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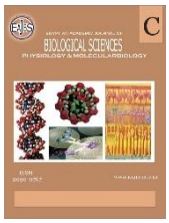

Anticonvulsant Luminal Affects the Arginine-Vasopressin Expression in Hypothalamus and the Locomotor Behaviour of Male Mice

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ABSTRACT

Luminal is an anticonvulsant drug that is commonly used in the control of neonatal seizures and epilepsy via mediating GABAergic signalling and inhibiting glutamatergic transmission. Although it is reported that Luminal may affect the neuronal activity in the cerebral cortex and hippocampus, its impact on the hypothalamic nuclei including the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) has not been elucidated. The PVN and SON are particularly important due to the release of arginine-vasopressin (AVP) which plays a crucial role in regulating cardiovascular functions, metabolism and locomotor behaviour, by their magnocellular neurons. In this study, we investigated the effect of chronic administration of Luminal (for 6 months) on the PVN and SON of male mice. We evaluated the expression of AVP by immunofluorescence and the changes in the cellular architecture by cresyl violet staining of PVN and SON. We also assessed the impact of Luminal administration on locomotor activity, which is largely influenced by AVP. Our findings indicated that chronic administration of Luminal decreased the expression of AVP in PVN and SON without significant changes in their neuronal architecture and influenced locomotor behaviour. Our findings provide novel insights into the central effect of anticonvulsant treatments on the AVP-producing neurons in the hypothalamus and could explain possible side effects on body physiology and behaviour. This may help optimize the therapeutic strategies used for seizure control.

INTRODUCTION

Anticonvulsants also referred to as antiepileptics, are medications that have been used to control seizures (Cotterman-Hart, 2015). Luminal is a barbituric acid derivative, phenobarbiturate, that is commonly used for the treatment of neonatal seizures (Kale and Perucca, 2004). As Luminal is a considerably safe anticonvulsant with low cost, it is commonly used in developing countries as 1st line of treatment for epilepsy (Kale and Perucca, 2004). Additionally, it has been considered recently as an effective treatment for refractory status epilepticus (Reddy *et al.*, 2020). Luminal induces its action through binding to the inhibitory gamma-aminobutyric acid $(GABA)_A$-subtype receptors. This binding alters the chloride currents via receptor channels, decreases glutamate-dependent depolarization and promotes synaptic inhibition (Debski *et al.*, 2020).

Luminal affects the cellular properties within the central nervous system (CNS) (Legan *et al.,* 2009), for instance, it induces some sort of neuroinflammatory reaction via activation of brain microglia and changes neuronal activity in the cerebral cortex and hippocampus (Endesfelder *et al.,* 2017, Tanaka *et al.,* 1997). However, the effect of Luminal on specific neuronal populations in various brain regions is still to be elucidated.

The Hypothalamus involves multiple nuclei that play essential endocrinal and metabolic functions (Florent *et al.,* 2019). The paraventricular nucleus (PVN) of the hypothalamus is a paired nucleus localized on both sides of the upper part of the third ventricle (Qin *et al.,* 2018). The PVN neurons could be categorized morphologically and functionally into three main types: 1. magnocellular neurons that release Arginine-vasopressin (AVP), which is also known as antidiuretic hormone, and oxytocin, and found mainly in the lateral portion of the nucleus 2. parvocellular neurons that produce mainly the hypothalamic releasing and inhibiting hormones and 3. descending neurons that coordinate the autonomic activity (Geerling *et al.,* 2010, Simmons and Swanson, 2009). Most PVN neurons are glutamatergic neurons while only a few neurons are GABAergic neurons (Ziegler *et al.,* 2005, Zhang *et al.,* 2019). In addition to its endocrinal functions, PVN is believed to play an essential role in energy balance, stress modulation and regulation of activity (Qin *et al.,* 2018, Li *et al.,* 2020). PVN shows higher neuronal activity during the activity phase compared to the rest phase. Stimulation of PVN glutamatergic neurons enhances wakefulness via PVN/ventral lateral septum neuronal circuitry, suggesting that PVN is an essential centre for wakefulness/sleep homeostasis (Chen *et al.,* 2021). On the other hand, the supra-optic nucleus (SON) is located in the anterior hypothalamus adjacent to the sides of optic chiasma, which is composed of magnocellular neurons and secretes similarly oxytocin and AVP, and is found mainly in the lateral portion of the nucleus. Unlike the PVN, only 25% of SON neurons are glutamatergic while around 40% are GABAergic (Oliet and Piet, 2004). Importantly, the neural peptide AVP produced within magnocellular neurons of PVN and SON is conveyed via their axons to the posterior pituitary gland to be secreted in the bloodstream (Soumier *et al.,* 2022). Additionally, scattered AVP-producing neurons were identified in the medial preoptic area, the dorsal suprachiasmatic nucleus, and the amygdala (Ueta *et al.,* 2011).

AVP plays multiple regulatory functions in the cardiovascular system including arterial blood pressure through direct vasoconstrictive effect and indirectly via antidiuretic properties on the kidney (Yu and J, 2023). Moreover, AVP has been shown to act as a neuromodulator that affects brain plasticity and animal behaviour (Mlynarik *et al.,* 2007) for instance, feeding (Pei *et al.,* 2014) and self-grooming (Islam *et al.,* 2022). AVP-releasing neurons in PVN play also a crucial role in sickness behaviour, including decreased locomotor activity, reduced motivation and increased anxiety (Whylings *et al.,* 2021) in addition to regulatory function on the hypothalamic-pituitary-adrenal (HPA) axis (Antoni, 2019). Aberrant AVP secretion may lead to hypertension due to dysregulation of salt and water homeostasis (Yemane *et al.,* 2010). Additionally, AVP deficiency results in central diabetes insipidus causing fluid and electrolyte imbalances (Leroy *et al.,* 2013).

