10	0.041
	適正	1.00				
	適正でない（高値）	0.85	0.48	—	1.49	0.562
適正（脂肪）	適正	1.00				
	適正でない	0.45	0.18	—	1.12	0.086
適正（カルシウム）	適正	1.00				
	適正でない	1.15	0.56	—	2.33	0.707
適正（ビタミンC）	適正	1.00				
	適正でない	0.45	0.10	—	2.12	0.312
適正（食物繊維）	適正	1.00				
	適正でない	1.12	0.57	—	2.20	0.741
適正（食塩）	適正	1.00				
	適正でない	0.92	0.17	—	4.88	0.919
第一因子得点	Q1	1.00				
	Q2	0.74	0.31	—	1.76	0.496
	Q3	1.38	0.55	—	3.45	0.497
	Q4	1.28	0.49	—	3.38	0.616
	Q5	0.61	0.21	—	1.79	0.369
第二因子得点	Q1	1.00				
	Q2	1.15	0.52	—	2.53	0.732
	Q3	1.20	0.53	—	2.74	0.659
	Q4	0.92	0.39	—	2.15	0.842
	Q5	1.72	0.76	—	3.91	0.194
第三因子得点	Q1	1.00				
	Q2	1.38	0.61	—	3.10	0.438
	Q3	1.43	0.64	—	3.21	0.390
	Q4	2.22	0.99	—	4.96	0.053
	Q5	2.36	0.99	—	5.63	0.053
世帯構造	ひとり暮らし	1.00				
	夫婦のみ	1.19	0.46	—	3.08	0.716
	二世代	0.81	0.30	—	2.19	0.678
	三世代	1.15	0.44	—	2.96	0.779
	その他	1.27	0.34	—	4.70	0.719

Q: quintile.

【考察】

平成17年度の介護保険制度改革で，高齢者の低栄養状態改善を目的とした予防重視の考え方へ改められた[9]。また平成18年4月には市町村地域支援事業介護予防事業特定高齢者施策が施行され，要支援・要介護状態になる可能性の高い者を，ハイリスクな特定高齢者として介護予防を行っている[9]。その中で栄養状態の判定は，6ヶ月間の体重減少，BMI，血清アルブミン濃度によってスクリーニングされており，本研究ではこれらの基準を参考とし，BMIと血清アルブミン濃度によって低栄養者を判定した。

今回，対象者の食事内容については，健康日本21[8]にある「適正な食事」に基づき評価した。その結果，久山町の高齢者の36.5%が適正な食事を摂取しており，全国平均で15.1%[8]，久山町住民全体で12.3%[11]であるのに比べて，良好な食事摂取状況であることが示された。その中でも，低栄養のリスクとして，エネルギー摂取の不足が認められた。高齢者は加齢によってエネルギー消費量が減少するが，その大部分が身体活動量と基礎代謝量の低下によるものである[4][12]。エネルギー摂取量が低下することは言い換えれば食事摂取量そのものが低下することであり，他の栄養素の摂取不足を招くことにもなる。したがって，高齢者の栄養アセスメントを適切に行い，必要なエネルギー量を十分に摂取することが，不足が懸念される微量栄養素の必要量を確保することにもつながると考えられる。また高齢者の食物消費パタンについては，食事パタンと低栄養に関連はみられなかった。他の報告では，動物性食品に富んだ食事パタンの者が栄養状態の良好な者が多く[13]生活機能も高いと言われている[14]。

今回の調査では，高齢者の世帯構造についても検討した。一般的に，高齢者の一人暮らし世帯では食事の質が低下し，低栄養のリスクが高いと考えられている[15][16]。久山町における1998年の先行研究においても「配偶者の有無」や「同居する家族」により栄養状態は影響を受けることが示唆されている[17]。しかし，一方で高齢者の一人暮らしは，食事内容が他の者と同居している者と変わらないといった報告[18]や，低栄養による死亡のリスクを増加させないといった報告[19]もある。今回の結果では，世帯構造と低栄養との関連はみられなかった。その一因として，血清アルブミン値が3.8g/dl以下の者が全体の1%程度で，対象高齢者のほとんどが自ら健診会場に足を運ぶことのできる者であったことが考えられる。加えて，久山町でも例外ではなく，現在の日本においてはコンビニエンスストア等の利用，外食・中食等の発達から，高齢者が炊事をしなくても，大きな負担なく食事を調達できるようになってきたことなどがその要因ではないかと推察された。

まとめとして，本研究では，地域在宅高齢者の栄養状態について，栄養摂取や世帯構造が及ぼす要因について検討した。

1) BMIと血清アルブミン値から低栄養と判定された者は，男性56名(11.3%)，女性58名(9.3%)であった。
2) 適正な食事をしている者の割合は，男性157名(31.7%)，女性252名(40.2%)で，全体としては36.5%の者が適正な食事をしていた。
3) 栄養状態との関連では，年齢とエネルギーの不足は低栄養のリスクを増加させ，BMIはリスクを低下させた。しかしながら，世帯構造の違いと栄養状態は関連を示さなかった。

以上のことより，高齢者の栄養状態を良好に保つためには，高齢者の栄養アセスメントを適切に行い，必要なエネルギー量を十分に摂取することが重要で，このことが不足が懸念される微量栄養素の必要量を摂取することにもつながると考えられた。

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Incidence and survival of dementia in a general population of Japanese elderly: the Hisayama study

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ABSTRACT

Objective: To estimate the incidence and survival rates of total and cause specific dementia in a general Japanese population.

Methods: A total of 828 subjects without dementia, aged 65 years or over, were followed-up prospectively for 17 years. Dementia was subdivided into cause specific subtypes: namely, Alzheimer's disease (AD), vascular dementia (VD), dementia with Lewy bodies (DLB), combined dementia and other types of dementia. During the follow-up, 275 subjects developed dementia; of these, 251 (91.2%) were evaluated morphologically, with 164 subjected to brain autopsy examination and the remaining 87 to neuroimaging.

Results: The incidences of total dementia, AD, VD, DLB, combined dementia and other types of dementia were 32.3 (n = 275), 14.6 (124), 9.5 (81), 1.4 (12), 3.8 (33), and 3.1 (16) per 1000 person years, respectively. The incidences of AD, combined dementia and other types of dementia rose with increasing age, particularly after the age of 85 years, but this tendency was not observed for VD or DLB. The survival curve of dementia cases aged 65–89 years was significantly lower than that of age and sex matched controls (10 year survival rate, 13.6% vs 29.3%; hazard ratio 1.67; 95% confidence interval 1.31 to 2.13). The 10 year survival rates were not significantly different among dementia subtypes.

