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Suggested Two Hypotheses on Dementia ("Anticholinergic Hypothesis" and "Cranial Skeletal Muscles Hypothesis") and the Therapeutic Agent

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Abstract

The present study was conducted with the objective of further developing the cholinergic hypothesis and not using the prevalent amyloid beta plaque hypothesis or the tau protein hypothesis on dementia. The experiment was conducted on mice using anticholinergic drugs scopolamine and biperiden to investigate the root cause of dementia. First, we measured the mice serum for liquid chromatography-tandem mass spectrometry (LC-MS/MS) after administration of scopolamine and biperiden and found an accumulation of anticholinergic drugs metabolites in the body. The Y-maze test and measurement of LC-MS/MS in the cranial skeletal muscle cells showed that the Scopolamine metabolites have a significant effect on the cranial skeletal muscles, leading to the conclusion that Methocarbamol is an effective treatment for dementia.

Keywords

Dementia, Alzheimer, Anticholinergic, Scopolamine, Methocarbamol, Ymaze, Skeletal Muscles

1. Introduction

Further development of the choline hypothesis

At the moment, there is no progress in the research on forms of dementia like the Alzheimer's disease. A major cause of the lack of progress is that no valid treatment strategy has been established from the studies on the prevailing amyloid beta protein and tau protein hypotheses.

As a result, one major pharmaceutical company has also discontinued their research.

One of the obvious reasons behind this is that the present research has come to a standstill but one of the other primary factors is that no new hypothesis has been found.

Currently, the only recognized treatment is cholinesterase inhibitors such as Aricept developed by Prof. Hachiro Sugimoto *et al.* [1].

Although Prof. Hachiro Sugimoto endorses the Choline hypothesis, he is aware that it is not a definitive treatment and continues his research on new therapeutic agents [2].

Therefore, the author considered to examine in mice based on many articles [3] [4] [5] that anticholinergic agents cause dementia.

The purpose of this experiment was to determine how much of the anticholinergic metabolite that causes dementia is accumulated in the mouse body, and to identify and determine the therapeutic agent based on the Y maze experiment.

Therefore, the serum of mice treated with anticholinergics is analyzed by LC-MS/MS, and Y-maze experiment of mice dosed with scopolamine and methocarbamol and LC-MS/MS analysis of cranial skeletal muscle.

2. Suggestion of "Anticholinergic Hypothesis" and "Cranial Skeletal Muscles Hypothesis"

2.1. Anticholinergic Hypothesis

As of now, cholinesterase inhibitors like Aricept are the only recognized therapeutic agents for Alzheimer's disease. Due to this fact, the choline hypothesis has become an extremely plausible theory.

However, it is also common knowledge that this drug only delays the progression of Alzheimer disease, and is not a definitive treatment.

In this paper, the author has introduced a concept of further developing the choline hypothesis.

Although there are reported cases in which anticholinergic drugs lead to the development of dementia symptoms, the details have not been elucidated yet.

However, there are an increasing number of papers suggesting that anticholinergic drugs are the cause of dementia [3] [4] [5].

Thereupon, the author came to the conclusion that accumulation of anticholinergic drugs or their metabolites in the body make acetylcholine ineffective, as a result of which it appears that acetylcholine has decreased.

Currently, not just prescription drugs but many types of over-the-counter medicines like gastrointestinal medicines, rhinitis medicines, eye-drops, and anti-travel sickness medicines available in the market also contain anticholinergic agents.

It is not uncommon to see circulation or accumulation of anticholinergic drugs or their metabolites in the body when they are taken regularly or continuously.

Therefore, it can be assumed that symptoms of dementia appear when the ac-

cumulation threshold is exceeded.

In particular, it is said that "you have to keep in mind that when you get older, bioaccumulation of drugs is likely to occur" [6].

In addition, as an example of accumulation of metabolites, although it is not dementia, morphine is likely to cause side effects such as impaired consciousness and delirium due to accumulation of its metabolites [7].