The current study aims to identify the effect of chronic administration of Luminal on the two essential AVP-secreting neuronal populations in the mouse hypothalamus: SON and the PVN as well as on the locomotor behaviour. Such novel findings will provide a better understanding of the central impact of anticonvulsant medications on the AVP-producing neurons and explain possible side effects on body physiology and behaviour; thus, helping optimization of therapeutic strategies used for seizure control.

MATERIALS AND METHODS

1.Experimental Animals and Drug Administration:

Male C57Bl/6 mice aged four weeks at the beginning of the study were divided into two groups: one group of mice was chronically administrated with Luminal (phenobarbital, Desitin, Hamburg, Germany) added to the drinking water at a dose of 3mg/kg/day for 6 months (Luminal group, n= 5 mice). Another group of mice (control group, n= 5 mice) was housed for the same period with no addition of luminal to drinking water. Mice were kept in standard Plexiglas cages in groups of two to three mice per cage on a normal 12h/12h light/dark schedule. Mice were housed under controlled temperature (around 22º C) and humidity conditions with free access to standard chow and water (*ad libitum*). Mice were used according to the Guidelines for Ethical Conduct for Use and Care of Animals in Research at Suez University (Ethical approval number: 121222, 1). All efforts were exerted to decrease animal suffering.

2.Tissue Processing:

After six months of Luminal administration, mice were sacrificed. Mice were deeply anesthetized via a single pentobarbital intraperitoneal injection at a dose of (40mg/kg). Intracardiac perfusion with phosphate-buffered saline (PBS) followed by 4% paraformaldehyde in PBS was done. The brains were carefully dissected from the skull and were post-fixed by immersion in 4% paraformaldehyde for an additional 24 hours, cryoprotected in sucrose 30% and then sliced on a cryo-microtome into 20 µm coronal sections.

3.Histology:

Brain sections including PVN and SON were processed for cresyl violet staining. Briefly, slices were hydrated in distilled water, incubated for 5 minutes in Na-acetate buffer then in cresyl violet acetate solution for an additional 5 minutes. Sections were immersed in three changes of 100% isopropanol each for 2 minutes. Slices then were cleared in two changes of Rothihistol, each for 5 minutes. Slides were copper-slipped using Entellan (Watson *et al.,* 2010).

4.Immunofluorescence:

The parallel coronal brain sections between bregma 0.50 mm to -1.70 mm according to (Franklin and Paxinos, 2013) were selected for the staining. The coronal brain sections were washed with PBS-triton three times each for five minutes at room temperature (RT). The sections were afterward incubated for one hour with 1% bovine serum albumin (BSA) and 5% goat normal serum in PBS-triton. This was followed by incubation with primary antibodies rabbit anti-vasopressin (1:1000, ab39363, Abcam, Cambridge, UK) overnight at 4°C. Next, sections were rinsed using PBS-triton three times each for five minutes. Sections were then incubated with anti-rabbit Alexa Fluor 488 secondary antibody (1:500, Abcam, Cambridge, UK) for one hour at RT. The sections were then rinsed with PBS triton. 4`, 6-diamidino-2-phenylindole (DAPI) nuclear counterstaining, which emits blue fluorescence due to nuclear DNA binding, was performed by incubating the section with DAPI solution (300nM, Thermo Fischer Scientific Inc, Massachusetts, USA) for five minutes at RT. This was followed by rinsing with PBS-triton. Sections were finally washed with PBS and coverslipped using an Entellan mounting medium (Hernández-Pérez *et al.,* 2019).

5.Image Acquisition and Analysis:

The images of stained sections were acquired using the Olympus® BX53 fluorescence microscope using the corresponding filter. The experimental conditions were coded during image acquisition and obscured during analysis to avoid bias. The conditions for image acquisition, processing and analysis were kept consistent throughout the whole experimental set.

In brain sections stained against AVP, the DAPI-counterstained nuclei were used for morphological orientation. Images were exported in TIFF format and the optical density (OD) of the AVP-stained neurons within the delineated area including PVN or SON was assessed using ImageJ software

(http://rsbweb.nih.gov/ij/index.html). The mean AVP-OD per mouse was calculated by averaging OD measurements obtained from both the right and left sides, as no significant differences were observed between both sides in one sample (Hernández-Pérez *et al.*, 2019). To assess the cellular architecture and the neurodegeneration, brain sections stained cresyl violet were imaged by Olympus® CX41 light microscope connected to the Olympus® SC100 digital camera using bright field mode. The morphology including the size and the cellular architecture of PVN and SON as well as the width of the 3rd ventricle were estimated (Qin *et al.*, 2018, Soliman *et al.*, 2015).

6.Behavioural Testing:

For behavioural testing, another cohort of mice was divided into two groups (5 mice per group): The luminal group and the control group as described above. Mice were housed individually in standard cages within the light, temperature and sound-tight chambers. To detect the effect of short- and long-term administration of Luminal on the locomotor activity of mice, the locomotor activity was recorded after 1 month and 6 months of Luminal administration. Movements of mice were detected with infrared detectors and data were evaluated by Clocklab software (Actimetrics). The locomotor activity counts during the light phase (represents the rest phase for mice), during the dark phase (represents the active phase for mice) as well as the total activity (the sum of both phases) was estimated (Öztürk et al., 2021).

7.Statistical Analysis:

GraphPad Prism 8.3.0 software was used for statistical analysis. Non-parametric Mann-Whitney -U test was used to compare differences between the two groups. Data were expressed as mean ± standard error of the mean (SEM). The results were regarded as statistically significant if $P < 0.05$.