Conclusions: Our findings suggest that the Japanese elderly population has a high risk for the development of dementia, specifically AD and VD, and once dementia is established, the risk of death is considerable.

Approximately 24.3 million people suffer from dementia globally, and this number is expected to double every 20 years to 81.1 million by 2040 because of the rapid increase in the number of elderly worldwide.[1] Effective prevention requires a strategy based on information about morbidity and mortality from dementia in general populations. Several population based studies have investigated the incidence[2–9] and fatality rates[10–13] of total and cause specific dementia but the current knowledge about the incidence and prognosis of dementia has derived mainly from studies done in Western populations, and it is unclear to what extent these findings apply to Japanese elderly populations. Here we present the incidence and survival of cause specific dementia in a 17 year follow-up study conducted in a Japanese community.

METHODS

Study population

Since 1985, a follow-up survey of dementia among individuals aged 65 years or older has been ongoing in the town of Hisayama, Japan.[9] The screening and assessment processes of the present analysis are shown in fig 1. In 1985, a total of 887 subjects aged 65 years or older (participation rate 94.6%) underwent a screening examination that included Hasegawa's dementia scale (HDS),[14] which is a neuropsychological test widely used in Japan comprised of 11 questions regarding orientation, memory function, common knowledge and calculation capacities, and questionnaires regarding psychological and medical symptoms, medical conditions and activities of daily living. Subjects with possible cognitive impairment underwent comprehensive investigations. After excluding 59 subjects with dementia at baseline, the remaining 828 subjects were enrolled in this study.

Follow-up survey

Subjects were followed prospectively from November 1985 to October 2002 (fig 1). Detailed information about the follow-up survey of dementia has been described elsewhere.[9] Briefly, we established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office. Regular health checks were given annually to obtain information on any stroke or dementia missed by the monitoring network. Health status was also checked yearly by mail or telephone for any subject who did not undergo a regular examination or who had moved out of town.

Follow-up screening surveys of cognitive function were conducted in 1992,[15] 1998 and 2005. The screening surveys included neuropsychological tests (HDS,[14] HDS revised version (HDS-R)[16] or Mini-Mental State Examination (MMSE)[17]) and questionnaires similar to those used at the first screening. For subjects whose test scores were below the cut-off points (22/32.5 for HDS, 21/30 for the HDS-R and MMSE), comprehensive investigations, including interviews of the families or attending physicians, physical and neurological examinations, and a review of the clinical records were conducted.

When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 553 subjects died, 439 of whom (79.4%) were subjected to autopsy. For dementia subjects with autopsy, detailed neuropathological evaluation was performed. No subject was lost to follow-up.

Diagnosis of dementia

The diagnosis of dementia was made clinically based on the guidelines of the Diagnostic and

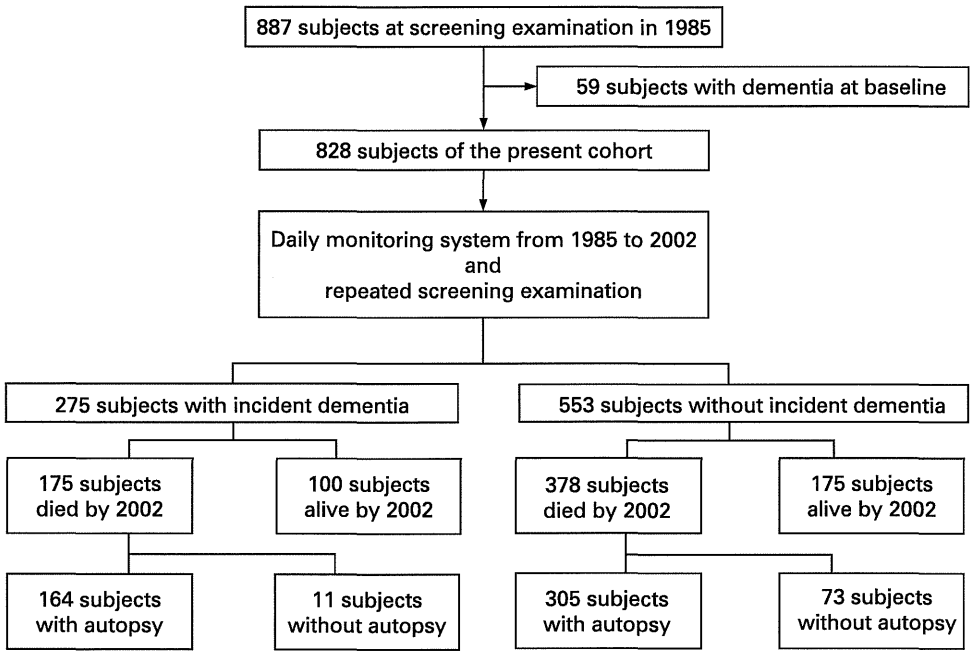

Figure 1 Flow chart for screening and diagnostic procedures.

Statistical Manual of Mental Disorders, revised third edition (DSM-III-R).[18]

Alzheimer's disease (AD), vascular dementia (VD) and dementia with Lewy bodies (DLB) were diagnosed based on the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[19] the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)[20] and the revised consensus guidelines described in the third report of the DLB consortium,[21] respectively.

