CHRONIC PAIN AND BRAIN CIRCULATION WELFARE

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Chronic pain is pain that lasted 3 months or longer; pain that persists > normal course of time associated with or without a particular type of injury.

Recommendation for Wait-times (IASP, 2009):

- **Most urgent (1 week):** acute painful severe condition with risk of deterioration or chronicity (new CRPS) or pain related to cancer or terminal or end stage illness (acute herpes zoster).
- **Urgent or semi-urgent (1 month):** severe undiagnosed or progressive pain and risk of increasing functional impairment generally 6 months duration or less (back pain not resolving,neuropathic pain, post surgical/post traumatic pain)
- **Routine or regular (4 months):** persistent long-term pain without significant progression.

Chronic pain divided by:

1. Nociceptive (caused by activation of nociceptors):

A. Superficial pain

→Initiated by activation of nociceptors

→Dull, aching, poorly-localized pain

B. Deep

B.1. Deep somatic

B.2. Deep visceral

→Originates in viscera (organs); “referred” pain

→Maybe well-localized/ difficult to locate

2. Neuropathic (caused by damage to or malfunction of the nervous system:

A. Peripheral neuropathic pain(originating in the peripheral nervous system);

→Describe as burning, tingling, electrical, stabbing, pins or needles

B. Central (originating in brain or spinal chord).

Ongoing or long-term pain: irritable, short-tempered, impatient, and with good reason. Constant pain raises the focus threshold for basic functioning→reduced ability to find solutions; unrelated problems: depression, anxiety, lack of sleep and trouble focussing.

Chronic pain:Portion of the brain→always active: the region associated with mood & attention. Brain scans: chronic back pain/ complex regional pain syndrome: smaller hippocampus.(Science Daily). Some recent studies : chronic pain→affect a person's brain chemistry & change the wiring of the nervous system.

Cells in the spinal cord and brain of a person with chronic pain, especially in the section of the brain that processes emotion, deteriorate more quickly than normal, exacerbating many of the depression-like symptoms. This regulator becomes smaller from reacting to the pain, making falling asleep more difficult for people with chronic pain.

Brain plays a critical role in chronic pain (National Institute of Neurological Disorders and Strokes). Volume of grey matter describes the area of the brain where the central bodies and branched antennae, or dendrites, of nerve cells reside.

Brain activity could be used to predict whether a subject recovered or experienced persistent pain. Neural mechanisms mediating the transition from acute to chronic pain remain largely unknown.(Courtessy of Apkarian lab, Northwestern Univerisity Feinberg School of Medicine).

The nucleus accumbens & medial prefrontal cortex. White matter structure connecting these brains regions is different between the subjects who recovered and those who had persistent pain. Certain brain networks are involved with chronic pain. Brain structural differences, most likely existing before the back pain-inciting event and independent of the back pain, predispose subjects to pain. (NIH/ National Institute of Neurological Disorders and Stroke; Mansour AR, Baliki MN, Huang L, Torbey S, Hermann KM, Schnitzer JT, Apkarian AV. Brain white matter structural properties predict transition to chronic pain. PAIN, 2013; 154 (10): 2160 DOI: 10.1016/j.pain.2013.06.044

Chronic Pain Resulting From Medical or Generalised Disease processes

Chronic Pain→uncomfortable,unpleasant→may arise from general medical or disease conditions and/or conditions which affect a particular region or site.

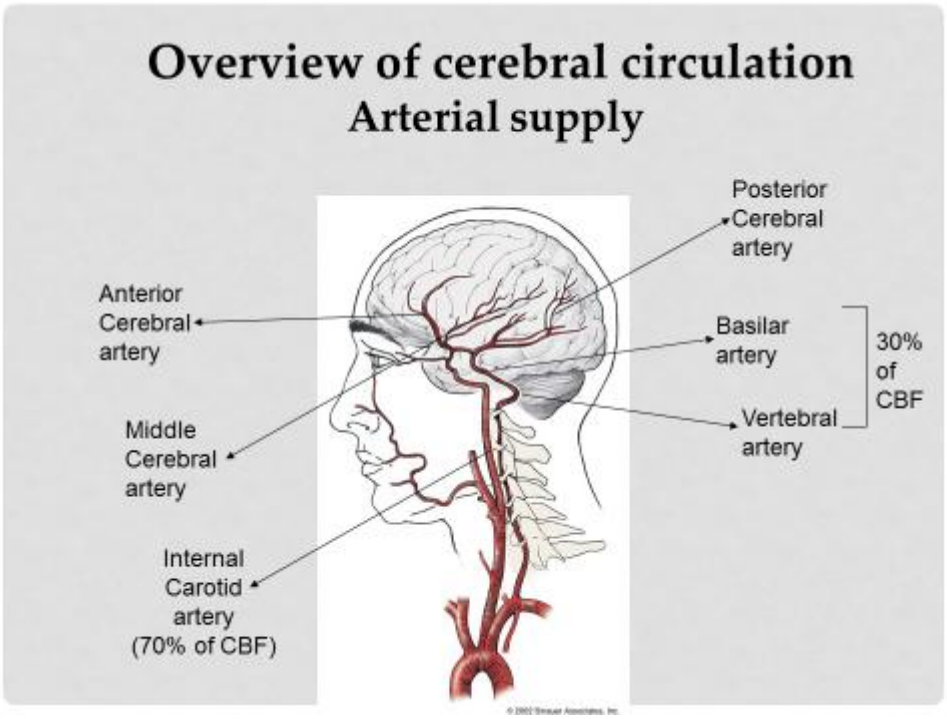
Regional pain: Abdominal,Gynaecological, Obstetric, Urological, Cardiovascular