RESULTS AND DISCUSSION

1.**Chronic Administration of Luminal Has No Effect on PVN and SON Neuronal Structure:**

The general neuronal architecture, as revealed by the cresyl violet staining, showed that PVN and SON seemed to be structurally normal. The cellular density and size of the PVN, located adjacent to the lateral ventricle, were not significantly different in both groups (control = 74731 ± 6424 μm^2; Luminal = 72697 ± 14029 μm^2; P = 0.8) (Fig. 1A, C, E). The PVN displayed a lateral area with compact magnocellular neurons while the medial area involved low-density smaller neurons (Figure 1B, D). The width of the 3rd ventricle was comparable in both groups (control = 165.2 ± 13.5 µm; Luminal = 158.7 ± 4.9 µm; P = 0.7) (Fig. 1F). The SON, situated at the dorsolateral aspect of optic chiasma, consists of two parts; medially, there is a slim portion of compact aggregated cells dorsal to optic chiasma and laterally, there is a wider portion that surrounds the lateral end of optic chiasma and is composed of groups or rows of magnocellular neurons. In the SON, the overall architecture, size, and the neuronal distributions were similar (control = 30970 ± 2263 μm^2; Luminal = 26588 ± 2133 μm^2; P = 0.2) (Fig. 2A, B, C).

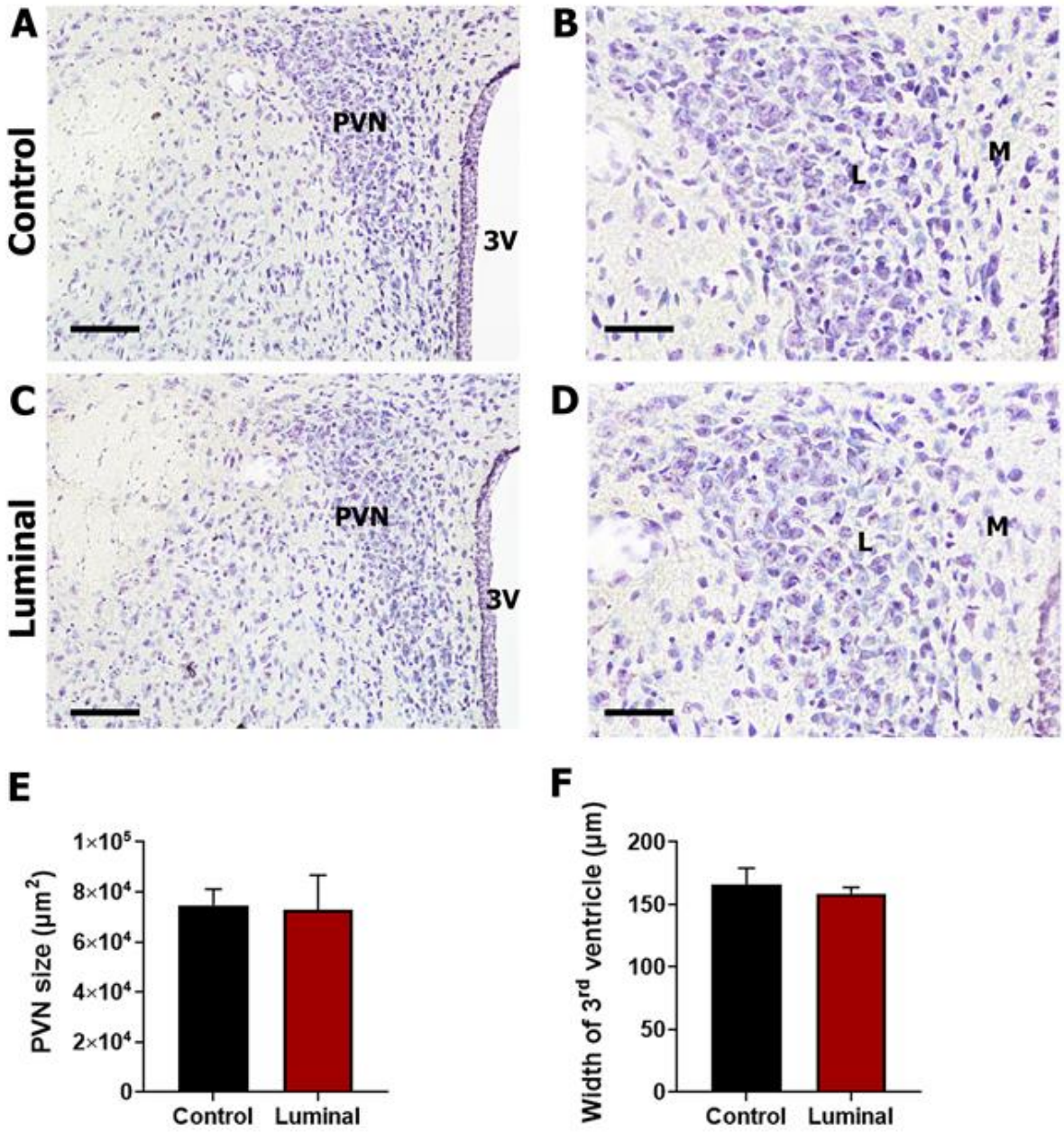

Fig. 1. Chronic Luminal administration doesn't affect the paraventricular nucleus (PVN) neuronal structure. A) Representative low-magnification and B) high-magnification photomicrographs of coronal brain sections of the control group stained with cresyl violet showing normal neuronal architecture of PVN of mouse hypothalamus. C) Representative low-magnification and D) high-magnification photomicrographs of coronal brain sections of the Luminal group stained with cresyl violet showing similar PVN architecture as in control group. 3V: third ventricle, L: lateral area with compact magnocellular neurons, M: medial area containing low-density smaller neurons. Scale bar = 100µm in A, C. Scale bar = 50µm in B, D. Quantification of E) Size of PVN in μm^2, F) Width of 3rd ventricle in control and Luminal-treated mice didn't show significant differences using a non-parametric test (Mann-Whitney-U test). n = 5 mice per group.

