



Living in the Past: The Pathology of Anterograde Amnesia

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Abstract. In this review, a model of anterograde amnesia was proposed, including the diencephalon, the medial temporal lobe and the routes that connect these two brain regions. Structures within these brain regions was proved to be related with anterograde amnesia in former studies. The structures are mamillary bodies and thalamus in the diencephalon, hippocampus in the medial temporal lobe, and fornix that links the hippocampus to the diencephalon. Damage to these brain structures could result in anterograde memory impairment. Results of several case studies were discussed in this review as pieces of evidence that support this model. In the second part of the review, the effect of different factors, including alcohol, hypoglycaemia and carbon monoxide, could have to these brain structures were stated. Dysfunction of the thalamus, hippocampus and mamillary bodies was believed to be responsible for anterograde amnesia after heavy alcohol consumption, and dysfunction of the hippocampus was ascribed for memory impairment following hypoglycaemia and carbon monoxide inhaling.

Keywords: anterograde amnesia · brain structures · diencephalon · alcohol

1 Introduction

By reading former studies about the pathology of anterograde amnesia, particularly the brain structures stated to be potentially responsible for memory impairment, I concluded a pathway that links the diencephalon and the medial temporal lobe. Either damage to the diencephalon and the medial temporal lobe or the routes that connect these two brain regions could cause anterograde amnesia. For some structures within this pathway (e.g., the hippocampus), lesions limited to that region is sufficient to produce memory impairment; as for other structures, currently they are believed only to affect the severity of amnesia, and limited damage to these structures are insufficient for the production of amnesia. In the second part of the review, I discussed how different factors, including alcohol, hypoglycaemia and carbon monoxide, may cause dysfunction of these structures and therefore lead to anterograde memory impairment.

2 Dysfunction of Different Structures that May Lead to Anterograde Amnesia

2.1 Diencephalon

2.1.1 Mamillary Bodies

A case study of a third-ventricle-craniopharyngioma patient who developed severe anterograde amnesia revealed the importance of mamillary bodies in memory formation. The tumour compressed mainly the mamillary bodies but the right hippocampus as well. However, the amnesia was ascribed to the compression to the mamillary bodies because of the following two reasons: 1) contradictory to the role of right hippocampus, the impairment of verbal and nonverbal memory was asymmetry lacked; 2) while the patient showed full recovery after surgery, the FDG uptake of right hippocampus showed very limited change [1]. There are other studies showed that instead of passively processing the information from the hippocampus, mamillary bodies may be playing another role in memory processing as they are contributing new things [2], therefore the importance of mamillary bodies in memory formation may be underestimated in former studies.

2.1.2 Thalamus

It was mentioned that the memory impairment caused by restricted lesions in the fornix or mammillary bodies was less severe compared with actual diencephalic amnesia, which is a piece of evidence supporting that thalamus may also be involved [3]. The effect of lesions in midline-thalamic nuclei and anterior thalamus were mentioned in a few cases studies.

2.1.3 Nuclei in the Midline of the Thalamus

The anterograde amnesia of 13 patients with alcoholic Korsakoff's syndrome revealed the relationship between memory impairment and damage to nuclei in the midline of the thalamus. This was proved by the change in the volume of the third ventricle of these patients observed on MRI, which was believed to be related with the lesions in these midline nuclei (including the mediodorsal nucleus, the intermediodorsal nucleus, the parataenial nucleus, the rhomboid nucleus, the reuniens nucleus, and the paraventricular nucleus). It was also suggested that the anterograde amnesia may become more severe as the number of affected nuclei increases [4]. It was suggested that the nucleus reuniens, one of the nuclei in the midline of thalamus, has similar features to the anterior thalamic nuclei. It connects to the hippocampus with some connections passing through fornix, and its projections allow it to pass signals from the mamillary body to the retrosplenial cortex. The electrophysiological studies in rats suggested that the nucleus reuniens may also have the potential to control excitation in the CA1 region of the hippocampus [3].