For neuropathological evaluation of AD, the frequency of senile plaques and neurofibrillary tangles (NFT) was evaluated using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria[22] and Braak stage.[23] The CERAD score and Braak stage were combined using the National Institute on Aging-Reagan Institute (NIA-RI) criteria,[24] and dementia cases with a "high likelihood" of AD pathology were defined as definite AD. Definite VD was defined as dementia with causative stroke or cerebrovascular change in neuroimaging and no neuropathological evidence of other forms of dementia. According to the DLB guidelines,[21] dementia cases with "high likelihood" criterion of DLB pathology were defined as definite DLB. Senile dementia of the neurofibrillary tangle type (tangle only dementia: SD-NFT) was diagnosed neuropathologically using Yamada's guideline.[25 26]

During the 17 year follow-up period, 275 subjects developed dementia. Of these, 175 cases died and 134 (76.6%) of these

Table 1 Comparison of the clinical diagnosis of dementia subtype and the final diagnosis using neuropathological findings among 164 incident dementia cases with autopsy: the Hisayama Study, 1985–2002

	Clinical diagnosis		
Final diagnosis using neuropathological findings	**AD (n = 71)**	**VD (n = 47)**	**Other (n = 46)**
Pure AD	35	16	11
Pure VD	17	21	12
DLB	2	1	6
Combined dementia	12	7	10
AD+VD	6	3	4
AD+DLB	3	2	1
VD+DLB	2	1	1
AD+VD+DLB	0	0	2
AD+chronic subdural haematoma	0	1	0
DLB+SD-NFT	0	0	1
AD+VD+hypothyroid	1	0	0
SD-NFT+carbon monoxide poisoning	0	0	1
Other	5	2	7

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; SD-NFT, senile dementia of the neurofibrillary tangle type; VD, vascular dementia.

Table 2 Frequency of each type of dementia among 275 incident dementia cases: the Hisayama Study, 1985–2002

Type of dementia	**n (%)**
AD	124 (45.1)
VD	81 (29.5)
DLB	12 (4.4)
Combined dementia	33 (11.6)
AD+VD	13 (4.7)
AD+DLB	9 (3.3)
VD+DLB	5 (1.8)
AD+VD+DLB	2 (0.7)
AD+chronic subdural haematoma	1 (0.4)
DLB+SD-NFT	1 (0.4)
AD+VD+hypothyroid	1 (0.4)
SD-NFT+carbon monoxide poisoning	1 (0.4)
Other	16 (6.2)
SD-NFT	8 (2.9)
Chronic subdural haematoma	2 (0.7)
Brain tumour	2 (0.7)
Head trauma	2 (0.7)
Pick's disease	1 (0.4)
Hypoxic ischemic encephalopathy	1 (0.4)
Unknown	9 (3.3)

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; SD-NFT, senile dementia of the neurofibrillary tangle type; VD, vascular dementia.

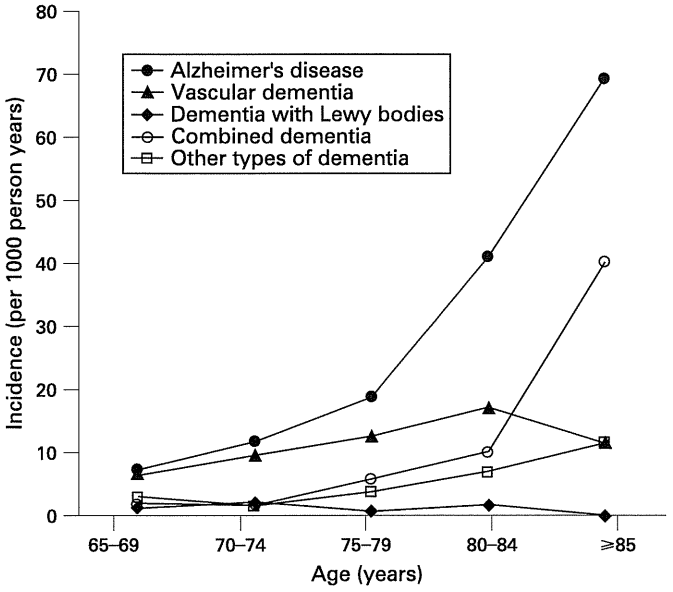

Figure 2 Incidence rates of cause specific dementia by age group.

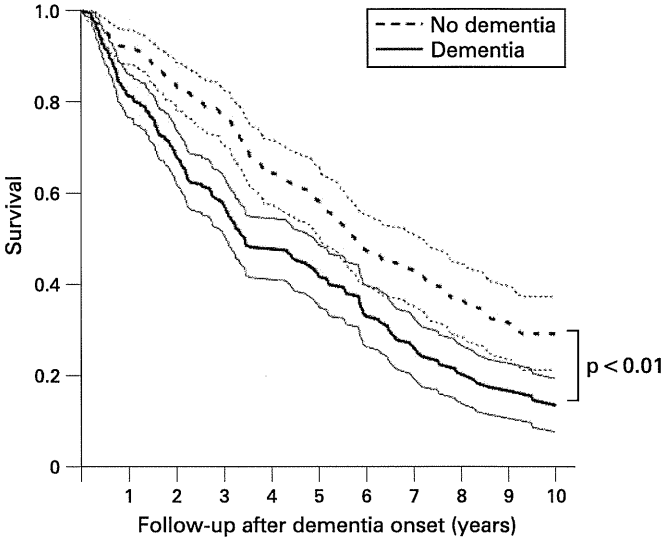

Figure 3 Survival rates and 95% confidence intervals for new onset dementia cases and for age and sex matched control participants without dementia onset.

cases underwent brain autopsy examination (fig 1). The brains were evaluated neuropathologically in an additional 30 subjects with dementia who died after the end of the follow-up period, from November 2002 to October 2005. A total of 164 of the 275 subjects with dementia (59.6%) were examined neuropathologically. We performed evaluation with neuroimaging on 248 subjects with dementia (90.2%); among the 111 subjects with dementia who did not have an autopsy examination, 87 underwent a neuroimaging examination. Therefore, 251 subjects with dementia (91.2%) were evaluated morphologically.

In the present analysis, we used the final diagnosis of dementia subtypes, which was made based on the clinical and neuropathological information for dementia subjects with autopsy and clinical information, including neuroimaging only for those without autopsy. Table 1 shows a comparison of the clinical diagnosis of dementia subtype, which was made without information on neuropathological findings, and the final diagnosis, which was made using neuropathological findings, among 164 incident dementia cases with autopsy. Although the clinical diagnosis was not necessarily the same as the final diagnosis, moderate agreement was observed between the clinical and final diagnoses (agreement rate = 60%, kappa coefficient = 0.48 for AD; agreement rate = 59%, kappa coefficient = 0.53 for VD). Table 2 shows the frequency of each type of dementia among 275 incident dementia cases. We found 124 pure AD cases (definite 62; probable 52; possible 10), 81 pure VD cases (definite 50; probable 31) and 12 pure DLB cases (definite nine; probable two; possible one). When causes of cognitive impairment were attributed to two or more types of dementia, we classified the dementia as "combined dementia". This category accounted for 33 cases. There were 16 cases of other types of dementia.