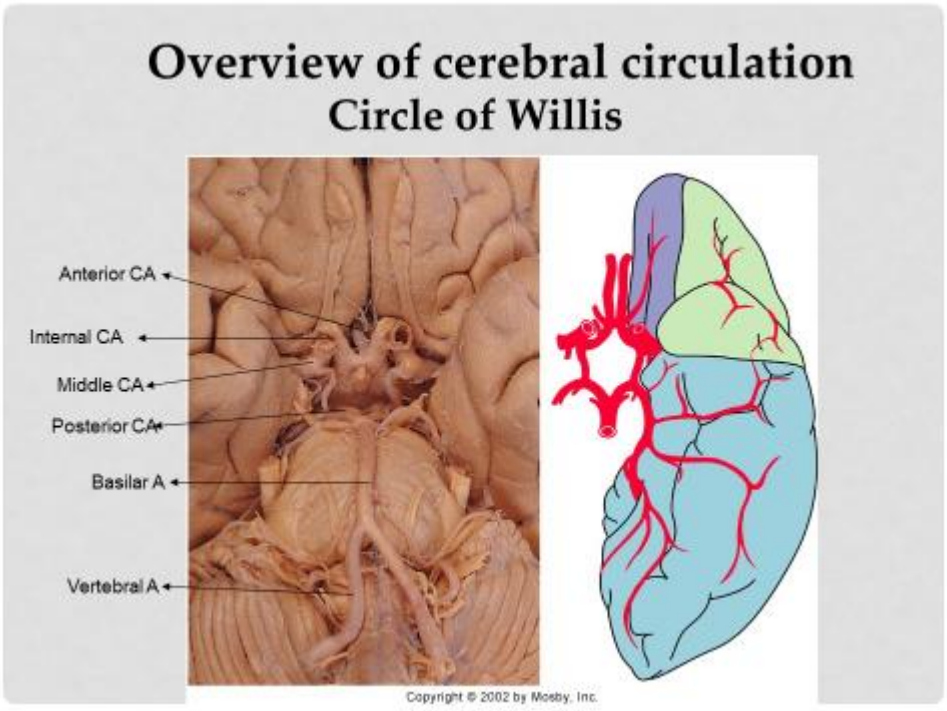
Disease processes : Rheumatological, Endocrine, Infectious [Source: BearingPoint, Atos Healthcare & DSP Copyright EBM Chronic Pain Disorders & Fibromyalgia Warrell et al (2004); BMJ Best Practice (2009)]

cerebral circulation

Cerebral metabolism, Regional cerebral blood flow requirements, Regulation of cerebral blood flow

Cellular mechanism of cerebral vasomotor, Nitric oxyde,Vasoactive peptides, Na & K Channels, Endothelin, Prostaglandin, Cerebral microcirculation, Hemodynamic factor, rheologic factors, Metabolic &chemical influences: CO_2, O_2, Temperature, Neurogenic influence,Anatomic consideration

- 
Overview of cerebral circulation
Arterial supply
Posterior Cerebral artery
Anterior Cerebral artery
Basilar artery
30% of CBF
Vertebral artery
Middle Cerebral artery
Internal Carotid artery (70% of CBF)

