Skin denervation in patients with hereditary and wild-type transthyretin amyloidosis

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Background: Hereditary transthyretin (TTR) amyloidosis is an autosomal-dominant disorder caused by mutations in TTR, characterized by accumulation of amyloid in various organs. These patients usually show small fiber neuropathy (SFN) including autonomic dysfunction. Patients with wild-type TTR amyloidosis, which is a non-hereditary systemic disorder, in the presence of wild-type TTR, often have SFN. Skin biopsy is a useful method for SFN by the quantification of intra-epidermal nerve fiber density (IENFD). Aim: To investigate skin denervation in hereditary and wild-type TTR amyloidosis. Methods: We investigated clinical findings, heat-pain detection thresholds measured by Computer Aided Sensory Evaluator IV, and IENFD in 34 patients with hereditary TTR amyloidosis, 11 asymptomatic mutation carriers, 5 patients with wild-type TTR amyloidosis, and 23 healthy volunteers. Results: IENFD values were decreased in patients with hereditary TTR amyloidosis (3.5 ± 3.2 /mm) and asymptomatic mutation carriers (5.0 ± 2.2/mm) than in healthy volunteers ($p < 0.05$). IENFD significantly correlated with peripheral neuropathy parameters, such as sensory impairment and autonomic dysfunction on the Kumamoto clinical score, disease duration, and heat-pain detection threshold. The IENFD values were also decreased in patients with wild-type TTR amyloidosis (3.1 ± 1.6 /mm). Conclusions: Skin denervation was found in hereditary and wild-type TTR amyloidosis patients. Skin biopsy may be a useful tool for evaluating SFN in hereditary and wild-type TTR amyloidosis.

Selective ablation of central pre-sympathetic neurons from the Rostral Ventrolateral Medulla prevents cardiac function impairment in heart failure rats with preserved ejection fraction

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Background: Heart failure with preserved ejection fraction (HFpEF) is a major public health concern, characterized by cardiac function deterioration and autonomic imbalance. It has been proposed that the rostral ventrolateral medulla (RVLM) contribute to sympathoexcitation and cardiac dysfunction in heart failure. However, a causal link between RVLM pre-sympathetic neurons and their contribution on cardiac autonomic imbalance and the progression of cardiac function deterioration in HFpEF is missing. **Aims**: We aimed to determine the role of RVLM C1 neurons on cardiac autonomic imbalance, arrhythmogenesis and cardiac function impairment in HFpEF rats. **Methods**: HFpEF was induced by volume overload in male Sprague-Dawley rats. RVLM C1 neurons ablation was performed by stereotaxic injection of dopamine beta hydroxylase-saporin toxin (DβH-SAP, 7.5ng/150nL). Cardiac function was studied by pressure-volume loops. Autonomic control was assessed by propranolol/atropine tests and by heart rate variability (HRV). Arrhythmia incidence was also scored. **Results**: Selective RVLM C1 neurons ablation improved both cardiac diastolic (0.009±0.001 vs. 0.004±0.001 mmHg/µl, HFpEF+Veh vs. HFpEF+DβH-SAP, respectively; $p<0.05$) and systolic function (0.2±0.01 vs. 0.5±0.1 mmHg/µl, HFpEF+Veh vs. HFpEF+DβH-SAP, respectively; $p<0.05$). Compared to vehicle treatment, SSP-SAP (HFpEF+Veh vs. HFpEF+DβH-SAP) normalized autonomic control (ΔHR −98.0±12.1 vs. −52.2±7.9bpm; LF/HFHRV 3.0±0.7 vs. 1.7±0.1; $p<0.05$). More importantly, SSP-Saporin significantly reduced arrhythmia incidence in HFpEF rats (91±21 vs. 48±15 events/hour, HFpEF+Veh vs. HFpEF+DβH-SAP; $p<0.05$). **Conclusions**: Our results show for the first time that C1 RVLM neurons play a pivotal role in HFpEF progression by contributing to the maintenance of cardiac autonomic function impairment and arrhythmogenesis.

Angiotensin II enhanced peripheral sympathetic nerve activity in the brainstem-spinal cord preparation from newborn rats

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Newborn rat brainstem-spinal cord preparations are useful for *in vitro* analysis of various brainstem functions including respiratory activity. In the study regarding the central control of sympathetic nerve activity (SNA), it is important to record peripheral outputs of the SNA. We developed an *in vitro* preparation in which neuronal connections between cardiovascular center in the medulla and SNA peripheral outputs are preserved. Newborn (0-3-day-old) Wistar rats were deeply anesthetized with isoflurane, and brainstem and spinal cord were isolated together with the partial right thoracic cage. The vertebrae and left side of the thoracic cage were removed, and a part of the right side of the thoracic cage attached with the right side of the spinal nerve roots was retained to record the SNA from the right thoracic sympathetic nerve trunk (T8–T10). The fourth cervical ventral root (C4) at right side and sympathetic nerve discharge were recorded with glass suction electrodes. The preparations were continuously superfused with ACSF (25–26°C) at a rate of 2.5–3 ml/min. SNA in this preparation was strongly modulated by inspiratory activity. Single-shot electrical stimulation of the ipsilateral rostral ventrolateral medulla (RVLM) induced transient increase of SNA. Bath application of angiotensin II induced an increase of SNA, and local ipsilateral microinjection of angiotensin II to the RVLM induced transient increase of SNA, suggesting that activation of medullary angiotensin II receptors resulted in an increase of peripheral SNA. This preparation allows analysis of the central control of the SNA *in vitro*.