The date of onset of VD was determined as the date when the responsible stroke occurred but the final diagnosis of VD was made more than 3 months after the stroke. The tentative time of onset, when the family or attending physician first noticed abnormal behaviour by the subject, was used for other types of dementia.

Statistical analysis

The incidence of dementia was estimated using a person year approach. We estimated survival curves for the first 10 years after the onset of dementia for 221 new onset dementia cases with ages at dementia onset ranging from 65 to 89 years, and for 221 age and sex matched control subjects randomly selected from 553 subjects without incident dementia by the Kaplan–Meier product limit technique. We excluded subjects aged 90 years or over from this analysis because the number of control subjects for this age group was too small. Comparison of survival rates was done by log rank test. We also compared age and sex adjusted cumulative survival rates among cases with different types of dementia using Cox's proportional hazards model.

RESULTS

The incidence of total dementia was 32.3 per 1000 person years. With regard to type, AD was the most frequent type of dementia (14.6 per 1000 person years), followed by VD (9.5) and then DLB (1.4). The incidences of AD, combined dementia and other types of dementia rose with increasing age, particularly after the age of 85 years, but this tendency was not observed for VD or DLB (fig 2).

Figure 3 shows the 10 year survival curves for new onset dementia cases and control subjects without dementia onset. The survival curve of dementia cases was significantly lower compared with that of the control subjects (10 year survival rate, 13.6% vs 29.2%; hazard ratio 1.67; 95% confidence interval 1.31 to 2.13; p<0.0001). Median survival time was 3.5 years in subjects with dementia and 5.8 years in those without dementia.

The age and sex adjusted survival curves for cases with different types of dementia are shown in fig 4. The survival rate of subjects with DLB tended to be lower than that of subjects with other types of dementia but the differences were not significant, probably because of the small number of subjects with DLB (10 year survival rates, 18.9% for AD, 13.2% for VD, 2.2% for DLB, 10.4% for combined dementia, 14.4% for other types of dementia).

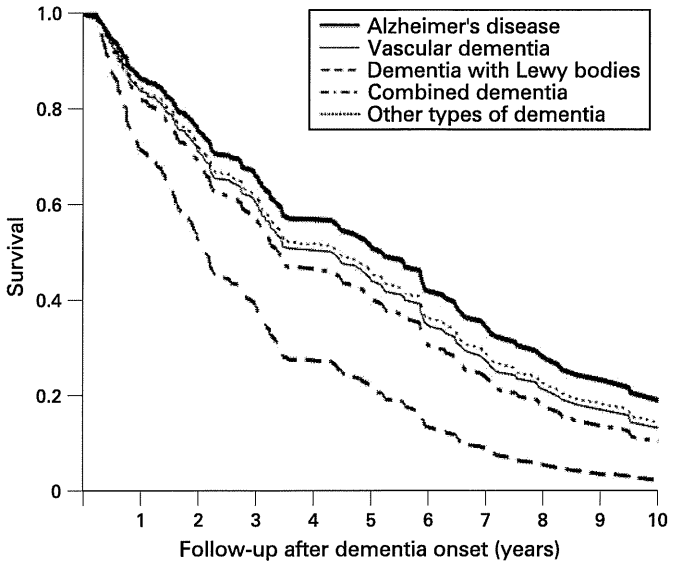

Figure 4 Age and sex adjusted survival rates of cause specific dementia.

DISCUSSION

The present analysis from a prospective cohort study has clearly demonstrated that the incidence of dementia was as high as 32.3 per 1000 person years in a general population of Japanese elderly, aged 65 years or older. We diagnosed dementia subtypes based on clinical and neuropathological examinations and found that AD, VD and DLB were the three major subtypes of dementia in this population. Another important finding was that the median survival time of subjects with new onset dementia was shorter than that of those without dementia onset.

Several population based cohort studies have reported the incidence of dementia for elderly populations.[2–9] The incidence of dementia of our study (32.3 per 1000 person years) was relatively higher than that obtained from the majority of other follow-up studies (13.5–25.5)[2–6] and similar to that of an Italian study (37.8)[7] and an African American study (32.4).[8] Possible reasons for the relatively higher incidence of dementia in our study were the frequently repeated screening surveys for dementia and the high follow-up rate.

In our subjects, DLB was the third most frequent type of dementia after AD and VD, with an incidence of 1.4 per 1000 person years. Although there have been several prevalence studies of DLB in general populations, little is known about the exact incidence of DLB.[27] Meich *et al* estimated the incidence of DLB as 0.57 per 1000 person years in a US population.[2] In contrast, no case of DLB was observed in the 4 year follow-up study of an Italian population.[7] It is possible that the higher incidence of DLB in our study resulted from a higher rate of neuropathological evaluation among subjects with dementia. Further cohort studies are needed to investigate the precise incidences of DLB.

In the present analysis, all types of dementia were associated with higher mortality, and the estimate of median survival time for subjects with total dementia was 3.5 years. This is shorter than that obtained from other population based cohort studies (5.2–7.6 years).[10–13] Most previous cohort studies estimated median survival time in follow-up surveys of subjects having dementia at the baseline examination. Therefore, it is possible that severe dementia cases with poor prognosis may not have been included, and that the survival time of patients with dementia may have been overestimated ("length bias"). In the Canadian Study of Health Aging, the crude median survival time was 6.6 years but the estimated survival time from the onset of dementia after controlling for "length bias" was 3.3 years.[13] This finding is comparable with the median survival time from the onset of dementia observed in the present analysis.

The strengths of our study include its longitudinal population based study design, long duration of follow-up, sufficient number of dementia events, 100% follow-up of subjects and examination of the brains of most dementia cases with autopsy and neuroimaging. A limitation of our study is that relatively low cut-off points of neuropsychological tests for comprehensive investigations of dementia in the follow-up examinations may have caused us to miss subjects in the early course of dementia. This limitation may have led to an underestimation of the incidence of dementia and survival time. Another limitation is that we compared the survival rates among subjects matched by age at dementia onset ranging only within 65–89 years because the number of control subjects aged 90 years or older without dementia was too small. However, subjects aged 90 years or older are not likely to live long, irrespective of the existence of dementia, and inclusion of subjects of this age group is not likely to have changed the findings of this study.