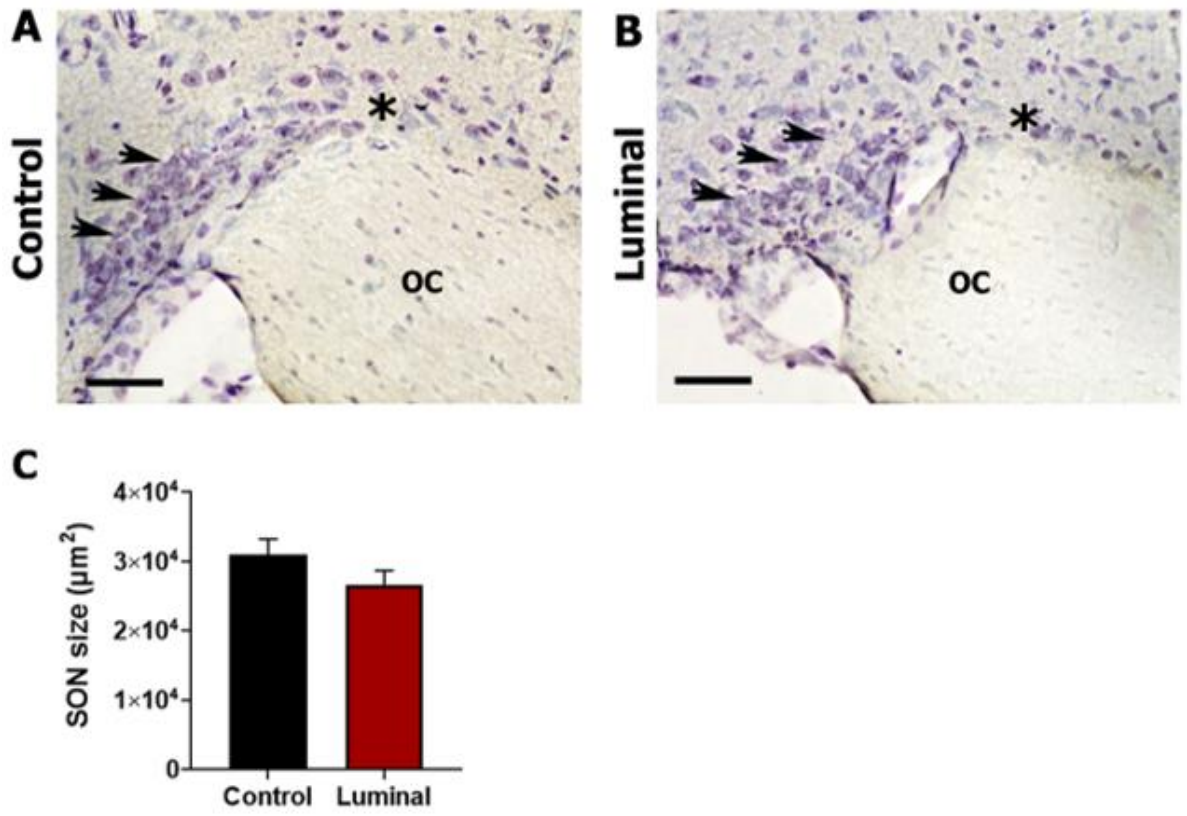

Figure 2. Chronic Luminal administration doesn't affect the the supraoptic nucleus (SON) neuronal structure. A) Representative photomicrographs of coronal brain sections of the control group, stained with cresyl violet staining, showing the normal neuronal architecture of SON of the mouse hypothalamus. B) Representative photomicrographs of coronal brain sections of the Luminal group, stained with cresyl violet staining, showing similar SON architecture to the control group. OC: optic chiasma, black arrows: lateral area composed of groups or rows of magnocellular neurons, black star: medial area containing a slim portion of compact aggregated cells. Scale bar = 100µm. Quantification of C) Size of SON in control and Luminal-treated mice didn't show significant differences using a non-parametric test (Mann-Whitney-U test). *n* = 5 mice per group.

2.Chronic Luminal Administration Affects the AVP-Releasing Neurons in PVN and SON:

AVP-positively stained neurons were found in PVN in both control and Luminal-treated mice. In the control group, the AVP was expressed within the cell bodies and axons of the magnocellular neurons of PVN. The AVP-immunoreactive neurons were located mainly in the upper and lateral parts of the PVN flanking the third ventricle. The optical density (OD) of AVP+ neurons in PVN was significantly decreased after chronic Luminal treatment of mice (OD = 3.3 ± 0.4) as compared to control mice (OD = 5.1 ± 0.2, P = 0.01) (Fig. 3A, B).