Brainstem sources of cardiac vagal tone and respiratory sinus arrhythmia.

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Cardiac vagal tone is a strong predictor of health, although its central origins are unknown. The rat working heart-brainstem preparation shows strong cardiac vagal tone and pronounced respiratory sinus arrhythmia. In this preparation, recordings from the cut left cardiac vagal branch showed efferent activity that was respiratory-linked and peaked in post-inspiration, ~0.5s before the cyclic minimum in heart rate (HR). We hypothesized that respiratory modulation of cardiac vagal tone and HR is intrinsically linked to the generation of post-inspiration. Neurons in the pontine Kölliker-Fuse nucleus (KF) were inhibited with bilateral microinjections of isoguvacine (50-70 nl, 10 mM) to remove the post-inspiratory phase of respiration. This also abolished the post-inspiratory peak of cardiac vagal discharge (and cyclical HR modulation), although a substantial level of activity remained. In separate preparations with intact cardiac vagal branches but sympathetically denervated by thoracic spinal pithing, chronotropic cardiac vagal tone was quantified by HR compared to its final level after systemic atropine (0.5 μM). Bilateral KF inhibition removed 88% of the cyclical fluctuation in HR but, on average, only 52% of the chronotropic vagal tone. Substantial chronotropic vagal tone also remained after transection of the brainstem through the caudal pons. Subsequent bilateral isoguvacine injections into the nucleus of the solitary tract further reduced vagal tone: remaining sources were untraced. We conclude that cardiac vagal tone depends on neurons in at least three sites of the pontomedullary brainstem, and much of it arises independently of respiratory sinus arrhythmia.

The activation of intraoral TRPV1 may induce selective brain cooling to protect the brain from overheating: a hypothesized function of gustatory sweating

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Background: The tasting of capsaicin induces gustatory sweating, primarily of the face. However, the significance of this phenomenon is unknown. Aim: We studied the significance of gustatory sweating by investigating a patient with hemifacial gustatory sweating disorder. Methods: The patient was a 25-year-old man with a hemifacial gustatory sweating deficit but no facial thermoregulatory sweating impairment. His sudomotor function was assessed using Minor's method (i.e., the iodine-starch test), and his skin temperature was simultaneously measured using infrared thermography. Various tastants were applied to the lingual apex at an ambient temperature of 25°C. Results: The application of Tabasco ® (capsaicin) and ginger (gingerol), which activate the transient receptor potential vanilloid 1 (TRPV1) channel, induced hemifacial sweating and flushing and decreased the skin temperature on the unimpaired side of the face. Sweating or hemifacial skin temperature differences were not elicited by the application of horseradish or oriental mustard (allyl isothiocyanate; activates TRPA (Ankyrin) 1), nor by gum syrup, salt, ume, or instant coffee, which activate sweet, salty, sour, and bitter taste receptor cells, respectively. Conclusions: The results suggest that physiological gustatory sweating may be induced by the activation of TRPV1, which is activated by hyperthermia (i.e., ≥ 43°C). TRPV1 activation-induced gustatory sweating may induce selective brain cooling at higher temperatures due to its largely facial distribution. Since gustatory sweating occurred immediately after tastant ingestion and increased rapidly, we hypothesize that it may be a form of feedforward regulation. In conclusion, gustatory sweating may protect the brain from overheating.

Validation of the Korean Version of the Composite Autonomic Symptom Scale-31 (COMPASS-31)

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Background and purpose: The Composite Autonomic Symptom Scale 31 (COMPASS-31) is a recently developed questionnaire for assessing symptoms of autonomic dysfunction. We aimed to evaluate the reliability and validity of the Korean version of COMPASS-31 (K-COMPASS-31). **Methods:** The COMPASS-31 was extracted from the well-established Autonomic Symptom Profile (ASP) questionnaire, and the ASP was translated into Korean previously by the Korean Society of Pain & Autonomic Disorders (KSPAD). So we translated the COMPASS-31 into Korean by the bilingual specialist, and check its accuracy based on the Korean version of the ASP. The K-COMPASS-31 was tested in patients with parkinsonism or cerebellar ataxia who also underwent autonomic function tests (AFT) including heart rate response to deep breathing, Valsalva test and head-up tilt test. **Results:** Totally 69 patients were enrolled and completed K-COMPASS-31 questionnaire in this study. Test-retest reliability and internal validity were assessed with 31 patients in a time interval of 4 weeks; the intraclass correlation coefficient was 0.896 and Cronbach's alpha coefficient was 0.738. The total K-COMPASS-31 score was well-correlated with all objective AFT results including the E:I ratio, Valsalva ratio and pressure recovery time (E:I ratio, r = -0.333, p = 0.011; Valsalva ratio. r = -0.309, p = 0.019; pressure recovery time, r = 0.399, p = 0.002). **Conclusions:** K-COMPASS-31 is a reliable and valid tool for evaluating the severity of autonomic dysfunction symptoms in Korea patients.