In the present experiment, we used biperiden and scopolamine as anticholinergic drugs.

Also, scopolamine is a typical drug used for measuring cognitive function in mice in Y-maze tests, etc. [8].

Again, biperiden is a drug used for Parkinson's and similar diseases [9].

2.2. Cranial Skeletal Muscles Hypothesis

In the current times, dementia is believed to be a disorder of the brain, however, the author believes that in dementia, there are problems in other parts as well.

Like this hypothesis, there are many theories that say that dementia has a cause other than the brain. According to them, it is said that the risk of dementia is increased due to infections such as periodontal disease and fungi, and differences in intestinal flora [10] [11] [12].

As per this hypothesis, other important parts that are also affected are the cranial skeletal muscles.

Cranial skeletal muscles refer to the frontalis muscles, temporal muscles, epicranial muscles, occipital muscles, masticatory muscles and the cranial meninges and nerves thereof.

The cause of headache is not derived directly from the brain, but scalp neuralgia is also one of the causes, so it is appropriate to consider that cranial skeletal muscle and the like are also included in part of the brain [13].

The same is true for cold stimulation headache.

In other words, in the cranial skeletal muscles, the neurotransmitters, such as acetylcholine, function well when the body is in a healthy state, but their function is impaired in the state of dementia.

Since the brains of lower animals are not developed enough, it is thought that their brains, including the cranial skeletal muscles, function as a whole. However, since the brains of humans are highly developed, our cranial skeletal muscles do not need to function as the brain. That is to say, that in humans, the cranial skeletal muscles have degenerated like the "Cecum", having absolutely no function in regular living and are not even noticed.

Therefore, it is difficult to identify this part as a cause of disease.

Moreover, this is the reason why there is no treatment for disorders of central nervous system in general.

It is assumed that instincts of animals are controlled by the lateral pterygoid muscles, and Intelligence of animals are controlled by the Cerebrum.

And, what connect the two are the cranial skeletal muscles and nerves.

But in humans, instincts do not materialize because the cranial skeletal muscle functions have degenerated.

A classic example of its effect is the drastically declining birth rates.

Furthermore, we guess that "The enlightenment of Gautama Buddha is, how can human thinking change by be conscious these unused skull muscles".

3. Test Samples

Reagent was orally administered (once a day) to mice, and later an experiment was conducted using the serum from the extracted blood.

Mice used were 10-week old male mice.

This is listed in Table 1.

The following mice were used for the Y-maze test and cranial skeletal muscle analysis, and drugs were orally administered to all.

Mice used for the Y-maze test were 4-week old male mice.

Mice used for frontalis muscle collection were 10-week old male mice.

This is listed in Table 2.

The reagents used in the present study are listed in Table 3.

LC-MS/MS conditions for experiment 1 and experiment 3 were as follows [14]:

LC-MS/MS measurement conditions;

LC/MS/MS;

Table 1. Anticholinergic drug inoculation method.

Sample no.	Administered reagent	Mon.	Tues.	Wed.	Thur	Fri.	Blood sampling time
1	Scopolamine				●▲		30-minute post administration
2	1 mg/kg				●	▲	24-hour post administration
3		●	●	●	●▲		30-minute post final administration
4		●	●	●	●	▲	24-hour post final administration
5	Biperiden				●▲		30-minute post administration
6	1 mg/kg				●	▲	24-hour post administration
7		●	●	●	●▲		30-minute post final administration
8		●	●	●	●	▲	24-hour post final administration

● Drug administration, ▲ Blood sampling

Table 2. Drug inoculation method for Y-maze test.

Sample no. (Y-maze)	Scopolamine (1mg/kg)	Methocarbamol (461mg/kg)	Frontalis muscles (Above the eye)	Occipital muscles (Back of the head)
A	—	—	A-1	A-2
B	30 minutes prior administration	—	B-1	B-2
C	30 minutes prior administration	24 hours prior + 2.5 hours prior administration	C-1	C-2

Table 3. Name of administered reagents.