In conclusion, relatively more Japanese elderly suffer from dementia than the proportion expected based on the results of other follow-up studies. Once dementia is established, the risk of death is 1.7-fold higher compared with subjects without dementia. It is important to elucidate risk factors for each type of dementia and establish dementia prevention strategies, especially in countries such as Japan where the elderly population is increasing rapidly, as dementia places a burden on families and communities.

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Anti-Inflammatory Effects of Antidepressants: Possibilities for Preventives Against Alzheimer's Disease

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Abstract: Increasing evidence of pro-inflammatory mediator expression in major depressions indicate that inflammatory changes may play a role. If this is true, the efficacy of antidepressants may be partially attributable to suppression of inflammation. Various types of antidepressants can suppress serum and plasma levels of pro-inflammatory mediators in patients with major depression. Therefore they can inhibit the production of pro-inflammatory mediators by immune cells. These include glial cells, which are the main sources and targets of cytokines in the brain. This review summarizes the evidence showing that antidepressants have an anti-inflammatory potential. The putative mechanisms are also discussed. Because of the anti-inflammatory effects of antidepressants, they might also act as preventives for neurodegenerative dementias including Alzheimer's disease, where the pathogenesis involves chronic inflammation associated with activated microglia.

Keywords: Antidepressants, major depression, Alzheimer's disease, inflammation, cytokines, microglia.

INTRODUCTION

The history of antidepressant drug development has been unique and fortuitous. The monoamine oxidase inhibitor iproniazid and the tricyclic antidepressant (TCA) imipramine were originally developed as a tuberculosis remedy and as an antihistamine, respectively [1]. These drugs were serendipitously found to have an antidepressant effect in the 1950s, and soon thereafter were shown to increase synaptic levels of noradrenaline (NA) and 5-hydroxytryptamine (5-HT) [1]. Currently, it has been shown that antidepressants modulate not only the monoamine neurotransmitter system but also the inflammatory system.

The association between inflammation and major depression has been supported by the well-known observation that pro-inflammatory cytokines such as interferon (IFN)-α, which is used to treat patients with hepatitis C, and interleukin (IL)-2, which is used to treat patients with certain cancers, frequently induce depressive symptoms as side effects. In addition, depression is often found in inflammatory diseases such as multiple sclerosis, allergies of different types, and rheumatoid arthritis, in which pro-inflammatory cytokines are over-expressed [2]. Animal studies also support this idea. Chronic administration of the endotoxin lipopolysaccharide (LPS) or pro-inflammatory cytokines into rats has been shown to induce symptoms similar to depression. These symptoms are referred to as sickness behavior, which includes appetite loss, suppressed sexual behavior and apathy [3, 4].

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It can be hypothesized that if inflammation plays a causative role in the pathogenesis of major depression, antidepressants may partially act by suppressing such inflammation. The first evidence indicating that antidepressants have anti-inflammatory effects appeared four decades ago. Martelli *et al.* (1967) showed that administration of TCAs inhibited chemically induced edema in the standard rat paw assay [5]. Ten years later, Horrobin and colleagues reported that the TCA clomipramine was a powerful antagonist of prostaglandin (PG) E_2 [6] and then proposed that diverse antidepressants are inhibitors of PG synthesis [7]. In fact, a recent *in vitro* study revealed that the selective serotonin reuptake inhibitor (SSRI) paroxetine attenuated cyclooxygenase (COX)-2 expression in human T cells stimulated with phytohemagglutinin (PHA) [8]. Furthermore, experimental evidence is accumulating that various types of antidepressants exert anti-inflammatory effects by decreasing pro-inflammatory cytokine levels or increasing anti-inflammatory cytokine levels.

This review focuses on the influence of antidepressants on inflammatory mediator levels, particularly serum and plasma cytokine levels, in depressed patients. It also focuses on glial production of those mediators *in vitro* since glial cells are the major immune cells responsible for inflammation in the brain. We also discuss possible mechanisms of the anti-inflammatory action of antidepressants and the potential of antidepressants to act as preventives against Alzheimer's disease (AD).

EVIDENCE FOR INFLAMMATION ASSOCIATED WITH MAJOR DEPRESSION

It has been reported that the levels of acute phase proteins such as C-reactive proteins (CRP), α2-macroglobulin, α1-acid glycoprotein, complement C4 and haptoglobin are

upregulated in major depression [9-14]. The levels of PGE_2 and thromboxane B_2 are also reported to be elevated in depressed patients [15-17]. Moreover, major depression is accompanied by increased levels of pro-inflammatory cytokines such as IL-1β, IL-6, IFN-γ and tumor necrosis factor (TNF)-α [18-23] whereas the anti-inflammatory cytokine transforming growth factor (TGF)-β1 has been shown to be decreased [24].

In contrast to many studies on serum and plasma levels, there have been few on cerebrospinal fluid (CSF) levels. Only IL-1β has been shown to be increased in major depression [25] while IL-6 was decreased [25] or not changed [26] and TNF-α was not changed [25].

It is uncertain whether inflammation is a cause or a result of major depression. In addition, it must be noted that not all studies have found such an association [27, 28]. Nevertheless, inflammation certainly appears to be a factor in at least some cases of major depression. Indeed, Müller *et al.* (2006) have recently shown interesting data that depressed patients treated for 6 weeks with the serotonin-noradrenaline reuptake inhibitor (SNRI) reboxetine plus the COX 2 inhibitor celecoxib showed significantly greater improvement in scores on the Hamilton Depression Scale compared to the reboxetine-alone group [29].

EFFECT OF ANTIDEPRESSANTS ON INFLAMMATORY MEDIATOR LEVELS IN PATIENTS WITH MAJOR DEPRESSION

Several groups have studied serum or plasma levels of various cytokines and their receptors in patients with major depression before and after antidepressant pharmacotherapy (Table **1**, for a summery of studies before 2000 see [30]). Tuglu *et al.* (2003) showed that administration of SSRIs for 6 weeks decreased serum levels of TNF-α and CRP [23]. Basterzi *et al.* (2005) showed that similar SSRI treatment diminished serum IL-6 levels [31]. In keeping with such an anti-inflammatory effect, Myint *et al.* (2005) reported that 8-weeks of antidepressant treatment increased plasma TGF-β1 levels [24]. Interestingly, it has been shown that plasma levels of TNF-α and IL-6 in patients with SSRI-resistant depression are significantly higher than those in healthy controls [32]. However, Kubera *et al.* (2000) demonstrated that a 6-week antidepressant treatment which elicited successful clinical remissions did not change significantly the serum levels of IL-6, IL-10 and IL-1 receptor antagonist [33]. Two studies even described increases in the plasma TNF-α levels following antidepressant treatment. Kraus *et al.* (2002) reported that a 4-week treatment with a tetracyclic antidepressant (i.e., mirtazapine) increased the plasma levels of TNF-α and soluble TNF-α receptors significantly while a similar treatment with the SNRI venlafaxine did not influence those levels [34]. Kagaya *et al.* (2001) showed that plasma TNF-α level was increased after 1-month pharmacotherapy consisting mainly of clomipramine. They also examined the plasma levels of IL-1β and IL-6. Those levels after treatment were lower than before treatment, but not significantly [35].