Activated astrocytes induce persistence of post-stress blood pressure elevation

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Hypertension is often seen in subjects who have accumulated psychological stress. When psychological stress is loaded to a subject, the sympathetic nervous system is excited, which reflexively evokes blood pressure elevation. Even after the stress is relieved, blood pressure elevation persists. However, cellular mechanisms of stress induced persistent blood pressure elevation have not been fully clarified. Because sustained blood pressure elevation could be assumed a consequence of neural plasticity of the sympathetic nervous activity and it has been revealed that not only neurons but astrocytes play active roles in neural plasticity in various brain functions, we hypothesized that astrocytes are involved in post-stress persistent blood pressure elevation. We tested this hypothesis by analyzing the effects of arundic acid, an inhibitory modulator of astrocytic function, on responses of blood pressure and heart rate to air-jet stress in unanaesthetized rats. Further, the effects of arundic acid on air-jet stress induced activation of neurons and astrocytes were examined by c-Fos immunohistochemistry. We have shown that inhibition of astrocytic activation suppressed air-jet stress induced blood pressure elevation during and after stress loading. Suppression of heart rate by arundic acid was not remarkable. Histochemically, pretreatment with arundic acid suppressed air-jet stress induced activation of neurons and astrocytes in the cardiovascular brain regions. We demonstrated that not only neurons but astrocytes are involved in stress induced blood pressure elevation and its post-stress persistence. We suggest that activated astrocytes play a role in the emergence of hypertension in stress loaded subjects.

Physiological correlates of emotional control in school-aged children

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Background. Emotional control is a raising concern in school-aged children. Emotional control may require support from different bodily systems as well as different cognitive processes. ***Aim.*** This study aims to examine the physiological correlates of emotional control in this population. ***Methods.*** We recruited 17 typically developing children who were aged 6 to 12 years old. Heart rate variability (HRV) and right frontal electroencephalogram at resting condition were examined simultaneously. Parents completed a checklist to report on inhibition, shifting and emotional control of their children in daily event. Pearson correlation analysis was conducted to examine the relationship between these physiological indexes and the score on (occurrence of problem of) inhibition, shifting and emotional control. ***Results.*** The score on emotional control was correlated with scores on inhibition (r = .53; p = .03) and shifting (r = .76; p < .001). Inhibition was correlated with theta to beta ratio (r = -.78; p = .02) and alpha to beta ratio (r = -.63, p = .04) of encephalogram. Shifting was correlated with high frequency (HF; r = -.51, p = .04) and low frequency to high frequency ratio (LF/HF; r = .52, p = .03) of HRV. Emotional control was also correlated with HF (r = -.53, p = .03) and LF/HF (r = .50, p = .04). ***Conclusion.*** Emotional control associates inhibition and shifting. The findings suggest that emotional regulation may require an integrated support from a balanced state of functioning (between and within bodily systems) in school-aged children.

Effect of glutamate receptor blockade in RVLM on PVN stimulation-elicited sympathoexcitation in anesthetized rats

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We previously found that stimulation of paraventricular hypothalamic nucleus (PVN) neurons projecting to the rostral ventrolateral medulla (RVLM) with optogenetics increases renal sympathetic nerve activity in anesthetized rats. Here, we examined the effect of glutamate receptor blockade in the RVLM on the sympathoexcitation due to activation of the PVN. Adult male Sprague-Dawley rats ($N = 6$) anesthetized with pentobarbital received a unilateral microinjection into the PVN of an adeno-associated virus (AAV) vector that encodes channelrhodopsin variant, ChIEF-tdTomato. Two-to-four weeks later, in the rats anesthetized with a mixture of urethane and α-chloralose, bilateral microinjections into the RVLM with saline or a cocktail of AP5 and CNQX, NMDA and non-NMDA receptor antagonists, respectively, was followed by 2-min photostimulation (473 nm wavelength, 8-10 mW) provided to the PVN into which the AAV had been injected in advance. After saline treatment, the photostimulation resulted in a significant ($P < 0.05$) increase in renal sympathetic nerve activity (RSNA) without changing arterial pressure. After AP5/CNQX treatment, on the other hand, the photostimulation did not change RSNA. These observations suggest that glutamate released from PVN-RVLM projection neurons plays a role in cardiovascular sympathoexcitation.

Heart rate variability and sluggish cognitive tempo behaviour among children with typical development

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Background. Children with sluggish cognitive tempo behaviour often appears to be hypoactive, lethargic and day dreamy. Researches have rarely investigate the relationship between autonomic functioning and sluggish cognitive tempo behaviour in order to understand the underlying mechanism of these behaviour. *Aim.* This study aims to examine the relationship between heart rate variability and sluggish cognitive tempo behaviour among children with typical development. *Methods*. Seventeen aged 6-12 children with typical development were recruited for the current study. Different measures of heart rate variability were recorded during the resting period. Pearson's *r* correlation was used to examine the relationship between heart rate variability and the total score on the sluggish cognitive tempo scale (SCT scale). *Results.* Significant negative relationship was found between the total score on the SCT scale and SD1-SD2 ratio of the HRV measures (r = -.490, p <.05). No significant relationship was found on RMSSD or SDNN with the total score on the SCT scale. *Conclusion.* Sluggish cognitive tempo behaviour was found to be negatively associated with the sympathovagal balance reflected by the SD1-SD2 ratio. The findings help to understand the underlying mechanism of sluggish cognitive tempo behaviour among children.