- 
Overview of cerebral circulation
Circle of Willis
Anterior CA
Internal CA
Middle CA
Posterior CA
Basilar A
Vertebral A
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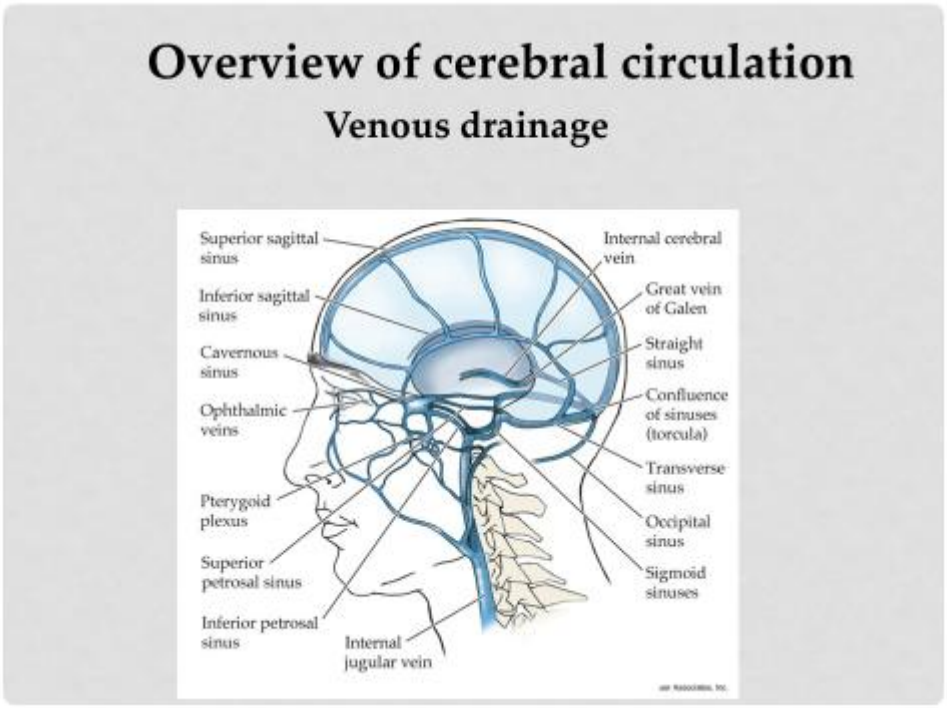
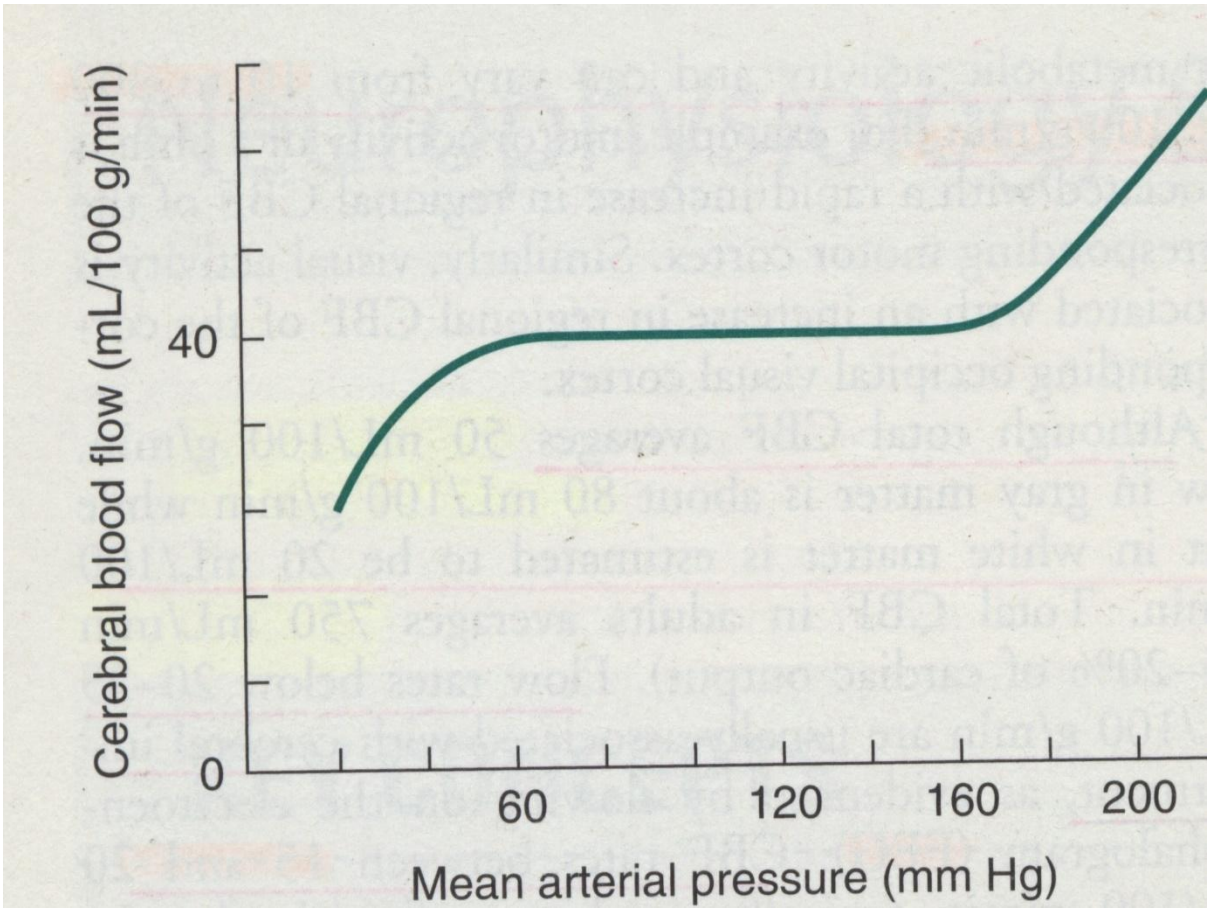