Taken together, the effect of antidepressants on serum and plasma levels of inflammatory cytokines in depressed patients is still controversial. Such an inconsistency may stem from the difference in methodology employed and the limitation due to the small numbers tested in these clinical studies (e.g., $n<30$ in each study). In addition, Kennis and Maes (2002) pointed out the technical difficulty in detecting serum and plasma levels of cytokines since circulating cytokine levels are very low in human subjects [30]. Therefore, early studies on the cytokine concentrations before and after antidepressant treatment often employed *ex vivo* methods. Specifically, cytokine levels in the supernatants of cultured whole blood or cultured peripheral blood mononuclear cells (PBMCs) from depressed patients were measured by enzyme-linked immunosorbent assay (ELISA). In both cases, cytokine production was induced by stimulation with LPS and/or mitogens such as PHA and concanavalin A. Such *ex vivo* studies have shown inconsistent results on protein levels (for review see [30]).

Recently, Tsao *et al.* (2006) examined mRNA expression of inflammatory cytokines in non-stimulated PBMCs from depressed patients before and after 3-month SSRI (i.e., fluoxetine) treatment by using reverse transcriptase-polymerase chain reaction (RT-PCR) assy. They found that such pharmacotherapy significantly diminished the mRNA expression of IFN-γ. The mRNA expressions of IL-1β and TNF-α were also inhibited, but not significantly [36].

EFFECT OF ANTIDEPRESSANTS ON GLIAL PRODUCTION OF INFLAMMATORY MEDIATORS *IN VITRO*

With regard to *in vitro* studies, various types of antidepressants have anti-inflammatory effects in terms of cytokine production by immune cells. Early studies focused on the effects of antidepressants on cytokine production by cultured PBMCs or cultured whole blood from healthy subjects or depressed patients. They demonstrated that *in vitro* treatment with various types of antidepressants decreased the production of pro-inflammatory cytokines including IFN-γ while increasing the production of such anti-inflammatory cytokines as IL-10 (for reviews see [30, 37]). Moreover, a TCA (amitriptyline) and a SSRI (fluoxetine) were shown to attenuate the production of pro-inflammatory cytokine-induced PGE_2 and nitric oxide (NO) by cultured human synovial cells [38].

Increasing evidence strongly suggests that changes in cytokine levels outside the brain cause changes in cytokine expression and activity in the brain, and *vice versa* [39]. In other words, the central and peripheral cytokine compartments are integrated but differently regulated [40]. In the brain, microglia and astrocytes are the major cell types that participate in the inflammatory system both as sources and targets of cytokines. This fact suggests that these glial cells may represent overlooked targets in the etiology of major depression. Several studies have recently investigated the effects of antidepressants on the glial production of inflammatory mediators *in vitro* (Table **2**).

Obuchowicz *et al.* (2006) examined the effects of amitriptyline and its metabolite nortriptyline on the production of IL-1β and TNF-α by rat microglial and mixed glial (i.e., microglia plus astrocytes) cultures stimulated with LPS, using both ELISA and quantitative RT-PCR. They found

Table 1. Summary of Studies on Serum/Plasma Levels of Inflammatory Mediators in Depressed Patients Before and After Antidepressant Therapy

Study	n	Antidepressants	Target Studied	Result
Tuglu *et al.* (2003)	26	SSRIs (mostly Sertraline/Citalopram)	TNF-α	Decrease
			CRP	Decrease
Basterzi *et al.* (2005)	23	SSRIs (not specified)	IL-6	Decrease
Myint *et al.* (2005)	10	Various types (mostly Paroxetine/Fluoxetine)	TGF-β1	Increase
Kubera *et al.* (2000)	9	Not specified	IL-6	No change
			IL-10	No change
			IL-1RA	No change
Kraus *et al.* (2002)	9	SNRI (Venlafaxine)	TNF-α	No change
			sTNF-Rs	No change
	11	Tetracyclic (Mirtazapine)	TNF-α	Increase
			sTNF-Rs	Increase
Kagaya *et al.* (2001)	12	Mostly TCA (Clomipramine)	TNF-α	Increase
			IL-1β	No change
			IL-6	No change

IL-1RA, IL-1 receptor antagonist
sTNF-Rs, soluble TNF receptors

Table 2. Summary of Studies that Examined the Effect of Antidepressants on Glial Production of Inflammatory Mediators *In Vitro*

Study	Cell Used	Antidepressants	Target Studied	Result
Obuchowicz *et al.* (2006)	Rat microglia Rat mixed glia	TCAs (Amitriptyline/Nortriptyline)	IL-1β	Decrease
			TNF-α	Decrease
			IL-1β mRNA	No change
			TNF-α mRNA	No change
Hashioka *et al.* (2007)	Mouse microglia (6-3)	TCA (Imipramine)	IL-6	Decrease
			NO	Decrease
		SSRI (Fluvoxamine)	IL-6	Decrease
			NO	Decrease
		SNRI (Reboxetine)	IL-6	Decrease
			NO	Decrease
		LiCl	IL-6	Increase
			NO	Decrease
Vollmar *et al.* (2008)	Rat mixed glia	SNRI (Venlafaxine)	IL-6	Decrease
			IFN-γ	Decrease
			TGF-β	Increase
			IL-10	No change

(Table 2) contd....

Study	Cell Used	Antidepressants	Target Studied	Result
Ha *et al.* (2006)	Mouse microglia (BV2)	SSRI (Fluoxetine)	NO	Increase
			iNOS mRNA	Increase
			IL-6 mRNA	Increase
			TNF-α mRNA	Increase
			NF-κB activity	Increase

that treatment with those antidepressants for 24 h significantly inhibited the secretion of both cytokines, but did not change the expression of the mRNAs [41].