Heart rate variability and working memory among children with typical development

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Background. Heart rate variability (HRV) has been hypothesized to be related to working memory function. It is rarely to associate heart rate variability with daily report of working memory function among children. *Aim.* This study aims to examine the relationship between HRV and working memory among children with typical development. *Methods*. Seventeen aged 6-12 children with typical development were recruited for the current study. Different measures of heart rate variability were recorded during the resting period. Parents of the subjects were asked to rate their children's performance on their children's working memory function in daily life on the working memory scale (higher score on the scale reflects more difficulties of working memory during daily life). Pearson's *r* correlation was used to examine the relationship between HRV and the scores on the working memory scale. *Results.* Significant positive relationship was found between the scores on the working memory scale and RMSSD of the heart rate variability (r = .517, p <.05). No significant relationship was found on SDNN with the scores on the working memory scale. *Conclusion.* Higher level of working memory difficulties was found to be associated with the RMSSD in the present study. This finding suggested the possibility that suboptimal level of parasympathetic influence may interfere with the working memory function in daily life among children.

Different effects of lipophilic and hydrophilic statin on muscle sympathetic nerve activity in heart failure with preserved ejection fraction

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Background: It has been proposed that increased sympathetic nerve play a role in pathogenesis of HFpEF. Recent study suggests that usage of statin is associated with the improvement in mortality in HFpEF. Accumulating evidence also revealed that lipophilic statins reduced sympathetic nerve activity by crossing the blood-brain barrier in patients with HT and HF with reduced ejection fraction. However, it remains unclear whether lipophilic and hydrophilic statins exert the different effect on sympathetic nerve activity. Aim: In this study, we evaluated the effect of atorvastatin 'lipophilic statin' or rosuvastatin 'hydrophilic statin' on muscle sympathetic nerve activity (MSNA) in HFpEF patients. Methods: This study was designed as a prospective randomized open-label crossover trial. Thirteen HFpEF (left ventricular ejection fraction (LVEF) >45%, E/E'>10) patients with dyslipidemia, participated in this study. A randomization schedule was used to assign subjects to either the atorvastatin (10 mg) or rosuvastatin group (2.5 mg) with each drug administered as 1 tablet daily for 8 weeks. After the first 8 weeks, the subjects underwent 1-week washout period, followed by taking the alternative drug daily for another 8 weeks. We directly recorded MSNA with using microneurography. Results: MSNA was significantly reduced in atorvastatin compared to baseline (38.4±12.0 vs. 49.0±12.2 bursts per minute, $P < 0.05$). However, MSNA did not change between rosuvastatin and baseline (41.2±8.4 vs. 49.0±12.2 bursts per minute, $P = 0.15$). Conclusion: Atorvastatin 'lipophilic statin' exerted a more beneficial effect on sympathetic nerve activity in HFpEF patients compared with rosuvastatin 'hydrophilic statin'.

Long-term effects of surgical treatment on baroreflex sensitivity in patients with obstructive sleep apnea

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Background: Depressed baroreflex sensitivity (BRS) have been reported in patients with obstructive sleep apnea (OSA). Several previous reports have shown improvement of BRS short-term after treatment, either by continuous positive airway pressure (CPAP) or by surgery. The information for the chronic treatment effects on BRS is lacking. ***Aim:*** This study aims to study the long-term effects of surgical treatment on BRS in patients with OSA. ***Methods:*** Patients with OSA who failed CPAP therapy and planned to undergo upper airway surgery were enrolled. Polysomnography (PSG) and cardiovascular autonomic tests were evaluated upon enrollment, and six and 18 months after surgery. For comparison, subjects without OSA were recruited as controls and evaluated in terms of PSG and cardiovascular autonomic tests. ***Results:*** Forty-four OSA patients (39 men, 5 women) and 20 control subjects (14 men, 6 women) were enrolled. The BRS before surgery in patient group was significantly decreased compared to the controls whereas other cardiovascular autonomic parameters were similar between groups. Then the BRS significantly increased 6 months and 18 months after surgery and it became similar to the control group in 18 months after surgery. ***Conclusions*:** This study shows the chronic effects of surgical treatment on BRS in OSA patients. The BRS impairment is reversible and these patients have potential for total recovery of baroreflex function after treatment.