Cerebral

Physiology

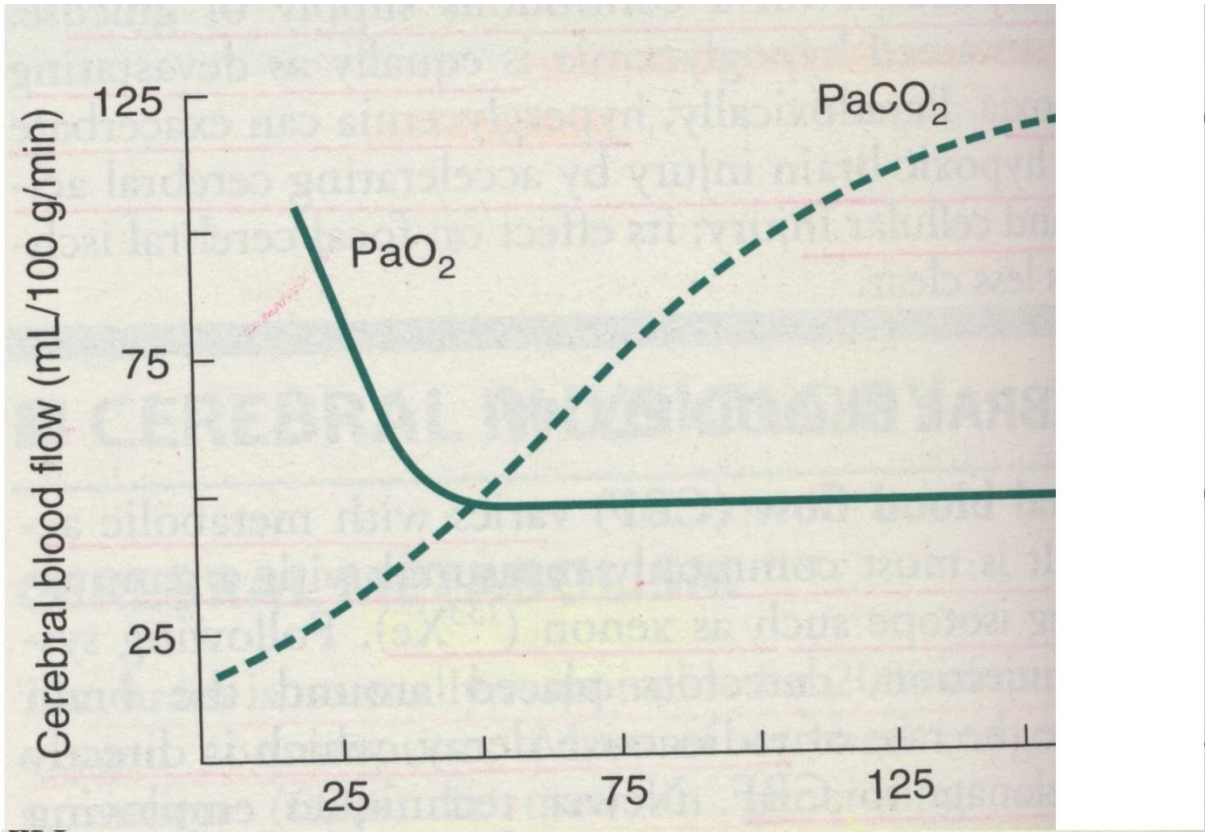
CMR O_2 3.5mL O_2 /100 g/min (arrousal, seizures, mental, anesthetics, temperature); CPP; CBF; temperature; $PaCO_2$, PaO_2; Autoregulation; CPP; Neurogenic reaction (Pain-severe/chronic); Viscosity effects; CBV.

