CAPSTONE

Circadian rhythm disruption and PACAP-38 in the pathophysiology of cluster headache

Sydney Wolfe

Cluster headaches (CH) are a rare, severe form of neurovascular headache that tend to occur on one side of the head.[1] Unlike typical headaches and migraines, the pain feels like a burning and stabbing sensation that lasts from 15 to 120 minutes up to 4 times per day.[1] In episodic sufferers, these bouts of headaches tend to occur around the same time each year with a pain-free period spanning one month or more.[2] In chronic sufferers, CHs are recurrent without a prolonged headache-free period. While not life-threatening, these headaches have dramatically decreased the quality of life for all sufferers. Up to 4 in every 1000 people suffer from CH attacks, the majority of them being men.[3] There is no known cause of CHs, although many studies point to structural and functional abnormalities of the hypothalamus. Patients suffering from CH have shown increased hypothalamic activation ipsilateral to the pain during acute attacks.[8] Furthermore, research has pointed to the potential involvement of the suprachiasmatic nucleus within the hippocampus. The suprachiasmatic nucleus is involved in the regulation of circadian rhythm. One study found that in episodic CH patients, a neuropeptide called PACAP-38 was elevated during active CH bouts when compared to headache-free periods.[5] PACAP-38 functions as a regulator of the circadian entrainment to light. Specifically, PACAP-38 release at the retinohypothalamic tract (RHT) leads to an influx of intracellular calcium at the suprachiasmatic nucleus.[4] The involvement of PACAP-38 in light and sleep circadian rhythms and the relationship between PACAP-38 and CH attacks may help to uncover a mechanism for CHs. Current treatments for temporary CH relief include oxygen inhalation and injectable triptans, although these do not prove useful for all patients.[6] In this review, the role of the PACAP-38 neuropeptide and its receptor in chronic and episodic CH will be explored as a novel target for effective long-term treatment.

Hypothalamic structural and functional abnormalities in cluster headache

Abnormalities of the hypothalamus have been a consistent finding in many CH studies, including gray matter volume differences between controls and CH and circuitry dysfunction.[7,8] Using voxel-based morphometry analysis, a study found that the anterior hypothalamus was bilaterally enlarged in the CH group when compared to healthy controls.[7] Hypothalamic gray matter was also increased in chronic and episodic CH sufferers when compared to migraineurs, implicating that there may be physiological differences between migraine and CH.[7] Another study that was conducted on nine CH patients found differences in bilateral hypothalamic gray matter volume during acute headache attacks in comparison to the inter-bout phase.[18] In contrast with the previous study, this volumetric difference was seen in the inferior posterior hypothalamus. This may suggest that CH impacts other areas of the hypothalamus. A structural MRI study also revealed weaker hypothalamic covariance patterns in CH patients when compared to controls. Significant differences were found in the correlation slope between the hypothalamic volume and vertex-by-vertex cortical thickness measurements. [8] Specifically, the hypothalamus showed weaker structural covariance with temporal and frontal areas of the brain when compared to healthy controls. Weaker structural covariance indicates less connectivity between left/right hypothalamus and temporal/frontal brain regions. However, no hypothalamic volume differences

between CH and healthy controls were found. While this could be due to differences in brain imaging methods between the two studies, one might extrapolate that CH is the result of pain circuitry dysfunction as opposed to structural dysfunction. Any structural compromises seen in the studies may have been a byproduct of circuitry dysfunction, but not a direct effect of CH. Despite the discrepancies in whether CH impacts hypothalamic volume or structure, studies implicate the hypothalamus as the origin of CH and an important target for treatment.

Circadian rhythm dysfunction in cluster headache

Circadian rhythmicity, a property of the suprachiasmatic nucleus in the hypothalamus, has also been closely linked to CH. In a study reporting on temporal changes of within-bout CH patients, 86 people (approximately half of the total study population) reported circadian patterns.[9] However, it is unknown whether the other half of CH patients experienced circadian rhythmicity in different bouts as the patients were only monitored during one bout. As the number of lifetime bouts increased, the incident of afternoon and hypnic circadian rhythmicity also increased.[9] Toward the beginning and end of the disease's progression (which varies from patient to patient), nighttime attacks were more frequent, whereas daytime attacks were more frequent during the middle of the disease's progression.[9] A similar study on sleep patterns found that in 80% of CH patients (n=275), a common trigger was sleep.[10] This was especially true for patients reporting diurnal (hours of the day that CH consistently occurs) rhythmicity. About 56% of patients reported yearly fluctuations in CH occurrence, revealing that the most common month for CH worsening was November.[10] This may be due to daylight savings, which ends in November. This abrupt alteration in the body's biological clock may be a trigger for CH. Of these patients, the majority were episodic patients instead of chronic patients. There is no direct linear relationship between CH and time/sleep, as there is wide variance in the reported patterns for CH. Still, based on the surveyed patients, CH tends to manifest itself differently depending on the time of the disease's course and the disease's form (chronic or episodic). The tendency of CH to be linked to circadian rhythmicity, especially as it relates to light and sleep, may implicate the suprachiasmatic nucleus as a key structure in CH.