We previously studied the effects of various types of antidepressants, as well as the mood stabilizer lithium chloride, on the release of the pro-inflammatory mediators IL-6 and NO from IFN-γ-activated murine 6-3 microglial cells by using ELISA and the Griess reaction, respectively [42]. We showed that 24-h pretreatment with the TCA imipramine, the SSRI fluvoxamine or the SNRI reboxetine significantly inhibited IL-6 and NO production in a dose-dependent manner. On the other hand, lithium chloride had a different spectrum of action, namely by enhancing IFN-γ-induced IL-6 production and inhibiting NO production.

Vollmar *et al.* (2008) measured IL-6, IL-10, IFN-γ and TGF-β concentrations in an astroglia-microglia co-culture treated with venlafaxine for 16 h by ELISA assay [43]. The culture system they employed allows mimicking of an inflammatory milieu by increasing the cultured microglial fraction without any inflammatory stimuli. They demonstrated an augmentation of TGF-β release with a concomitant reduction in the secretion of IL-6 and IFN-γ. Furthermore, they found a significant change of microglial phenotype from activated to resting morphology.

In contrast to those studies, Ha *et al.* (2006) demonstrated that treatment of murine microglial BV_2 cells with fluoxetine resulted in significant increases in NO and in the mRNAs of inducible NO synthase (iNOS), IL-6 and TNF-α [44]. They furthermore showed that fluoxetine increased the DNA binding activity of transcription factor nuclear factor-κB (NF-κB), whose activation mediates inflammatory responses. However, the study did not measure the concentrations of IL-6 and TNF-α released from microglial cells. Based on this study and the study by Obuchowicz *et al.*, it can be presumed that antidepressants inhibit the glial secretion of pro-inflammatory cytokines but do not decrease their mRNA levels. Thus, antidepressants may induce post-transcriptional changes in pro-inflammatory cytokines or increase their degradation as Obuchowicz *et al.* suggested.

Although the majority of studies have shown that antidepressants of various classes decrease the glial production of pro-inflammatory cytokines and increase the anti-inflammatory cytokine production, the limitation of such *in vitro* studies should be addressed. Considering the fact that antidepressant treatment needs at least 10-14 days for any clinical effectiveness to appear, the treatment of glial cells with antidepressants for 16-24 h appear to reflect only acute effects of the drugs. In addition, we should note the antidepressant concentrations those studies employed. Maes *et al.* (1999) indicated that 1 μM corresponds to the plasma concentrations attained during clinical treatment [45]. Pharmacokinetic studies in animals have shown that the concentrations of antidepressants detected in certain organs such as the brain and spleen are 10-20 times higher than plasma concentrations due to the lipophilic property of antidepressants [46, 47]. Nevertheless, the concentrations 50-100 μM used in some *in vitro* studies seem to be rather higher than clinically relevant concentrations.

POSSIBLE MECHANISMS OF ANTI-INFLAMMATORY ACTIONS OF ANTIDEPRESSANTS

The exact mechanism by which antidepressants exert anti-inflammatory effects remains to be elucidated. Although one should remember the possible differences between the mechanism underlying anti-inflammatory effects of drugs *in vitro* and *in vivo*, several mechanisms are possible.

One of the most plausible involves an increase in intracellular cyclic adenosine monophosphate (cAMP) levels. A number of *in vivo* studies have shown that many antidepressants increase intracellular concentrations of cAMP through activation of monoamine receptors such as the receptors for 5-HT and NA [48, 49]. Also, *in vitro*, data indicate that antidepressants of several classes increase intracellular cAMP levels [50, 51]. We demonstrated that TCA, SSRI and SNRI inhibited IFN-γ-induced microglial production of IL-6 and NO *in vitro*. These inhibitions were reversed by the cAMP inhibitor SQ 22536 and by the protein kinase A (PKA) inhibitor Rp-adenosine3', 5'-cyclic monophosphorothioate triethylammonium salt (Rp-3', 5'-cAMPS), suggesting that the anti-inflammatory effects of various antidepressants on microglia are at least partially mediated by the cAMP-dependent PKA pathway [42]. These results are consistent with findings in a study on human whole blood [52]. We also demonstrated that lithium chloride reduced IFN-γ-induced microglial production of NO. Interestingly, the inhibition by lithium chloride was not reversed by either SQ 22536 or Rp-3', 5'-cAMPS, indicating such an inhibitory effect of lithium chloride is not mediated by the cAMP/PKA pathway.

In a number of cell types, the activation of the cAMP/PKA pathway has been shown to inhibit NF-κB activity [53], whose activation is known to induce the gene expression of iNOS and various pro-inflammatory cytokines. Specifically, in rat primary astrocytes [54] and human monocytes [55], the activation of the cAMP/PKA pathway

inhibits LPS-mediated induction of NF-κB binding activity. Activation of the cAMP/PKA pathway not only down-regulates NF-κB activity, it also down-regulates the Janus family kinase (JAK)/signal transducer and activator of transcription (STAT) 1 pathway. Upregulation of the pathway is known to transactivate IFN-γ-responsive genes including iNOS [56] and IL-12 [57]. Recently, Delgado *et al.* (2003) demonstrated in mouse microglia that vasoactive intestinal peptide inhibited IFN-γ-induced JAK/STAT1 activation through upregulation of the cAMP/PKA pathway [58]. Therefore, antidepressant induced upregulation of the cAMP/PKA pathway may mediate inhibitory effects of antidepressants on LPS or IFN-γ-evoked inflammatory transactivations in immune cells (Fig. **1**).

The manner in which *in vivo* anti-depressant treatment increases intracellular cAMP levels appears to be strait forward. Explicitly, it is believed that antidepressants increase synaptic levels of 5-HT and NA through inhibiting reuptake by their transporters on presynaptic neurons. Thus causes activation of their receptors which are coupled to G proteins that can regulate the cAMP system. Through G-protein activation of adenylate cyclase (i.e., through the activation of 5-HT or NA receptor subtypes positively coupled to adenylate cyclase), cAMP production is increased.

It remains unclear as to how antidepressants increase intracellular cAMP levels *in vitro*. Antidepressants may act on cells *in vitro* independently of monoamine receptors coupled to G proteins. A recent genetic study has shown that genes of phosphodiesterases (PDEs), which degrade cAMP, are associated with a susceptibility to major depression and to antidepressant treatment response [59]. Accordingly, antidepressants may directly affect PDE functions in cells and thus increase the intracellular cAMP *in vitro*. Alternatively, we can presume that antidepressants could have direct effects on G proteins.