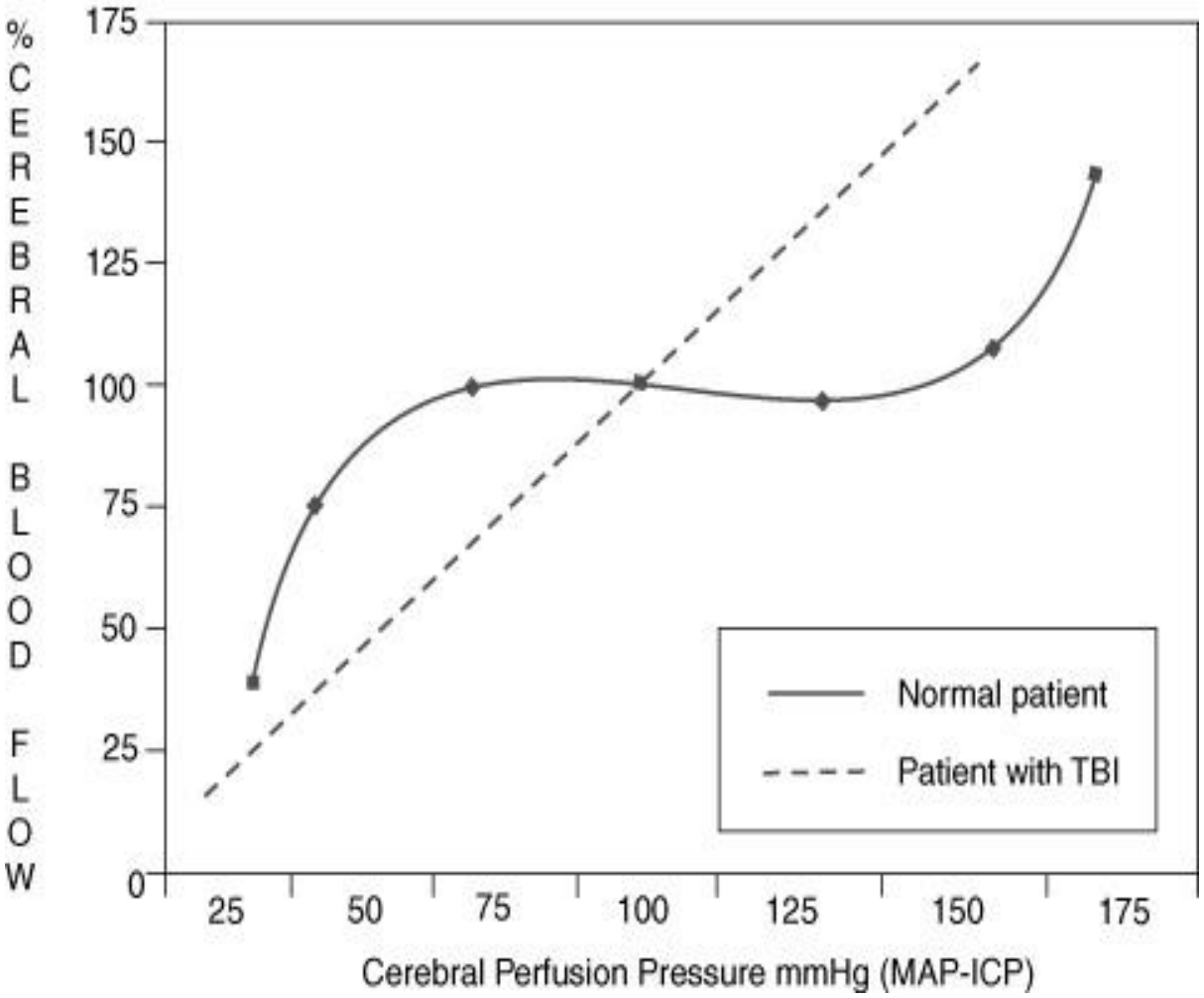
CBF determined by: chemical/metabolic ($CMRO_2$, $PaCO_2$, PaO_2, Vasoactive drugs. CPP = MAP - ICP

- 

Factors influencing CBF

- ***CHEMICAL/METABOLIC***
- ***MYOGENIC***
- ***RHEOLOGIC***
- ***NEUROLOGIC***


125
75
25
Cerebral blood flow (mL/100 g/min)
PaO_2
$PaCO_2$
25
75
125



CBF	
GLOBAL	45-55ml/100g/min
CORTICAL	75-80ml/100g/min
SUBCORTICAL	20ml/100g/min
$CMRO_2$	3-3.5ml/100g/min
CVR	2.1mmHg/100ml/min/ml
Cerebral venous Po_2	32-44mmhg
Cerebral venous So_2	55%-70%
ICP(supine)	8-12mm Hg