PACAP-38 and the suprachiasmatic nucleus

In an exploratory study on episodic CH, PACAP-38 was found to be involved in the inter-bout and ictal phases of CH.[5] PACAP-38 is a neuropeptide involved in nociception, neuromodulation, and circadian rhythm regulation.[11,12,14] Animal models involving PACAP manipulation have been shown to exhibit alterations in sleep and in somatic factors, such as breathing, heart rate, and headache.[13] Concerning headache, PACAP-38 has been found to induce vasodilation in rats *ex vivo*.[12] Application of PAC_1 antagonist reversed vasodilation effects, showing promise in alleviating pain caused by primary headaches.[12] Only one human study exists on the relationship between PACAP-38 and CH. Blood plasma was measured in nine age-matched healthy male controls and five male episodic CH sufferers.[5] PACAP-38 concentrations were measured in the CH group during the inter-bout phase (headache-free periods lasting longer than a month) and during the ictal (during bout) phase. There was no significant difference in PACAP-38 concentrations between the healthy controls (mean=30.5 fmol/ml) and the CH ictal phase (28.8 fmol/ml).[5] There was a significant difference in PACAP-38 concentrations between the CH ictal phase (28.8 fmol/ml) and the CH interbout phase (24.4 fmol/ml), suggesting that PACAP-38 may be released upon CH onset.[5] The ability of PACAP-38 to impact circadian phase change has been demonstrated in a few studies. Hannibel et al. found PACAP-38 to be in high concentrations in the retinohypothalamic tract (RHT). At the same time, its receptor PAC_1 was expressed at high levels in the SCN.[15] Binding of PACAP-38 to the PAC_1 receptor causes activation of RHT, which then relays light information to the SCN.[15] The glutamatergic neurotransmission induced by PACAP caused circadian phase-shifting during the day.[15,16] The

existence of glutamatergic neurotransmission via PACAP-38 was confirmed by the application of NMDA antagonists, MK-801 and AP-5, before PACAP application[15] Both antagonists completely blocked circadian phase shift in the presence of PACAP-38.[15] PACAP-38 was also found to have dualistic effects in one study, coding for "light information" in doses lower than 1 nM while coding for "dark information" in doses higher than 10 nM. [17] PACAP-38 is known to selectively target PAC_1, which is tied to several signaling cascades, including ERK and phospholipase C. [14] PACAP-38 has widespread effects that expand beyond circadian regulation and CH. However, its high levels in the SCN, involvement in circadian rhythm shift, and release in CH ictal bouts call for further investigation.

Conclusion

Cluster headache is a painful condition which warrants more attention than it has received. While this disease is rare, the few people that do suffer from these agonizing headaches have expressed depression, anxiety, and suicidality at a higher rate than non-sufferers.[17]
There is no confirmed mechanism for CH. However, emerging studies on the relationship between CH and circadian rhythm, PACAP-38, and the suprachiasmatic nucleus provide a promising avenue for further studies. The current body of research points to the hypothalamus being the origin of cluster headache, circadian rhythm abnormalities being a hallmark in most sufferers, and the release of PACAP-38 being a biomarker in episodic suffers. Still, there are limitations on the number of studies exploring PACAP-38 release *in vivo*. While the exploratory study by Tuka et al. found significant results, the sample size was quite small (n=5), and the study only focused on episodic CH sufferers. It is unknown whether chronic CH, which lacks the pain-free intervals of episodic CH, involves the release PACAP-38. Chronic CH sufferers have also shown less circadian rhythmicity than episodic sufferers, indicating the possibility of a separate mechanism. Future studies should focus on characterizing the distinct differences in the temporal patterns of chronic vs. episodic CH. Additionally, studies must address the role of PACAP-38 in chronic CH. Understanding the pathophysiology of CH is imperative to expand current treatment options for sufferers. Selective targeting of the PAC_1 receptor by PACAP-38 to regulate circadian rhythm may prove to be a promising drug target for CH, although more clinical trials are still needed.[11,12] While no clinical trials have been published, preclinical trials have used PACAP-38 and PAC_1 antibodies in *in vivo* rat studies. Application of the PAC_1 antibody, AMG 301, was able to alleviate nociceptive activity, with an effectiveness rate comparable to triptans.[12] Studies are needed to investigate the side effects of long-term PAC_1 blockade.