Skin coldness and painful cold: the common symptom in patients with clinically suspected small fiber neuropathy in Korea

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Background: Small fiber neuropathy (SFN) is a disorder of thinly myelinated Aδ and unmyelinated C fibers and characterized by neuropathic pain and autonomic symptoms. In this study, we investigated the clinical characteristics of clinically suspected SFN patients with diagnostic tools of QST and QSART. **Methods:** We prospectively enrolled adult patients with clinically suspected SFN in two tertiary care hospitals between March 2016 and March 2017. Patients underwent blood tests for the etiology work-up, QST(cold detection threshold, CDT) and QSART. The SFN-Symptom Inventory Questionnaire and the Neuropathic Pain Symptom Inventory were also assessed, in addition to the presence and severity of skin coldness. **Results:** Among patients with clinically suspected SFN (N=79; F:M=43:36; mean[SD] age, 55[13]), 62% of patients (N = 49) were idiopathic. The common symptoms were skin coldness (88.3%), dry eye (62.3%), sensitive skin (57.1%) and burning feet (55.8%). The painful cold (mean VAS, 5.4), tingling (4.1), evoked pain by cold (3.1), electric shock like pain (2.9), and burning pain (2.8) were the pain symptoms in order of severity. The CDT and QSART were abnormal in 67.6% (N=46/68) and 65.2% (N=43/66) patients, respectively and only 6.3% (N=5/79) of patients were double negative in CDT and QSART. Abnormal CDT was associated with the severities of electric shock-like pain (p=0.034) and provoked pain by pressure (p=0.029), although there was no pain characteristics correlated with QSART abnormality. **Conclusions:** Skin coldness and painful cold were common and severe neuropathic pain symptoms among patients with clinically suspected SFN in Korea.

NOS-immunoreactive inhibitory neurons are also Netrin-1-immunoreactive neurons in mature myenteric plexus

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Background: Netrin-1 serves as an axonal guidance cue that is required for the normal development of the enteric nervous system (ENS). It is a diffusible ligand that mediates axonal outgrowth and neuronal migration via engaging its receptor called deleted in colorectal cancer (DCC). DCC-expressing neural crest cells have been found to migrate towards Netrin-1, and form the enteric nerve plexuses. Subsequent *in vitro* study indicated that embryonic enteric neurons synthesise Netrin-1 [1]. However, Netrin-1-expressing neurons are yet to be characterised in the mature ENS. **Aim:** The aim of this study was to determine the characterisation of Netrin-1-positive neurons in the mature myenteric plexus. **Methods:** Colon tissues were collected from young adult Balb/c mice aged 8-10 weeks. The wholemount preparations of the myenteric plexus were labelled for immunofluorescence, and the images were prepared using confocal microscopy and analysed using MatLab. **Results:** The immunoreactivity (IR) of Netrin-1 and DCC was observed in the myenteric plexus. Nearly 45% of neurons within ganglia indicated a strong Netrin-1-IR on their cytoplasm. Approximately 30% of neurons per ganglion exhibited nitric oxide synthase (NOS)-IR, and all those inhibitory NOS-positive neurons were co-lablled with a strong Netrin-1-IR. Furthermore, most choline acetyltransferase (ChAT)-positive excitatory neurons were also Netrin-1-positive. However, approximately 30% of neurons in ganglia were distinctively positive for either ChAT or Netrin-1. **Conclusions:** All the NOS-positive inhibitory myenteric neurons were also found to be Netrin-1-positive. This data suggests that Netrin-1 may be involved in characterising functional phenotype of neurons.

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Electrogastrography in healthy elderly persons

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Background and Objective: Electrogasrography can detect gastric pacemaker rhythm, so-called “slow wave”. The aim of this study is to construct reference ranges of electrogastrogram (EGG) parameters in healthy elderly persons. **Method**: EGG was recorded in the supine position for 30 min before and 50 min after the meal ingestion (400 kcal) in 20 healthy elderly persons (12 female, age 72 ± 5.3 years). Three 20 min-segments, including preprandial, early-postprandial and late-postprandial phases, were selected for EGG analysis. Dominant frequency (DF), the percentage of the low, normal and high frequency components (LFR%, NFR% and HFR%) and instability coefficient of DF (ICDF) were calculated for each EGG segment. **Results**: EGG parameters in preprandial, early-postprandial and late-postprandial phases are shown as follows. DF; 3.1 ± 0.27 /min, 2.7 ± 0.41 /min and 3.1 ± 0.36 /min ($p < 0.0067$), %LFR; 11 ± 5.4%, 17 ± 12% and 16 ± 9.0%, %NFR; 77 ± 10%, 70 ± 16% and 71 ± 12%, %HFR; 12 ± 7.9%, 14 ± 7.5% and 13 ± 6.7%, ICDF; 4.4 ± 5.5%, 19 ± 8.8% and 13 ± 11% ($p < 0.0000081$). In correlational analysis, preprandial %NFR was positively correlated with age ($p < 0.021$), and preprandial %HFR and early-postprandial ICDF were negatively correlated with age ($p < 0.045$, $p < 0.0049$). **Discussion**: ICDF, an index of slow wave variability, appeared to decrease with age, as it's well known that heart rate variability decreases with age. There is a possibility that ICDF reflects gastric parasympathetic activity.