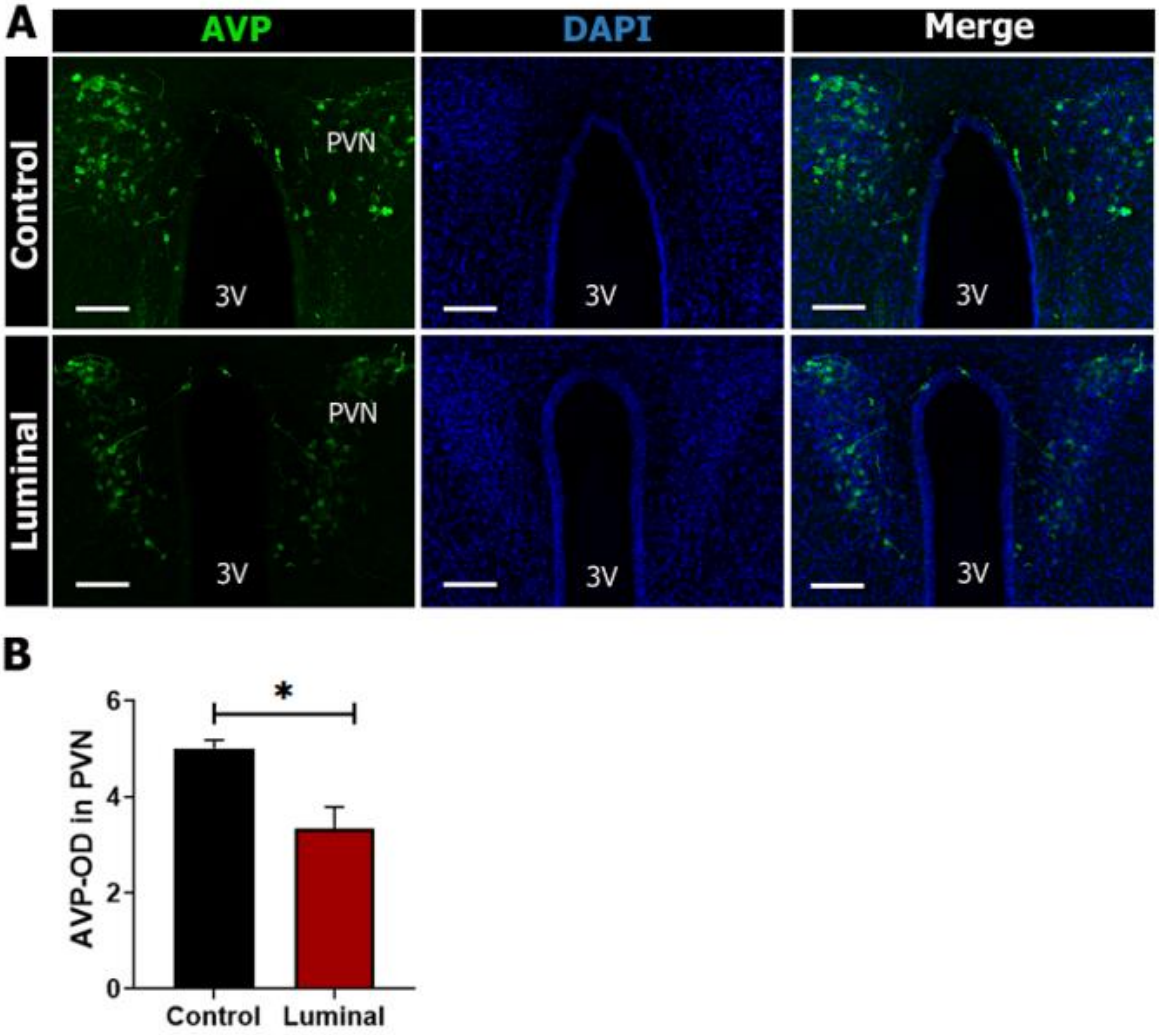

Fig. 3. Chronic Luminal administration affects the arginine-vasopressin (AVP)-releasing neurons in the paraventricular nucleus: A) representative photomicrographs of coronal brain sections showing AVP-positively stained neurons (green) and DAPI counterstained nuclei (Blue) in the paraventricular nucleus (PVN) of mouse hypothalamus. 3V: third ventricle, Scale bar = 100µm. B) Quantification of optical density (OD) of AVP-stained neurons in the paraventricular nucleus (PVN) showing significantly decreased AVP-OD in PVN of Luminal-treated mice. *: $P < 0.05$ using non-parametric test (Mann-Whitney-U test). $n = 5$ mice per group.

Similarly, within the SON, AVP+ neurons were detected in both control and Luminal-treated mice. In the control group, the AVP was expressed within the cell bodies and axons of the magnocellular neurons of SON. The AVP-immunoreactive neurons were located mainly in the lateral part of the SON surrounding the dorsal lateral end of the optic chiasma. The optical density of AVP+ neurons in SON was dramatically reduced in Luminal-treated mice (OD = 4.0 ± 0.3) as compared to control mice (OD = 5.3 ± 0.4, P = 0.03) (Fig. 4A, B).