2.1.4 Anterior Thalamus

A right cerebellar infarcted patient with anterograde amnesia was reported. The mechanism of this syndrome was hypothesized to be the disconnection of cerebello-cerebral

fibre tracts. The brain SPECT result revealed a blood flow decrease in the left anterior thalamus. As a relay centre of the cerebello-cerebral pathway, the dysfunction of left anterior thalamus, which was the result of the disconnection of the fibre tracts, was believed to be responsible for the memory impairment [5]. A case of neuro-Behcet's disease patient with anterograde amnesia and minimal retrograde amnesia was reported. Lesions caused by vasculitis was discovered in right anterior thalamus and left hippocampus. However, there was no further research on differentiating the effect of the dysfunction of these two brain regions. It was concluded that the amnesia in this case was caused by the combined action of the lesions in right anterior thalamus and left hippocampus [6].

2.2 Medial Temporal Lobe

2.2.1 Hippocampus

The most important structure for memory formation in medial temporal lobe is the hippocampus. There was research which supported the notion that lesions limited to hippocampal formation is sufficient for the production of amnesia. The researches induced neuron damage in rats by domoic acid, damaged neurons took up about 95% of CA3, 40% CA1 and 60% of dentate cells in the brain of these domoate-treated rats. Those rats had poor performance in Morris water task, indicating the presence of severe memory impairment [7]. Another study that supported this notion concluded findings from several patients and proposed that even incomplete damage limited to hippocampal formation is sufficient for the production of anterograde memory impairment, and the severity of amnesia is directly proportional to the extension of lesions within the hippocampal formation [8]. Memory retrieval processes which may be interrupted by damage to the hippocampus was discussed. There are two main processes of anterograde memory retrieval: recollection and familiarity. Accurate contextual detail is involved in recollection, while familiarity is being aware of the occurring of something without contextual information. It was believed that the hippocampus is essential for both recollection and familiarity [9].

2.2.2 Cholinergic Afferent

Instead of limiting lesions to the hippocampal formation and considering the medial temporal lobe as a whole. It was suggested that interfering specifically cholinergic neuron projections originate at the basal forebrain and terminate at the medial temporal lobe and inferior temporal cortex could lead to severe anterograde amnesia [10].

2.3 Connection

2.3.1 Fornix

Because of the important role fornix plays in connecting the hippocampus to diencephalic structures including mamillary bodies and anterior thalamus, it was considered to be the centre of the amnesia model proposed by Aggleton [3]. It was concluded that the anterograde amnesia in Wernicke-Korsakoff syndrome may be caused by the disconnection of

medial temporal lobe due to damage to the pathway that links the hippocampus and diencephalon, which is exactly the role of the fornix. It was stated that lesions in the fornix could also explain the decreased metabolism in Wernicke-Korsakoff patients that was observed [11]. In addition, it was stated that the degree of atrophy of fornix is associated with the severity of amnesia. Whether memory impairment is restricted to lesions in specific positions of fornix was discussed. The acute-onset amnesia patient studied had infarction in both the fornix and the genu of the corpus callosum. Findings of this patient only proved the relationship between anterior fornix damage and memory impairment. However, it was also mentioned that anterograde amnesia resulted from posterior fornix lesions was reported as well [12].

2.3.2 Cingulum Bundle

The efferent of the hippocampus to anterior thalamic nuclei via fornix is essential for the normal functioning of hippocampus. There is also an inverse projection from the anterior thalamus to the hippocampus via cingulum bundle. These two pathways, as parts of the hippocampal-diencephalic system, play an important role of the encoding and retrieval of new episodic memory, and their damage can lead to the production of memory impairment [2].

3 How Different Factors May Lead to the Dysfunction of These Structures

3.1 Alcohol

The relationship between alcohol consumption and the dysfunction of the thalamus was revealed. It was mentioned that the decreased volume of thalamus can be resulted from heavy intake of alcohol. The reason why thalamus and mamillary bodies are more vulnerable to alcohol and thiamine deficiency than other brain structures was discussed: thiamine is involved in the process of glucose metabolism, the lack of thiamine can cause decreased glucose metabolism and therefore decreased production of energy; then another energy production pathway becomes more important which is the metabolism of alcohol to acetate; the transport of acetate into cells requires a specific transporter MCT, however, the expression of MCT and AcCoAs (an enzyme essential for producing energy using acetate) are both relatively low at the thalamus and mamillary bodies; and therefore insufficient energy for normal cellular activities, as the combined effect of alcohol and thiamine deficiency, may lead to the dysfunction of the thalamus and mamillary bodies. The thalamus is involved in two brain networks: the Papez circuit and the frontocerebellar circuit. It was stated that the anterograde amnesia due to the dysfunction of thalamus is a result of interrupting the Papez circuit instead of the frontocerebellar circuit [13]. There are also studies focused on the effect of alcohol on the medial thalamic nuclei and the anterior thalamus [4, 14].