References

1. Cluster headache. (2019, June 4). Retrieved from https://www.mayoclinic.org/diseases-conditions/cluster-headache/symptoms-causes/syc-20352080
2. Kivi, R. Cluster Headache. (2016, February 26). Retrieved from https://www.healthline.com/health/cluster-headache#treatment
3, Rossi, P., Whelan, J., Craven, A., & Ruiz De La Torre, E. (2016). What is cluster headache? Fact sheet for patients and their families. A publication to mark Cluster Headache Day 2016. *Functional neurology*, *31*(3), 181–183. doi:10.11138/fneur/2016.31.3.181
4. Goadsby, P. J., & Holland, P. R. (2019). An Update: Pathophysiology of Migraine. *Neurologic Clinics*, *37*(4), 651–671. doi: 10.1016/j.ncl.2019.07.008
5. Tuka, B., Szabó, N., Tóth, E., Kincses, Z. T., Párdutz, Á., Szok, D., Körtési, T., Bagoly, T., Helyes, Z., Edvinsson, L., Vécsei, L., & Tajti, J. (2016). Release of PACAP-38 in episodic cluster headache patients - an exploratory study. *The journal of headache and pain*, *17*(1), 69. doi:10.1186/s10194-016-0660-7
6. Brazier, Y. (2019, January 3). Cluster headaches: Treatment, symptoms, and causes. Retrieved from https://www.medicalnewstoday.com/articles/172387
7. Arkink, E. B., Schmitz, N., & Schoonman , G. (2017). The anterior hypothalamus in cluster headache. *Chephalagia* , *37*(11), 1039–1050. doi: 10.1177/0333102416660550

8. Chong, C. D., Aguilar, M., & Schwedt, T. J. (2020). Altered Hypothalamic Region Covariance in Migraine and Cluster Headache: A Structural MRI Study. *Headache: The Journal of Head and Face Pain*, *60*(3), 553–563. doi: 10.1111/head.13742
9. Lee, M. J., Cho, S.-J., Park, J. W., Chu, M. K., Moon, H.-S., Chung, P.-W., … Chung, C.-S.(2019). Temporal changes of circadian rhythmicity in cluster headache. *Cephalalgia*. doi: 10.1177/0333102419883372
10. Barloese, M., Lund, N., Petersen, A., Rasmussen, M., Jennum, P., & Jensen, R. (2015). Sleep and chronobiology in cluster headache. *Cephalalgia*, *35*(11), 969–978. doi: 10.1177/0333102414564892
11. Vollesen, A. L. H., & Ashina, M. (2017). PACAP38: Emerging Drug Target in Migraine and Cluster Headache. *Headache: The Journal of Head and Face Pain*, *57*, 56–63. doi: 10.1111/head.13076
12. Rubio-Beltrán, E., Correnti, E., Deen, M., Kamm, K., Kelderman, T., Papetti, L., … Edvinsson, L. (2018). PACAP38 and PAC1 receptor blockade: a new target for headache? *The Journal of Headache and Pain*, *19*(1). doi: 10.1186/s10194-018-0893-8
13. Ross, R. A., Hoeppner, S. S., Hellberg , S. N., O'Day, E. B., Rosencrans, P. L., Ressler, K. J., … Simon, N. M. (2020). Circulating PACAP peptide and PAC1R genotype as possible transdiagnostic biomarkers for anxiety disorders in women: a preliminary study. *Neuropsychopharmocology* . doi: 10.1038/s41386-020-0604-4
14. Strother, L. C., Srikiatkhachorn, A., & Supronsinchai, W. (2018). Targeted Orexin and Hypothalamic Neuropeptides for Migraine. *Neurotherapeutics*, *15*(2), 377–390. doi: 10.1007/s13311-017-0602-3
15. Hannibal, J., Ding, J. M., Chen, D., Fahrenkrug, J., Larsen, P. J., Gillette, M. U., & Mikkelsen, J. D. (1998). Pituitary Adenylate Cyclase Activating Peptide (PACAP) in the Retinohypothalamic Tract: A Daytime Regulator of the Biological Clock. *Annals of the New York Academy of Sciences*, *865*(1 VIP, PACAP, A), 197–206. doi: 10.1111/j.1749-6632.1998.tb11179.x
16. Kopp, M. D. A., Meissl, H., Dehghani, F., & Korf, H.-W. (2008). The pituitary adenylate cyclase-activating polypeptide modulates glutamatergic calcium signalling: investigations on rat suprachiasmatic nucleus neurons. *Journal of Neurochemistry*, *79*(1), 161–171. doi: 10.1046/j.1471-4159.2001.00553.x
17. Jumani, L., Kumari, R., Kataria, D., Kumar, V., Usama, S. M., Chandnani, A., & Zubair, U. (2019). Depression Among Patients with Chronic Cluster Headaches. *Cureus*, *11*(10), e5912. doi:10.7759/cureus.5912
18. May, A., Ashburner, J., Büchel, C., Mcgonigle, D., Friston, K., Frackowiak, R., & Goadsby, P. (1999). Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nature Medicine*, *5*(7), 836–838. doi: 10.1038/10561