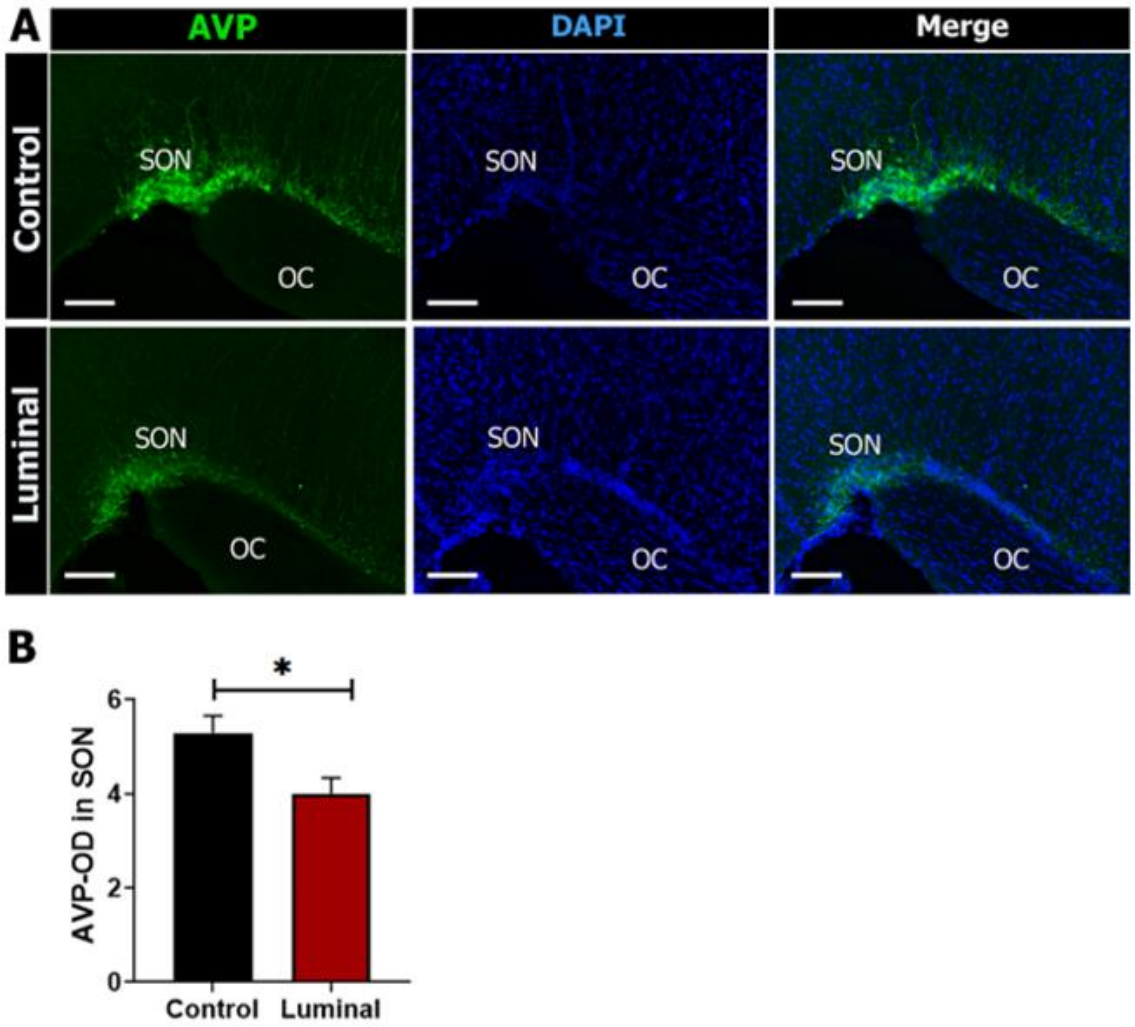

Fig. 4. Chronic Luminal administration affects the arginine-vasopressin (AVP)-releasing neurons in the supraoptic nucleus: A) representative photomicrographs of coronal brain sections showing AVP-positively stained neurons (green) and DAPI counterstained nuclei (Blue) in the supraoptic nucleus (SON) of mouse hypothalamus. OC optic chiasma, Scale bar = 100µm. B) Quantification of optical density (OD) of AVP-stained neurons in the supraoptic nucleus (SON) showing significantly decreased AVP-OD in SON of Luminal-treated mice. *: $P < 0.05$ using non-parametric test (Mann-Whitney-U test). $n = 5$ mice per group.

3.Chronic Luminal Administration Alters Locomotor Behaviour:

Short-term administration of Luminal for 1 month didn't induce substantial change in the mouse's total locomotor activity (Fig. 5A). Only the locomotor activity during the dark phase (activity phase) was significantly increased in the Luminal group as compared to control group (P = 0.04), while the locomotor activity during the light phase (rest phase) of treated mice was comparable to control group (P = 0.6, Fig. 5B, C). Long-term administration of Luminal for 6 months significantly increased the day activity as compared to control mice of the same age (P = 0.002, Figure 5B). In addition, long-term administration caused a decrease in the night activity and a reduction in the total locomotor behaviour of mice as compared to short-term administration for 1 month (P = 0.002, P = 0.003; respectively; Fig. 5A, C). The control mice didn't show significant differences in locomotor behaviour between the two tested ages (P > 0.05).