Age-related Changes in Coherent Activity of Low-Band Frequency Fluctuations between Pulse Waves from face Laser Speckle Flowgraphy and Autonomic functions; Heart Rate, Systolic or Diastolic Pressure Variabilities during the Resting-State

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[Background] Laser Speckle FlowGraphy (LSFG) is able to monitor non-invasive, accurately and continuously blood flow of whole face skin area and to extract as a form of pulse-waves (PWs) containing low-frequency fluctuations (LFFs). **[Purpose]** To reveal age-related changes in the LFFs between PW and autonomic function; Heart rate, Systolic and Diastolic variabilities (HRV, SBPV and DBPV). **[Methods]** We evaluated healthy Japanese of 60 women (20s, 30s, 40s, 50s, 60s and 70s) during the resting-state. They were grouped into Young group (YG: 20s, 30s, 40s) and Elderly group (EG: 50s, 60s, 70s). The surface electrocardiography (ECG), instantaneous lung volume (ILV) by the inductance method, and beat-by-beat tonometric blood pressure were monitored simultaneously by a 16-bit A/D converter (500 Hz sampling) for 6 minutes, while the subject's face image were continuously recording by LSFG (30 f/sec). **[Results]** 1) Mean power spectrum of PWV was larger in young group. 2) There was a strong negative correlation between age and transfer HF-gain (respiration vs HRV). 3) Squared mean coherence between LF-DBP or LF-HRV and LF -PWV showed very high value (> 0.7). 4) Mental arithmetic (MA) task markedly enhanced a spectral peak at 0.1 Hz in the range of LFFs. The results demonstrate the LBF of PWV closely link with the autonomic regulation, especially sympathetic nerve activity in the resting-stage. **[Conclusions]** PWV extracted from LSFG in the LFF closely dependent on aging and related to DBP variability, suggesting the SNA.

Refereneces

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Netrin-1 might determine functional phenotype of neurons in the adult gastrointestinal tract

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Background: Netrin-1 serves as an axonal guidance cue that is required for the normal development of the enteric nervous system. It is a diffusible ligand that mediates axonal outgrowth and neuronal migration via engaging its receptor called deleted in colorectal cancer (DCC). DCC-expressing neural crest cells have been found to migrate towards Netrin-1, and form the enteric nerve plexuses. Subsequent *in vitro* study indicated that embryonic enteric neurons synthesise Netrin-1 [1]. However, Netrin-1-expressing neurons are yet to be characterised in the mature enteric nervous system. **Aim:** The aim of this study was to characterise Netrin-1-positive neurons in the mature myenteric plexus. **Methods:** Colon tissues were collected from young adult Balb/c mice aged 8-10 weeks. The wholemount preparations of the myenteric plexus were labelled for immunofluorescence, and the images were prepared using confocal microscopy and analysed using MatLab. **Results:** The immunoreactivity (IR) of Netrin-1 and DCC was observed in the myenteric plexus. Nearly 45% of neurons within ganglia indicated a strong Netrin-1-IR on their cytoplasm. Approximately 30% of neurons per ganglion exhibited neuronal nitric oxide synthase (nNOS)-IR, and all those neurons demonstrated strong Netrin-1-IR. Furthermore, most choline acetyltransferase (ChAT)-positive neurons were also Netrin-1-positive. However, approximately 30% of neurons in ganglia were distinctly positive for either ChAT or Netrin-1. **Conclusions:** All nNOS-positive neurons were also found to be Netrin-1-positive. This data suggests that Netrin-1 may be involved in determining functional phenotype of neurons in the adult gut.

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The difference of the autonomic nerve (AN) balance between the heart rate variability (HRV) and papillography

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AN balance in HRV indices was not always parallel with AN balance by papillography. The aim of this study was to compare the correlation of both AN balances. AN balance of female out patients who complains of the cold at the lower part and hot at the upper part of the body (A group, n=10), and of the cold at internal and hot on surface of the body (B group, n=10) were examined using the ratio of low and high frequency (LF/HF ratio) of the heart rate variability at rest by equipment detects real time autonomic nerve changes, and using the ratio of parameter in pupillary dilatation time and pupillary constriction time (t5/t3 ratio) by the electronic papillography device of the right eye. Peason's correlation coefficient test was used for an analysis. AN balance between LF/HF ratio and t5/t3 ratio showed significant positive correlation (R=0.82 and P=0.00312) in A group, and significant negative correlation (R= - 0.87 and P=0.00096) in B group. Though both high value in LF/HF ratio and low value in t5/t3 ratio indicate the sympathetic nerve predominance, these results suggested that the balance of peripheral and central AN was competed each other in A group, and the balance of peripheral and central AN was synchronized in B group. These differences may be associated with excitement of a sympathetic nervous system by lumbago in A group. AN balance by HRV and electronic papillograph was likely to different in some situations or condition of the disease.

Mesenchymal stem cell treatment for enteric neuropathy associated with colitis

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Mesenchymal stem cells (MSCs) derived from bone marrow and other tissues have strong anti-inflammatory and neuroprotective properties. Aim of this study was to test therapeutic potential of MSCs to alleviate enteric neuropathy and gastrointestinal dysfunction associated with acute and chronic intestinal inflammation. Neuroprotective effects of MSCs were tested in acute trinitrobenzene sulfonate (TNBS)-induced colitis and in *Winnie* mice with spontaneous chronic colitis resulting from a mutation in the *Muc2* mucin gene. MSC treatment significantly reduced morphological damage of the colon, infiltration of immune cells to the level of myenteric ganglia, damage to neuronal processes projecting to mucosa and loss of myenteric neurons observed in the inflamed colon. Treatment with MSCs restored changes in gastrointestinal motility in both acute and chronic models of colitis. *Winnie* mice receiving multiple MSC treatments demonstrated significant long-term inhibtion of colitis confirmed by a non-invasive highly sensitive biomarker for intestinal inflammation. Administration of MSCs by enema and intravenous, but not intraperitoneal injection, effectively reduced inflammation and increased the density of nerve fibers in the colon of *Winnie* mice. These results correlated with alleviation of clinical symptoms of colitis: harder stools, no rectal bleeding, weight gain observed in *Winnie* mice after MSC treatment. This is the first study investigating therapeutic potential of MSCs in the animal model of spontaneous chronic colitis. Our studies demonstrated that neuroprotective efficacy of MSC-based therapies can be exerted independently to their anti-inflammatory effects. We identified numerous factors with strong neuroprotective activity released by MSCs used in our studies.