Ingredient name	Name of manufacturer	Product name	Purity, composition
Scopolamine	FUJIFILM Wako	Scopolamine Hydrobromide n-Hydrate	Purity 98.5%
Biperiden	Union (Taiwan)	Akineton	Composition 1.0%
Methocarbamol	Ying-Yuan	Bolaxin	Composition 76.9%

LC part;

Shimadzu Corporation's Prominence;

Separation column COSMOSIL 5C18-MS-II by Naclai Tesque 2.0 mm I.D. × 150 mm;

Fluid A 10 nmol/L ammonium formate;

Fluid B methanol;

Flow rate 0.2 mL/min;

Test liquid injected dose 10 μL;

MS/MS part;

Shimadzu Corp LCMS-8045.

4. Experiment 1—LC-MS/MS Measurements of Mice Serum

4.1. Experimental Methodology

In order to understand what kind of transformation do scopolamine and biperiden undergo inside the body, we analyzed serum sample numbers 1 to 8 using LC-MS/MS.

Blood serum of the mice was pretreated in the following way for the LC-MS/MS analysis.

Methanol water mixed solution (1:1) 990 μL was added to precisely 10 μL of blood serum to prepare a diluted solution. The diluted solution was passed through a membrane filter (0.20 μm) and was used as the test solution for LC-MS/MS.

4.2. Experiment Results

Comparisons of the main peak area ratios obtained from the analyses are shown in Table 4 and Table 5.

Considering the highest molecular weight of 124.2 in the peak area which was common to all as the control, and the peak area value as 100, it was compared with other peak area ratios.

4.3. Consideration

Firstly, the common observation in all the samples was that scopolamine and biperiden ingested by the mice were not detected in the same composition. Inside the body, they quickly converted into metabolites.

Scopolamine

In the comparison of Samples 1 and 3, not many metabolites were found in Sample 1, but Sample 3 was found to have a large number of metabolites. It be-

came clear that it takes not just one but 4 consecutive days of intake for the drug to get accumulated in the body.

Again, comparison of Samples 3 and 4 showed the same level of metabolites in both the samples. The values of 30-minute post administration in Sample 3 and values of 24-hour post administration in Sample 4 were the same, indicating that the accumulation amount stabilizes when the intake is continued.

Comparison of Samples 2 and 4 showed higher values in Sample 4. This demonstrates that continued intake poses a high risk of increased accumulation.

Biperiden

In the comparison of Samples 5 and 6, the values of 30-minute post adminis-

Table 4. Comparison of peak area ratios of serum samples of scopolamine-administered mice Samples 1 to 4.

Peak molecular weight	Non administration	1	2	3	4
124.2	100	100	100	100	100
149.15	-	5.54	11.42	13.59	14.74
171.25	-	-	5.29	5.65	5.66
181.2	-	-	5.49	6.69	7.22
199.25	-	-	5.79	6.26	6.41
205.25	-	-	6.64	7.58	7.86
217.2	-	-	7.11	7.69	7.67
219.25	-	-	-	5.01	5.11
228.3	-	-	6.54	7.52	7.59
259.25	-	-	-	5.28	5.32
273.25	-	-	-	5.26	5.33
274.35	-	-	-	-	5.04
277.2	-	-	-	-	5
282.35	-	-	-	5.27	5.94
316.25	-	-	5.46	6.32	6.64
338.45	-	5.92	12.83	15.92	16.68
358.45	-	-	5.29	6.09	6.26
361.35	-	5.68	11.34	12.2	12.37
391.4	-	-	-	5.44	5.67
404.35	-	-	6.67	7.48	7.66
419.45	-	-	13.98	18.88	21.29
420.45	-	-	-	6.32	7.09
425.35	-	5.02	12.87	15.07	16.19
441.3	-	-	-	5.36	5.65
475.5	-	-	7.01	9.39	10.69
497.45	-	-	7.09	7.12	6.96

Table 5. Comparison of peak area ratios of serum samples of biperiden-administered mice Samples 5 to 8.