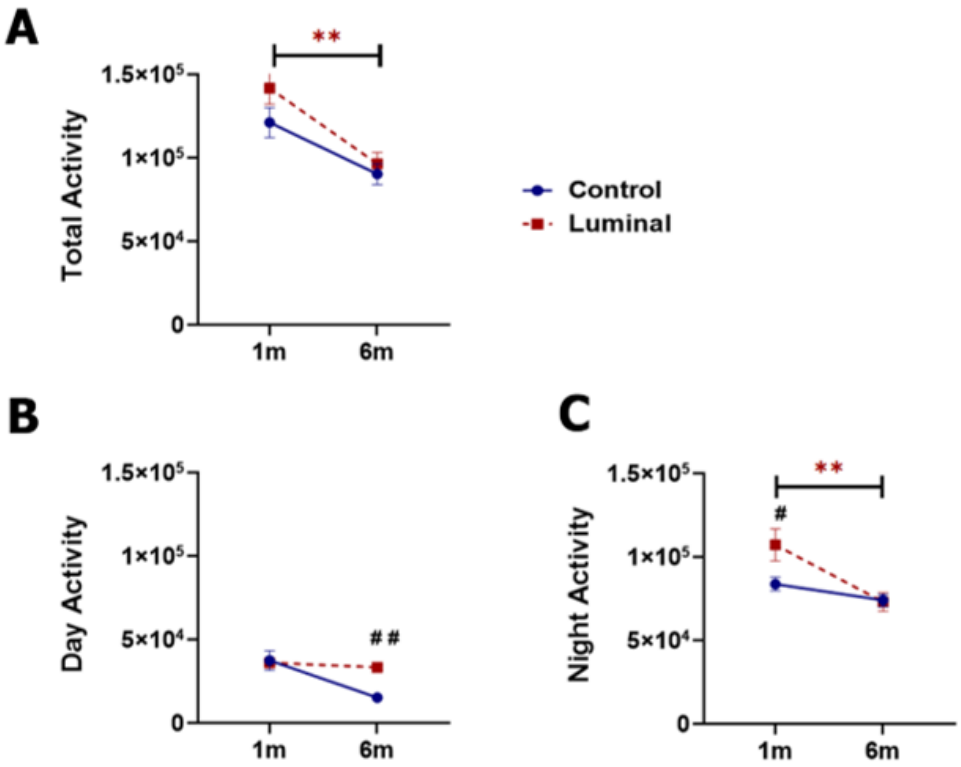

Fig. 5. Chronic Luminal administration alters locomotor behaviour: A) Analysis of total locomotor behaviour after 1 month showing higher activity after 1 month of luminal administration compared to mice after 6 months of Luminal treatment (dotted red line). B) Analysis of locomotor behaviour during the day (rest) phase after 1 month (1m) and 6 months (6m) showing increased activity after 6 months of luminal administration (dotted red line) compared to control mice (blue line). C) Analysis of locomotor behaviour during the night (active) phase showing increased activity after 1 month of luminal administration compared to control mice as well as treated mice 6 months after Luminal administration. #: $P < 0.05$ between the Luminal group and control group. **: $P < 0.01$ between 1 month and 6 months of Luminal administration.

DISCUSSION:

In this study, we demonstrated, for the first time, that chronic administration of Luminal resulted in the downregulation of AVP expression in the PVN and SON, the two essential AVP-secreting subregions in the mouse hypothalamus. Importantly, these two brain areas, receive to a wide extent, similar inputs from multiple brain areas and are comparably regulated (Wei *et al.,* 2021). In agreement with our observations, administration of anti-seizers including phenobarbital decreased the neuronal activity in various mouse brain areas including the cerebral cortex (Tanaka *et al.,* 1997) and hippocampus (Akasaki, 1993). Similar findings were reported in *in vitro* models of epilepsy (Nardou *et al.,* 2011b) as well as in the marmoset's brain indicated via decreased expression of the neuronal activity marker c-Fos (Pontes *et al.,* 2016). This inhibition of the neuronal activity is likely mediated by enhancing the γ-aminobutyric acid (GABA) inhibitory neurotransmission via $GABA_A$ receptors (Löscher and Rogawski, 2012), the main mechanism of action of phenobarbital as an anticonvulsant (Nardou *et al.,* 2011b, Debski *et al.,* 2020). Thus, it is presumed that Luminal treatment reduced the AVP expression through a GABAergic-dependent mechanism. Supporting this notion, previous studies showed that the secretion of AVP by magnocellular neurons as well as their firing rate in PVN and SON predominantly

inhibited via GABA-mediated currents (Decavel and Van den Pol, 1990, Kim *et al.*, 2013). Moreover, local administration of the $GABA_A$ receptor antagonist resulted in increased expression of neuronal activity marker c-Fos and AVP mRNA in the neurons of PVN, indicating that GABA singling promotes an inhibitory effect on AVP-releasing neurons in PVN (Cole and Sawchenko, 2002). On the other hand, Phenobarbital is cable to act as an antagonist for the glutamatergic neurotransmission, which is an important regulator of AVP neuron activity, and decreases the amplitude of AMPA/kainate receptor-mediated excitatory postsynaptic currents (Nardou *et al.*, 2011a). Thus, the downregulation of AVP+ neurons may be regulated not only by the enhancement of GABAergic neurotransmission but also by the inhibition of glutamatergic signalling.

Importantly, Phenobarbital treatment did not lead to increased neuronal death (Cleary et al., 2013). This is in line with our results that showed, as previously described, the normal morphological architecture of PVN (Qin *et al.*, 2018) and SON (Soliman *et al.*, 2015). This also indicates that the decreased AVP is not due to neuronal death but rather a down-regulation of AVP within intact neurons by chronic administration of Luminal.

Furthermore, in line with our findings, previous studies in humans showed a correlation between anticonvulsant treatments and AVP blood levels. For instance, the administration of carbamazepine, which is one the most widely used anticonvulsants, induced abnormal AVP secretion, while phenytoin was reported to decrease the AVP release (Pacifici and Pelkonen, 2001).

Importantly, AVP plays a crucial role in body fluid homeostasis and electrolyte balance. It is worth mentioning that antiepileptic drugs were reported to increase the risk of electrolyte imbalance (Yamamoto *et al.*, 2019). In particular, chronic treatment with oxcarbazepine was often associated with hyponatremia (Falhammar *et al.*, 2018). This effect of anti-seizure treatments could rely centrally on dysregulation of blood AVP/ADH level, commonly known as syndrome of inappropriate antidiuretic hormone secretion (SIADM), or on peripheral alteration in the response of renal tubules to AVP (Lu and Wang, 2017). Furthermore, carbamazepine and oxcarbazepine are believed to modulate AVP receptor sensitivity irrespective of blood AVP levels (Berghuis et al., 2016). However, the central influence of the anti-convulsant drugs on the expression of the AVP neuropeptide in the hypothalamus has not been determined. Here, we showed that chronic treatment with Luminal decreases AVP expression suggesting an additional underlying central mechanism, via which the anticonvulsant drugs could influence the AVP level and, consequently, the fluid and electrolytes homeostasis.