Maes and colleagues hypothesized that the mechanism is related to the effect of antidepressants on the serotonergic system by 5HT influencing cytokine production [30, 60]. Obuchowicz *et al.* suggested that the mechanism might be nonspecific because antidepressants are potent inhibitors of sodium and calcium influx [61]. Further studies on this subject are clearly warranted.

POTENTIAL OF ANTIDEPRESSANTS AS PREVENTIVES AGAINST ALZHEIMER'S DISEASE

Dementia and major depression are frequently comorbid among elder people. There is enough evidence from epidemiologic and neuropsychologic studies that major depression is associated with AD, even though it is uncertain whether major depression represents an early sign of dementia or a risk factor for dementia (for review see [62]).

It is well established that inflammatory processes are closely associated with the pathogenesis of a broad spectrum of neurodegenerative diseases [63, 64]. In AD, senile plaque is one of the neuropathological hallmarks of AD and a site of inflammatory processes, as evidenced by the presence of degenerating neurons and numerous reactive microglia and astrocytes [65, 66]. A number of *in vitro* studies have shown that amyloid-β-activated microglia damage or kill neurons by the release of inflammatory mediators such as pro-inflammatory cytokines, nitric oxide and superoxide radicals [67-70]. Therefore, chronic inflammation may be involved in the pathogenesis of both major depression and dementia.

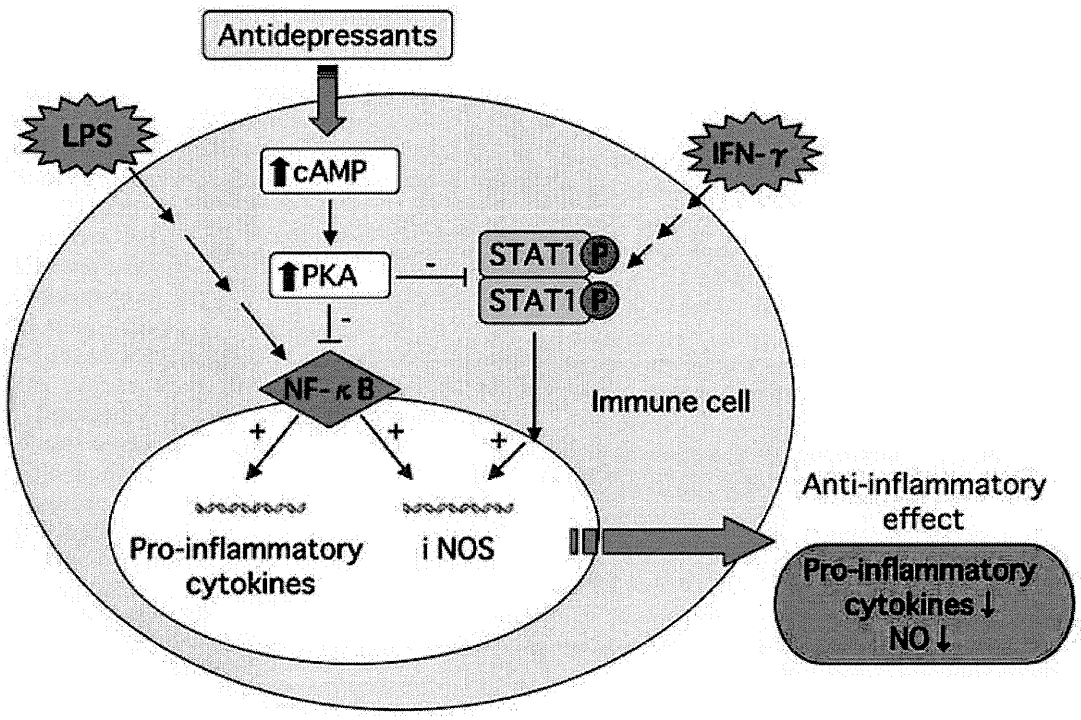

Fig. (1). Scheme for possible mechanism by which antidepressants exert anti-inflammatory effect in immune cells. Antidepressants may inhibit LPS or IFN-γ-evoked inflammatory transactivations through the up-regulation of cAMP/PKA pathway in immune cells. See text for details.

More than twenty epidemiological studies have shown that individuals are relatively spared from AD if they have been taking nonsteroidal anti-inflammatory drugs (NSAIDs) or have suffered from conditions where such drugs are routinely used (for review see [71]). In this regard, it is tempting to speculate that antidepressants with anti-inflammatory effects could be useful treatments for neurodegenerative diseases including AD. Interestingly, pre-symptomatic and chronic treatment with paroxetine has been shown to decrease AD-like pathology and reverse memory impairments in 3x transgenic AD mice [72]. Furthermore, in a small, 8-week double-blind placebo-controlled clinical study, fluoxetine was effective in reducing cognitive decline and behavioral abnormalities in patients with mild cognitive impairment [73]. This suggests that antidepressants could ameliorate AD or inhibit the progression of major depression to dementia.

It should be noted that such positive effects of antidepressants on memory and cognitive impairment might not be due to anti-inflammatory effects. Experimental evidence shows that chronic treatment with various antidepressants enhances neurogenesis in adult hippocampus [74, 75]. Clinical evidence indicates that long-term paroxetine treatment increases memory and hippocampal volume in patients with post traumatic stress disorder [76]. Accordingly, improvement of memory and cognition in the aforementioned two studies might be due to the hippocampal neurogenesis induced by antidepressants. Nevertheless, the anti-inflammatory properties of antidepressants may still be involved since the inflammation associated with LPS-activated microglia has been demonstrated to suppress hippocampal neurogenesis in adult rats [77].

CONCLUSIONS

Accumulating evidence indicates that major depression is associated with inflammation and that various types of antidepressants possess anti-inflammatory properties even though the exact mechanisms remain to be elucidated. Association between major depression and neurodegenerative diseases including AD may be based on the importance of chronic inflammation in the pathogenesis. Some preliminary studies support the hypothesis that antidepressants could prevent AD or inhibit the progression of major depression to dementia. Further studies along these lines are clearly warranted, even though careful consideration of the side effects of antidepressants is required in studies on aged people.

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