Age-related white matter changes (ARWMC) on brain MRI have been associated with cognitive, motor, mood and urinary disturbances. These factors are known to contribute to disability in elderly people, but the impact of ARWMC and of their progression on the transition to disability is not determined. The LADIS (Leukoaraiosis and Disability in the Elderly) study aims at assessing the role of ARWMC as an independent predictor of the transition to disability in initially nondisabled elderly (65–84 years). Subjects who are not impaired or impaired on only 1 item of the Instrumental Activity of Daily Living (IADL) scale, presenting with different grades of ARWMC severity, were enrolled. Eleven European centers are involved. All the patients were assessed at baseline using an extensive set of clinical and functional tests including global functioning, cognitive, motor, psychiatric and quality of life measures. MRI studies were performed at baseline and will be repeated at the end of the follow-up period to evaluate changes of ARWMC and other lesions. ARWMC were categorized into mild, moderate or severe using the scale of Fazekas et al. For each ARWMC severity class, the primary study outcome is the transition to disability defined as an impairment on 2 or more IADL scale items. Secondary outcomes are the occurrence of dementia, depression, vascular events or death. Six-hundred and thirty-nine subjects (mean age 74.13 ± 5.0 years, M/F: 288/351) were enrolled in a hospital-based setting and are being followed up for up to 3 years. The large and comprehensive set of measures in LADIS enables a comprehensive description of their functional and clinical features to be examined in relation to different morphological patterns and severity of ARWMC. The longitudinal design will give insight into the possible role of ARWMC and their progression as an independent contributor to disability in the elderly, eventually helping to develop preventive strategies to reduce the burden of disability in late life. The study results may also help to standardize, on an international basis, tools and criteria to identify early stages of disability.

It is a well-known phenomenon that cerebral blood flow is coupled to neural activation induced by non-noxious somatosensory stimulation. However, basic questions related to pain-induced cerebral blood flow changes remain unanswered. In the present study, the sciatic nerve of anesthetized rats was subjected to electric stimulation with noxious and non-noxious parameters. Changes in local cerebral

blood flow and neuronal activity were determined simultaneously in the sensory cortex and in the thalamus by laser-Doppler flowmetry and c-*fos* immunohistochemistry, respectively. The role of different vasoregulatory mechanisms and the pain-induced increase in mean arterial blood pressure (MABP) were examined with specific blocking agents and by means of rapid intra-arterial transfusion. Noxious stimulation resulted in significant enhancement of neuronal activity both in the thalamus and in the somatosensory cortex indicated by marked c-*fos* expression in these areas. Cortical and thalamic blood flow (cBF and tBF) increased by 47±4 and 44±3% during the stimulation while the MABP elevated by 35±2%. Similar changes in MABP induced by intra-arterial transfusion had no effect on tBF, while cBF increased only by 18±5%. Blockade of ATP sensitive potassium channels (K^+_{ATP}) and sympathetic β-receptors significantly attenuated the pain-induced blood flow increases in both investigated areas, while inhibition of nitric oxide synthase was effective only in the thalamus. The blockade of the sympathetic α-receptors, opiate receptors, and the cyclooxygenase enzyme had no effect on the pain-induced cerebral blood flow elevations. These findings demonstrate that during noxious stimulation, cerebral blood flow is adjusted to the increased neural activity by the interaction of vasoconstrictor autoregulatory and specific vasodilator mechanisms, involving the activation of sympathetic β-receptors, K^+_{ATP}-channels and the release of nitric oxide.

This review provides a scientific comment on the welfare of ruminants slaughtered by ventral-neck incision without stunning. Evidence is derived from studies of calves, sheep and goats. Reference is also made to findings in other mammals including humans.

Pain is an inherently subjective experience and only indirect indices are available in animals. Neurophysiological tools are widely used in humans to assess pain and have demonstrated that electroencephalographic (EEG) variables correlate well with subjective evaluations of pain. These neurophysiological tools have also been applied in animal studies.

In humans pain is associated with major cutting injuries and it is widely accepted that farm animals also experience pain due to such injuries. Overwhelming international scientific opinion has long been that slaughter by neck incision of

conscious animals causes pain. A series of studies in calves demonstrated that slaughter by ventral-neck incision is likely to be perceived as painful. It is proposed that, as in cattle, non-stunned sheep and goats would experience pain in a similar manner.

The precise assessment of the point after slaughter at which non-stunned animals become insensible remains a major methodological challenge. In sheep it is at least 2–8 seconds, but may be 8–20 seconds in duration. In cattle the mean duration is similar, but can commonly be extended to longer than 60 seconds with occasional instances of even greater durations. Taken together, these findings indicate that because the slaughter of cattle, sheep and goats by ventral-neck incision without prior stunning is likely to cause pain, this poses a risk to animal welfare.