It was stated that ethanol could inhibit the long-term potentiation (LTP) of the hippocampus, especially in the granule cells. The cellular long-term potentiation is essential for learning and memory formation, therefore interrupting the LTP process by alcohol could explain the anterograde amnesia after heavy alcohol consumption and the damage

of alcohol to the normal function of hippocampus as well [15]. There was a case study suggested that the anterograde amnesia shown by their Korsakoff syndrome patients was resulted from the shrinkage of the mamillary bodies and gliosis at the paratenial nucleus (one of the nuclei in the midline of thalamus) [16].

3.2 Hypoglycaemia

Anterograde amnesia was reported as one of the negative effects of hypoglycaemia, because of the limited amount of glucose that could be transported through blood-brain barrier, the brain is susceptible to hypoglycaemia, especially the hippocampus, thalamus and the globus pallidum [17, 18]. Because of the key role hippocampus plays in the formation of episodic memory, memory impairment following hypoglycaemia can be seen as a result of hippocampal damage [17]. A case study also mentioned how amnesia came as a result of damage to the hippocampus as the normal functioning of Papez circuit was disrupted. From the findings of that patient, researchers proposed that the memory impairment and lesions observed on MRI is reversible and can be recovered [19].

3.3 Carbon Monoxide

Due to the effect of carbon monoxide on oxygen transport, inhaling carbon monoxide could lead to cerebral anoxia. Some brain structures are more susceptible to low oxygen concentration, including the pallidum and the hippocampus. The damage of the hippocampus can therefore cause anterograde amnesia or other memory disorders [20].

4 Conclusion

In former studies of anterograde amnesia, the importance of the thalamus, mamillary bodies, hippocampus and fornix were discussed. In this review, an integrated model was proposed based on those studies. The proposed pathway originates at the diencephalon and terminates at the medial temporal lobe, linking these two brain regions which both plays an important role in memory formation. Mamillary bodies and thalamus are included in the diencephalic structures. A case study described how lesions in the mamillary bodies could cause anterograde amnesia [1]. As for the thalamus, both midline-thalamic nuclei and anterior thalamic nuclei were mentioned. Research suggested the correlation between the number of damaged nuclei in the midline of the thalamus and the severity of memory impairment [4]. A specific midline-thalamic nucleus was mentioned, the nucleus reuniens. It was believed to have an important role as it connects to the hippocampus like anterior thalamic nuclei [3].

Hippocampus was discussed as the most important structure for memory in medial temporal lobe. Two case studies proved that lesions limited to the hippocampal formation is sufficient to produce anterograde amnesia [7, 8]. Both of the two anterograde memory retrieval processes: recollection and familiarity, could be affected by hippocampal damage [9]. The role of cholinergic afferents to the medial temporal lobe was also briefly mentioned [10]. As fornix connects the hippocampus to diencephalic structures

(mamillary bodies and anterior thalamus), lesions in fornix could cause the disconnection of medial temporal lobe and therefore lead to anterograde memory impairment [11]. It was mentioned that either anterior or posterior damage of the fornix could result in anterograde amnesia [12]. In addition, a reverse pathway via cingulum bundle which passes information from anterior thalamus back to the hippocampus was also essential for memory processing [2].

Alcohol is believed to have an impact on the thalamus, the hippocampus and the mamillary bodies. It affects the thalamus and mamillary bodies by producing energy insufficiency which affect normal cellular activities, and affects the hippocampus by inhibition of long-term potentiation in granule cells [13, 15]. The effect of hypoglycaemia to the brain can be explained by the limited amount of glucose that could be transported through blood-brain barrier, which makes the brain very vulnerable under low-level of glucose, especially for the hippocampus, and that could explain anterograde amnesia following hypoglycaemia [17, 18]. Carbon monoxide has a huge effect on the transportation of oxygen. Inhaling carbon monoxide could result in cerebral anoxia, and because the hippocampus is more susceptible to low oxygen levels, carbon monoxide may result in memory impairments as well. However, due to the limited research this review covers, the findings and proposed model may be inaccurate. In fact, there are findings from different studies that support the opposite of the conclusion of studies selected in this review. Further laboratory experiments or case reports are required to prove the model proposed in here.

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