Peak molecular weight	Non administration	5	6	7	8
124.2	100	100	100	100	100
139.2	-	6.14	5.74	6.19	6.13
149.15	-	16.44	11.42	17.73	17.4
171.25	-	5.76	5.29	5.72	5.7
181.2	-	8.07	5.49	8.67	8.46
199.25	-	6.52	5.79	6.6	6.53
205.25	-	8.59	6.64	9.01	8.85
214.2	-	-	-	5.09	5.05
217.2	-	8.04	7.11	8.11	8.03
219.25	-	5.28	-	5.42	5.28
228.3	-	8.13	6.54	8.24	8.04
259.25	-	5.54	-	5.59	5.64
273.25	-	5.58	-	5.85	5.47
274.35	-	5.17	-	5.19	5.08
277.2	-	5.08	-	5.04	5.03
282.35	-	5.39	-	5.86	5.79
316.25	-	7.07	5.46	7.17	7.36
338.45	-	18.44	12.83	18.79	18.01
358.5	-	6.41	5.28	6.7	6.49
361.35	-	12.97	11.34	13.08	12.74
391.4	-	5.9	-	6.09	5.85
392.4	-	-	5.56	-	-
404.35	-	8.15	6.67	8.22	8.13
419.45	-	24.36	13.97	26.97	26.31
420.45	-	8.26	-	9.1	8.69
425.35	-	17.63	12.87	17.68	17.18
441.3	-	6.1	-	6.22	6.14
475.55	-	12.29	7.01	13.74	13.68
476.5	-	5.14	-	5.46	5.38
497.45	-	6.24	7.09	6.64	8.02

tration were found to be generally significantly higher than the values 24 hours post administration. This was attributed to expulsion of biperiden metabolites from the body when biperiden was taken only one time.

The comparison of Samples 7 and 8 did not reveal any changes in the values of either sample. This shows the same tendency as scopolamine.

Comparison of Samples 6 and 8 showed higher values in Sample 8. This shows the same tendency as scopolamine.

Summary

The results of experiments on scopolamine and biperiden show that continuous intake of these drugs leads to accumulation or increase in amount of circulation of anticholinergic drugs in the body.

The accumulated metabolites are thought to be the primary factor behind dementia.

5. Experiment 2—Y-Maze Test

5.1. Experimental Methodology

Experiment was conducted using mice Types A, B, and C.

The mice were placed in a Y-shaped maze and were allowed to act freely for 6 minutes. Since mice have a habit of always choosing new paths, the order and frequency of entry into each of the 3 arms were measured and the accuracy rate was calculated using the ratio of the number of entries to the number of correct entries to evaluate the degree of memory impairment [15].

5.2. Experiment Results

Based on the data obtained from the Y-maze test, the overall physical activity and percentage of correct answers in altered behavior were analyzed.

5.2.1. Overall Physical Activity (Frequency)

Data on overall physical activity are shown in Figure 1 and Table 6.

The results were in the following order: scopolamine> no administration > methocarbamol + scopolamine (B > A > C).

5.2.2. Percentage of Correct Answers in Altered Behavior (%)

Data on the percentage of correct answers in altered behavior are shown in Figure 2 and Table 6.

The results were in the following order: no administration > methocarbamol + scopolamine > scopolamine (A > C > B).