Food Restriction Increases Angiotensin II AT1 Receptors in the Brain of Female Fisher Rats

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Food restriction (FR) can trigger cardiovascular dysfunctions such as ventricular hypertrophy, hypotension and bradycardia. FR rats showed increased activity of endothelial α1 adrenergic receptors and increased peripheral AT_1 receptor(R) responsiveness. The brain angiotensin (Ang) system regulates the sympathetic nervous system (SNS). Therefore, the goal of this study was to evaluate the effect of FR on the expression and function of AT_1R in brain regions that regulate the SNS. Fischer female rats, weighing 200g, had reduced the food intake in 60% for 14 days. At day 7, a guide cannula was placed the lateral ventricle (LV) and day 14, the femoral artery was catheterized to record mean arterial pressure (MAP) and heart rate (HR)Eh. Another group had the brains frozen for receptor autoradiography for AT_1R with ^{125}I-Sar^{1}Ile^{8}AngII. The FR reduced body weight ~12% (C:201.6g±1.8, n=2 vs. FR:176.1g±2.1, n=26; $p<0.05$). The pressor response to intracerebroventricular (icv) injection of AngII was reduced in FR rats (C:D18.9mmHg ± 1 vs. FR:D11.4mmHg±2; n=8, p=0.0156) without change the HR. Losartan icv, lowered MAP more in FR rats (C:D-0.03mmHg±1, n=7 vs. FR: D -4.5mmHg±1, n=11; p=0.0280). FR increased AT_1R in the PVN (C:101.6fmol/g±16, n=6 vs. FR:139.5fmol/g±18 n=6; p=0.0025) and in the rostral ventrolateral medulla (16.8fmol/g±13 vs. 27.2fmol/g±8; p=0.0452). There were no differences in AT_1R binding in the amygdala, subfornical organ, vascular organ of lamina terminalis, median preoptic, solitary tract nucleus and caudal ventrolateral medulla. These results suggest that increased sympathetic activity in FR rats may result from changes in AT_1R activity in the PVN and RVLM.

Sympathetic regulation of ovarian functions under chronic estradiol treatment in rats

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Activation of the sympathetic nerve to the ovary (superior ovarian nerve: SON) decreases ovarian blood flow and estradiol secretion in rats in the estrous phase. The present study examined the effects of long-term estradiol treatment on the sympathetic regulation of both ovarian blood flow and estradiol secretion. Non-pregnant Wistar rats received sustained subcutaneous estradiol (5 μg/day) or saline for 4 weeks. Chronic estradiol treatment did not affect ovarian blood flow at rest, while changed the basal ovarian estradiol secretion rate, i.e., narrow ranges (4–34 pg/min) in estradiol-treated rats, versus wide ranges (3–192 pg/min) in saline-treated rats of different estrous cycles. SON was electrically stimulated at different frequencies (2, 5 and 20 Hz). Ovarian blood flow was decreased by SON stimulation in a stimulus frequency-dependent manner in both saline- and estradiol-treated rats, but the threshold was shifted from 2 Hz to 5 Hz after chronic estradiol treatment. Ovarian estradiol secretion rate was not significantly changed by SON stimulation at any frequency in saline-treated rats, while it was markedly decreased by SON stimulation at high frequencies (5 and 20 Hz) in estradiol-treated rats. In conclusion, chronic estradiol treatment augments sympathetic inhibition of ovarian estradiol secretion perhaps by inhibiting the hypothalamic–pituitary–ovarian axis.

Demonstration of blood pressure dysregulation controversy in supine hypertension with neurogenic orthostatic hypotension syndrome