The chronic constriction injury model is a rat model of neuropathic pain based on a unilateral loose ligation of the sciatic nerve. The aim of the present study was to test its sensitivity to various clinically validated and experimental drugs. Mechanical allodynia and thermal hyperalgesia developed within one week post-surgery and were reliably present for at least 7 weeks. Mechanical allodynia was strongly attenuated by morphine (minimal effective dose in brackets: 8 mg/kg, p.o.) and the cannabinoids Δ^9-tetrahydrocannabinol (3 mg/kg, p.o.) and (−)-*cis*-3-[2-hydroxy-4(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl) cyclohexanol (CP 55,940; 0.05 mg/kg, i.p.), and weakly/moderately attenuated by the anticonvulsants gabapentin (50 mg/kg, i.p.) and carbamazepine (32 mg/kg, i.p.), the muscle relaxant baclofen (3 mg/kg, i.p.), and the adenosine kinase inhibitor 4-amino-5-(3-bromophenyl)-7-(6-morpholino-pyridin-3-yl)pyrido[2,3-*d*]pyrimidine (ABT-702; 30 mg/kg, i.p.). Thermal hyperalgesia was strongly attenuated by morphine (16 mg/kg, p.o.), Δ^9-tetrahydrocannabinol (6 mg/kg, p.o.), CP 55,940 (0.025 mg/kg, i.p.), carbamazepine (32 mg/kg, i.p.) and the antidepressant amitriptyline (32 mg/kg, p.o.), and weakly/moderately attenuated by gabapentin (50 mg/kg, i.p.), the anti-inflammatory cyclooxygenase-2 inhibitor rofecoxib (30 mg/kg, i.p.) and the adenosine A_1 receptor positive allosteric modulator 2-amino-4,5,6,7-tetrahydrobenzo(*b*)thiophen-3-yl 4-chlorophenylmethanone (T62; 30 mg/kg, i.p.). Both symptoms were hardly or not affected by the nonselective *N*-methyl-D-aspartate receptor antagonists ketamine

and dizocilpine, and the *N*-methyl-D-aspartate receptor NR2B-selective antagonists ifenprodil and *R*-(*R**,*S**)-α-(4-hydroxyphenyl)-β-methyl-4-(phenyl-methyl)-1-piperidine propranol (Ro 25-6981). The finding that mechanical allodynia and/or thermal hyperalgesia are attenuated by various established compounds further supports the validity of the chronic constriction injury model for the study of neuropathic pain and its use for the identification of novel treatments.

The success of gene therapy for inherited neurodegenerative diseases such as metachromatic leukodystrophy (MLD) depends on the development of efficient gene delivery throughout the brain guarded by the blood–brain barrier and achieves distribution of the deficient enzyme throughout the brain. Direct injection of viral vector into the brain parenchyma is too invasive and may not be sufficient to treat the entire brain. As an alternative approach, we examined the feasibility of intrathecal (IT) injection of adeno-associated viral vector serotype 1 (AAV1).

Buprenorphine is a potent opioid analgesic clinically used to treat moderate to severe pain. The present study assessed its analgesic efficacy in a broad range of rodent models of acute and chronic pain. In the phenylquinone writhing, hot plate, and tail flick mouse models of acute pain, full analgesic efficacy was obtained (ED_{50} values: 0.0084–0.16 mg/kg i.v.). Full analgesic efficacy was also obtained in yeast- and formalin-induced inflammatory pain (ED_{50} values: 0.0024–0.025 mg/kg i.v., rats and mice) and in mustard-oil-induced spontaneous pain, referred allodynia, and referred hyperalgesia in mice (ED_{50} values: 0.018–0.025 mg/kg i.v.). Buprenorphine strongly inhibited mechanical and cold allodynia in mononeuropathic rats, as well as mechanical hyperalgesia and cold allodynia in polyneuropathic rats (ED_{50} values: 0.055 and 0.036 mg/kg i.v. and 0.129 and 0.038 mg/kg i.p., respectively). It is concluded that buprenorphine shows a broad analgesic profile and offers the opportunity to treat different pain conditions, including neuropathic pain.

Diminished cardiac vagal activity and higher heart rate predict a high mortality rate of chronic heart failure (CHF) after myocardial infarction. We investigated the effects of chronic electrical stimulation of the vagus nerve on cardiac remodeling and long-term survival in an animal model of CHF after large myocardial infarction.