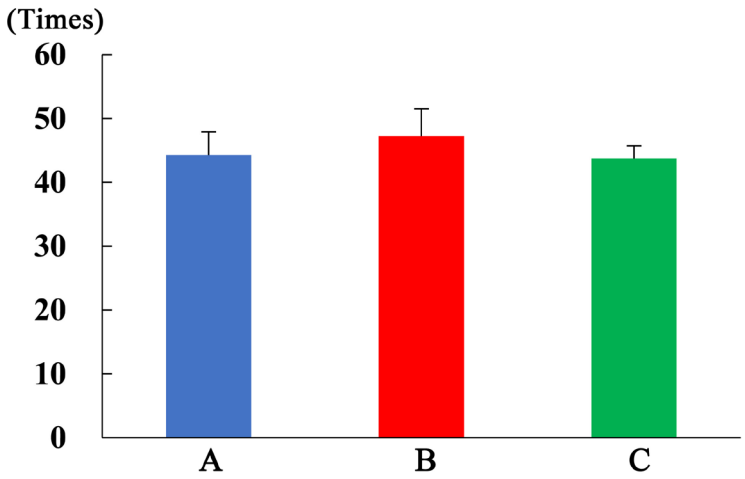

Figure 1. Comparison of overall physical activity in Y-maze test.

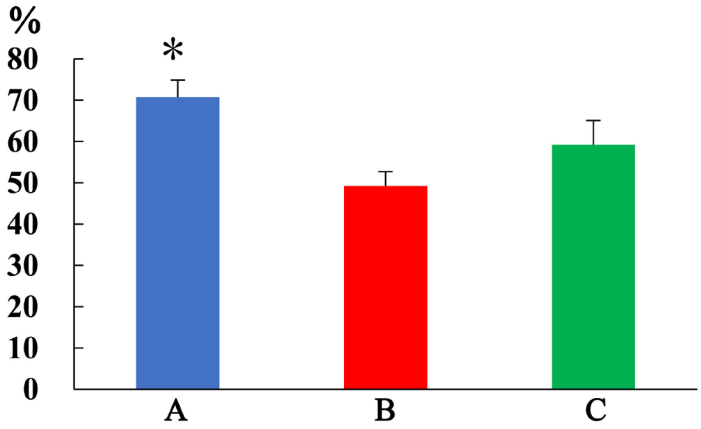

Figure 2. Comparison of percentage of correct answers in altered behavior in Y-maze test.

Table 6. Results of Y-maze test.

Type	Administered group		Overall physical activity	Percentage of correct answers in altered behavior
A	Non administration	Average	44.3	70.7
		Standard deviation	3.6	4.2
		Vs scopolamine	0.6101	0.0073**
B	Scopolamine	Average	47.3	49.3
		Standard deviation	4.2	3.5
		-	-	-
C	Methocarbamol + scopolamine	Average	43.8	59.2
		Standard deviation	1.9	5.9
		Vs scopolamine	0.4801	0.1931

N = 4. **Significant difference found.

5.3. Consideration

As for the overall physical activity and percentage of correct answers in altered behavior, compared to the scopolamine administration group, the values of the methocarbamol + scopolamine administration group were closer to the normal state (scopolamine non-administration state), indicating that methocarbamol suppresses the action of scopolamine.

In other words, methocarbamol is presumed to be effective against dementia.

6. Experiment 3—Analysis of Cranial Skeletal Muscles

6.1. Experimental Methodology

The condition of the cranial skeletal muscles of mice was examined under the conditions of the Y-maze test.

In order to confirm the presence of scopolamine and its metabolites in the cranial skeletal muscles, 6 samples from 2 sites × 3 types were compared using LC-MS/MS.

In addition, for mice types A, B, and C, the drug administration conditions were the same as for Experiment 2.

The only difference was that 10-week old mice were used for this experiment.

Conditions of LC-MS/MS were the same as for Experiment 1.

For the LC-MS/MS analyses, the muscle cells collected from mice were pre-treated using the following method.

Methanol 0.2 mL was added per 50 mg of shredded cranial skeletal muscles of mice and was homogenized for 3 minutes. After which, it was filtered by centrifugation. Methanol 0.2 mL was added to the residue and it was centrifuged again. Thereafter, the filtrates were combined to form an extracting solution which was injected in the LC-MS/MS system.

6.2. Experiment Results

Respective distinctive results of the LC-MS/MS analyses for the frontalis and occipital muscles are shown in the diagrams below.