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Background: Cardiovascular (CV) homoeostasis disruption caused by CV dysautonomia involves vagal as well as sympathetic control dysfunction and supine hypertension with neurogenic orthostatic hypotension (SH-OH) syndrome can occur. Aim: Presentation of therapeutic dilemma in the management of SH-OH syndrome encompassing the opposite hemodynamic situations. Methods: Report of case: 75 year old white man, with history of intestinal polyposis, transient loss of consciousness and presyncope; hypotension with intermittent confusions, progressive fatigue, inefficiency, constipation and emictory problems, was treated with timolol and brinzolamide due to glaucoma. Mild rigidity and bradykinesia on neurological examination. BP 115/75 mm Hg, HR 56/min, Physiological finding on carotid arteries, lungs and heart auscultation, coronarography and myocardial SPECT. Echocardiography:septal hypertrophy, LVEF 60 %, diastolic dysfunction. Brain MR: atrophy, abnormal signal in basal ganglia. Skin biopsy reduction of fine nerve fibers. Autonomic testing: HUTT 45 minutes without syncope: mean HR 64/min, mean BP 90/ 64 mm Hg. Deep breathing test: I-E 1.96 (beats/min), I/E 1.04, Orthostatic test: RR max/RR min 1.01, 30:15 0.95, BI (%) 0.88, 5 minute supine HR variability (ms2): Power LF 8.55, Power HF 71.24, Total Power 117.46. Standing baroreflex mean slope 3.43. Cardiac scintigraphy I-123-MIBG: low uptake in all left ventricle is indicative of adrenergic innervation disturbance. Conclusions: Advanced autonomic neuropathy based on neurodegenerative etiology - primary dysautonomia. Individual approach is necessary because of no guidelines are available for SH-OH syndrome management. Our current therapeutic target is focused on OH and therefore fludrocortison administration was started in order to improve patient´s quality of life.

The impact of diurnal emotions on autonomic activation during sleep

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Diurnal emotional experiences seem to affect several characteristics of sleep course. In particular, electrodermal activity, a sympathetic robust indicator of emotional arousal, differs depending on the sleep stage. The present research aimed to identify the specific effects of pre-sleep emotional states on the sympathetic activation of the subsequent sleep period. Twelve healthy volunteers participated in the experiment and each one slept a total of 9 nights at the laboratory, divided into 3 sessions, one per week. Each session was organized over three nights. A reference night, allowing baseline pre-sleep and sleep recordings, preceded an experimental night before which participants watched a negative, neutral, or positive movie. The third and last night was devoted to analyzing the potential recovery or persistence of emotional effects induced before the experimental night. Standard polysomnography and electrodermal activity were recorded during all the nights. Firstly, the valence of the pre-sleep movie impacted the sympathetic activation during Non-Rapid Eye Movement stage 3 sleep, which increased after negative induction and decreased after positive induction. Secondly, we also found that experimental pre-sleep emotional induction increased the Rapid Eye Movement sleep rate following both negative and positive movies. In conclusion, pre-sleep controlled emotional states impacted the sympathetic activity and the Rapid Eye Movement sleep rate during the subsequent sleep period. The outcomes of this study offer interesting perspectives to the role of autonomic activation for the emotion processing during the sleep and its potential impact on diurnal life regulation of emotions.

Autonomic failure following solid organ transplantation

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Background: Autonomic function has been variably reported to stabilize or improve following solid organ transplantation when performed for diabetes mellitus or end-stage liver disease. We have identified a form of autonomic failure that develops in the days to weeks following solid organ transplantation, that ultimately resolves after several months. **Aims:** To describe the features of post-transplant autonomic failure. **Methods:** Clinical features, laboratory findings, and results of autonomic testing were reviewed in patients who developed post-transplant autonomic failure. **Results:** We identified 8 patients who developed severe and refractory autonomic failure that required multiple medications to treat orthostatic hypotension. Autonomic failure in these patients manifested with symptoms of orthostatic intolerance and syncope along with gastrointestinal symptoms that began concurrently. Autonomic failure in these patients resulted in prolonged hospitalizations or recurrent hospitalizations primarily to manage orthostatic hypotension. Autonomic symptoms were minimal or not present prior to transplant in 7 patients. Autonomic findings in those tested confirmed an autonomic neuropathy, and autoantibodies associated with autonomic neuropathy were demonstrated in 3 of 4 patients tested (N-type, and acetylcholine ganglionic antibodies). Autonomic failure in these patients resolved completely in all patients. **Conclusion:** Post-transplant autonomic failure results in severe and refractory, but ultimately self-limited autonomic signs and symptoms. We propose that this condition results from an autoimmune autonomic neuropathy.

The effect of aerobic capacity on spontaneous baroreflex sensitivity in African American women

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African American women (AAW) experience disproportionately higher levels of cardiovascular disease (CVD) versus Caucasian women (CW). Decreased baroreflex sensitivity (BRS) is associated with negative cardiovascular health and AAW have been found to have significantly lower BRS versus CW. Increased aerobic capacity (AC) is associated with increased BRS and improved cardiovascular health in the general population. Despite having lower BRS and being at greater risk for CVD along with the understanding that increased AC is associated with improved BRS, there is a paucity of research examining how AC would affect BRS in AAW. Therefore, the study aim was to determine the effect of AC on BRS in AAW and CW. Method: Fifteen (AAW-7; CW-8) healthy, age, height and weight matched college aged women were examined for AC and BRS. Aerobic capacity was determined by VO_2 max, while BRS was determined by the alpha index. Results: Linear regression showed that AC explained 30% of the variation in BRS in AAW and 3% in CW, with the slope of the relationship between AC and BRS in AAW= 0.45 and that of CW= -0.24. ANOVA demonstrated that the models were not significant - AAW ($P = 0.06$) and CW ($P = 0.37$). Conclusion: Preliminary data suggest that AC is not a significant predictor of BRS in AAW or CW. However, based on $P = 0.06$ for the AAW group there seems to be a trend towards AC being a predictor of BRS in AAW.