Interestingly, short-term administration of Luminal showed no significant change in the mouse's total locomotor behaviour and the locomotor behaviour during the day/rest phase as compared to control group. However, the locomotor behaviour during the night/activity phase was significantly increased in the Luminal group as compared to control group. Consistently with this, the phenobarbital treatment for immature rats displayed anxiety-like behaviour (Quinlan *et al.*, 2018). This anxiety could explain the increase in motor activity during the activity phase in the young mice (1 month) after the administration of Luminal in the present study. On the other hand, the long-term administration of Luminal for 6 months caused a significant increase in locomotor behaviour during the rest phase as compared to control mice of the same age. Thus, it could reflect a sleep disruption. In agreement with our observations, it was reported that exposure to anti-seizure drugs in the early stages of rats could cause various cognitive and behavioural deficits including motor abnormalities later in the adult age (Forcelli *et al.*, 2012). Importantly, AVP neurons in PVN play also a crucial role in the regulation of

locomotor behaviour (Whylings *et al.,* 2021). Therefore, the observed decrease in activity during the night/activity phase and total locomotor behaviour of mice after long-term administration of Luminal as compared to short-term administration for 1 month could be partially due to the decrease in the expression of AVP by the PVN neurons, which was observed in the current study. It is of note that the administration of phenobarbital in rats for one week at a young age had no subsequent effect on locomotor behaviour during adult age (Frankel *et al.,* 2016). This controversial result could be due to the shorter administration period of the phenobarbital, as the side effects of anti-seizure drugs are age-, duration of treatment- and dose-dependent and hence, the response could vary including hyperkinetic behaviour, suppression of the locomotor activity or no response (Koneval *et al.,* 2020).

Generally, anti-seizers could influence locomotor activity by altering the neuronal properties and astrocyte responses (Forcelli *et al.,* 2012, Kaindl *et al.,* 2008) or via impairment of neurotransmitters' receptors (Saxe *et al.,* 2006, Stefovska *et al.,* 2008). Moreover, there is a correlation between epilepsy and activation of the HPA axis (Marek et al., 2010, Galimberti *et al.,* 2005). Thus, the anti-seizure drugs were shown to decrease cortisol levels in epileptic patients (Morimoto *et al.,* 2018). Moreover, chronic treatment with phenobarbital caused a blunt in serum corticosterone levels in transgenic mice throughout the day (Hassan et al., 2021). Interestingly, it was reported that high locomotor activities of female rats in a novel environment were followed by an increase in corticosterone levels indicating a close relationship between glucocorticoid secretion and locomotor activity (Cavigelli *et al.,* 2008).

Importantly, AVP of PVN parvocellular origin is co-synthesized and functions synergistically with corticotropin-releasing hormone (CRH) (Scott and Dinan, 2002) and rescuing AVP secretion in the SON of AVP-knockout rats restored normal levels of adrenocorticotropic hormone (ACTH) (Török *et al.,* 2022), suggesting that AVP may contribute to HPA axis modulation, and thus, which could be an additional indirect mechanism of regulating the locomotor behaviour.

In conclusion, our data provide novel evidence on the impact of anticonvulsant Luminal on AVP-producing neurons in mouse hypothalamus and could explain possible side effects on the physiology including cardiovascular functions and metabolism as well as on the locomotor behaviour. This better understanding could help refine the treatment approaches used for seizure control. It is still to be elucidated in future studies the other possible underlying mechanism of this drug that could alter AVP release and function on its receptors centrally and in the peripheral organs.

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ARABIC SUMMARY

تأثيرمضاد التشنجات لومينال على اظهار الارجنين فازوبرسين على منطقة ما تحت المهاد و السلوك الحركى فى ذكور الفئران

اميرة امين حسن على [1-3] سها عبد العليم حسن [2]

1- قسم التشريح الادمى و علم الاجنة بكلية الطب جامعه المنصورة مصر

2- قسم علوم الحيوان بكليه العلوم جامعة قناة السويس مصر

3- قسم التشريح بكليه الطب جامعة دوسيلدورف المانيا

لومينال هو دواء مضاد للاختلاج يستخدم بشكل شائع فى السيطرة على نوبات الصرع و نوبات التشنجات فى حديثى الولادةعن طريق دعم مستقبلات جابا و تثبيط انتقال الجلوتامات. على الرغم من الدراسات السابقه اللتى اشارت الى تاثير لومينال على النشاط العصبى فى القشرة الدماغيه و الحصين الا انه لم يتم بعد دراسه تاثير لومينال على منطقه ما تحت المهاد اللتى تشمل العديد من الانويه العصبيه مثل النواة الوطائيه فوق البصريه و النواة الوطائيه المجاورة للبطين.

للنواة الوطائيه فوق البصريه و النواة الوطائيه المجاورة للبطين اهميه قصوى و ذلك لانهم المصدر الاساسى لافراز هرمون الارجنين فازوبرسين الذى يلعب دور اساسى فى تنظيم وظائف القلب و الاوعيه الدمويه و التمثيل الغذائى و السلوك الحركى. فى هذة الدراسه لاحظنا تاثير التعاطى المزمن للومينال على اظهار الخلايا العصبيه فى النواة الوطائيه فوق البصريه و النواة الوطائيه المجاورة للبطين للارجنين فازوبرسين فى ذكور الفئران بالاضافه الى دراسه النشاط الحركى الذى يتاثر بشكل قوى بالارجنين فازوبرسين.

تشير النتائج اللتى توصلنا اليها ان التعاطى المزمن للومينال يقلل من اظهار الارجنين فازوبرسين فى الخلايا العصبيه فى النواة الوطائيه المجاورة للبطين و النواة الوطائيه فوق البصريه دون تغييرات كبيرة فى البنيه العصبيه للنواتين كما اثر التعاطى المزمن للومينال على النشاط الحركى .

توفر النتائج التي توصلنا إليها رؤى أعمق حول التأثير المركزي للعلاجات المضادة للاختلاج على الخلايا العصبية في منطقة ما تحت المهاد ويمكن أن تفسر الآثار الجانبية المحتملة على فسيولوجيا الجسم وسلوكه. قد يساعد هذا في تحسين الاستراتيجيات العلاجية المستخدمة للتحكم فيى نوبات الصرع .