Considering the highest molecular weight of 124.2 in the peak area which was common to all as the control, and the peak area value as 100, it was compared with other peak area ratios.

These data are listed in Table 7 and Table 8.

6.3. Consideration

Distinctive results were observed only in the frontalis muscles of B-1 that showed a peak molecular weight of 340.45. This was not observed in the occipital muscles of B-1.

For this reason, it is believed that impairment of cognitive functions occurs mainly in the frontalis muscles due to accumulation of a molecular weight of

Table 7. Frontalis muscles peak area ratio comparison table.

Molecular weight	A-1	B-1	C-1
124.2	100	100	100
267.3	-	-	5.09
272.35	-	-	5.27
340.45	-	6.88	-
382.4	-	-	6.73
397.4	-	-	5.54

Table 8. Occipital muscles peak area ratio comparison table.

Molecular weight	A-2	B-2	C-2
124.2	100	100	100
271.35	-	-	6.5
341.45	-	-	9.3
385.4	-	-	5.94

around 340.45, which is the molecular weight of scopolamine metabolites.

Also, the presence of methocarbamol seems to hinder the accumulation of molecular weight of 340.45 in the frontalis muscles of C-1.

7. Conclusions

Based on the three experiments, we have made the following presumptions, which can be summarized to suggest "anticholinergic hypothesis on dementia" and "cranial skeletal muscle hypothesis on dementia".

In addition, we propose methocarbamol as an effective therapeutic agent.

1) The anticholinergic drug breaks down after ingestion and does not remain in the blood after a certain time period.

2) However, some metabolites of anticholinergic drugs remain in the blood even after 24 hours.

3) They gradually get accumulated in the body and increase over a period of time.

4) One of the sites where they accumulate is the cranial skeletal muscles.

5) This is what hinders the action of the neurotransmitter acetylcholine.

6) This eventually results in dementia.

7) Causative agents of dementia are metabolites of anticholinergic drugs with an approximate molecular weight of 340.45.

8) In order to treat dementia, forced degradation and forced extracorporeal elimination of these metabolites will be essential.

9) Methocarbamol is an effective therapeutic agent for dementia.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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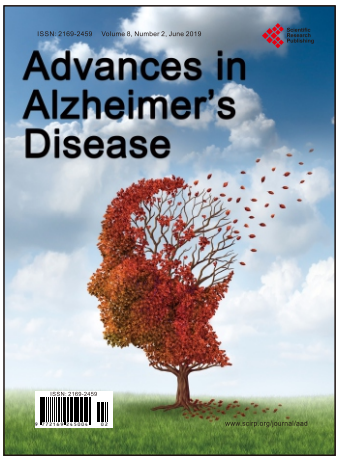

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- Alzheimer's Disease and Down Syndrome
- Animal Models of Alzheimer's Disease
- Behavior and Treatment
- Brain Disorder
- Caregiving and Dementia
- Cell Cycle and AD
- Dementia during Aging and in Alzheimer's Disease
- Epidemiology of Alzheimer's Disease
- Etiology of Alzheimer's Disease
- Genetics of Alzheimer's Disease
- Inflammation in Alzheimer's Disease
- Neural Circuit Dysfunction in Alzheimer's Disease
- Neurodegeneration
- Oxidative Stress and AD
- Pathogenesis of Alzheimer's Disease
- Patient Care and Prevention of Alzheimer's Disease
- Progress in Alzheimer's Disease Diagnosis
- Protein Misfolding
- Psychosocial Intervention
- Therapeutic Development
- Understanding of Alzheimer's Disease Pathogenesis

We are also interested in: 1) Short reports—2-5 page papers where an author can either present an idea with theoretical background but has not yet completed the research needed for a complete paper or preliminary data; 2) Book reviews—Comments and critiques.

Notes for Intending Authors

Submitted papers should not have been previously published nor be currently under consideration for publication elsewhere. Paper submission will be handled electronically through the website. All papers are refereed through a peer review process. For more details about the submissions, please access the website.

Website and E-Mail

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