Two weeks after the ligation of the left coronary artery, surviving rats were randomized to vagal- and sham-stimulated groups. Using an implantable miniature

radio-controlled electrical stimulator, we stimulated the right vagal nerve of CHF rats for 6 weeks. The intensity of electrical stimulation was adjusted for each rat, so that the heart rate was lowered by 20 to 30 beats per minute. The treated rats had significantly lower left ventricular end-diastolic pressure (17.1±5.9 versus 23.5±4.2 mm Hg, $P<0.05$) and higher maximum dp/dt of left ventricular pressure (4152±237 versus 2987±192 mm Hg/s, $P<0.05$) than the untreated rats. Improvement of cardiac pumping function was accompanied by a decrease in normalized biventricular weight (2.75±0.25 versus 3.14±0.22 g/kg,$P<0.01$). Although the 140-day survival of the untreated group was only half, vagal stimulation markedly improved the survival rate (86% versus 50%, $P=0.008$). Vagal stimulation therapy achieved a 73% reduction in a relative risk ratio of death.

Vagal nerve stimulation markedly improved the long-term survival of CHF rats through the prevention of pumping failure and cardiac remodeling.

The paper that explores the perceived barriers to return to work presented by unemployed patients with chronic musculoskeletal pain. The findings are based on one to one in depth semi-structured interviews conducted with patients from four sites in the UK. Interview data were recorded from 38 patients (15 male, 23 female) aged between 29 and 62 years the sample included patients who had participated in a vocational rehabilitation scheme, those who had refused to participate and a naïve group. Patients were in receipt of long-term social welfare benefits (incapacity benefits) and recruited via local Job Centres. The mean duration of work absence was over 5 years. The data was transcribed and analysed by means of thematic analysis. Several themes were identified as barriers to return to work from the data including pain related issues, uncertainty (both financial and physical), the healthcare system, interaction with benefits providers, perceptions of employers and personal limitations. The uncertainty and the pain condition itself were the overarching barriers from which other obstacles stemmed. This is the first qualitative study of long term unemployed benefit recipients with chronic pain. Others authors have reported psychosocial factors as barriers to work among disabled populations however, this qualitative study has identified barriers specific to unemployed chronic pain patients. The themes identified will help with the planning and development of future initiatives for returning chronic pain patients to employment.

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Despite considerable research, effective and safe treatments for human pain disorders remain elusive. Understanding the biology of different human pain conditions and researching effective treatments continue to be dominated by animal models, some of which are of limited value. British and European legislation demands that non-animal approaches should be considered before embarking on research using experimental animals. Recent scientific and technical developments, particularly in human neuroimaging, offer the potential to replace some animal procedures in the study of human pain. A group of pain research experts from academia and industry met with the aim of exploring creatively the tools, strategies and challenges of replacing some animal experiments in pain research with ethically conducted studies of human patients and healthy volunteers, in combination with *in vitro* methods. This report considers how a range of neuroimaging techniques including functional magnetic resonance imaging, magnetoencephalography and positron emission tomography, singly and combined, can address human pain conditions. In addition, microdialysis in human subjects; genome-wide association research, twin studies and other epidemiological approaches; and *in vitro* cell and tissue research, are examined for their replacement potential in combination with neuroimaging. Recommendations highlight further opportunities to advance the replacement of animal studies with robust methods of relevance to understanding and treating human pain.

SUMMARY

- Chronic pain is pain ≥ 6 months associated with or without a particular type of injury;& multifactorial.
- Chronic pain is essentially caused by the bombardment of CNS with nociceptive impulses, which causes changes in the neural response→ provokes changes in the behavior of the patient.
- Cerebral circulation determined by rate of CBF
- Regulation of CBF determined by regional flow, NO, CO2, autoregulation determined by CPP, PaO2, Neurogenic factor (eg. Pain), Hct, Hypothermia.

- Chronic pain as neurogenic factor can influence cerebral circulation (Adrenergic, cholinergic, serotonin release)& shifting autoregulation curve.
- Cerebral structure changes (white matter, gray matter, etc) can predispose or precipitating chronic pain→the clear mechanisms is still debate?
- Episodic brain disorders (EBD) form an intriguing group of neurological diseases in which at least some of the symptoms occur in attacks. The hypothalamus integrates many brain functions, including endocrine and autonomic control, and governs various body rhythms. It seems a likely site in which the initiation of attacks of EBD can be modulated. Indeed, the hypothalamus has a crucial role in EBD such as narcolepsy and cluster headache. The same may be true for migraine and depression. Here we summarise the evidence supporting an important role for the hypothalamus in the initiation of disease episodes in various EBD. Study of the various pathophysiological concepts of EBD within the context of the hypothalamus may prove a fruitful example of cross-fertilisation between various research areas.

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Vagal Nerve Stimulation Markedly Improves Long-Term Survival After Chronic Heart Failure in Rats

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