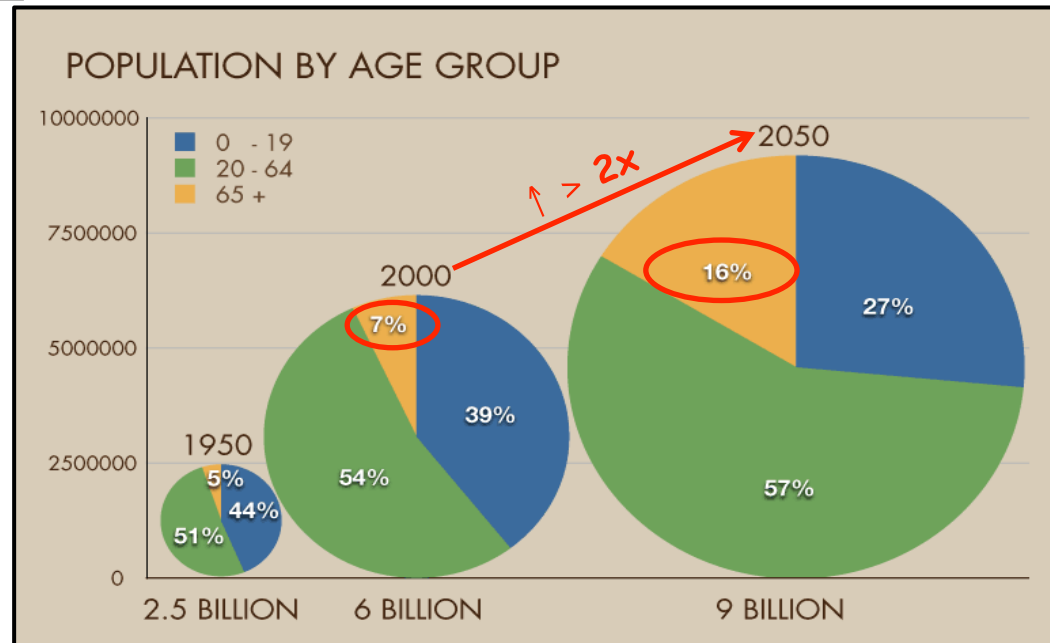




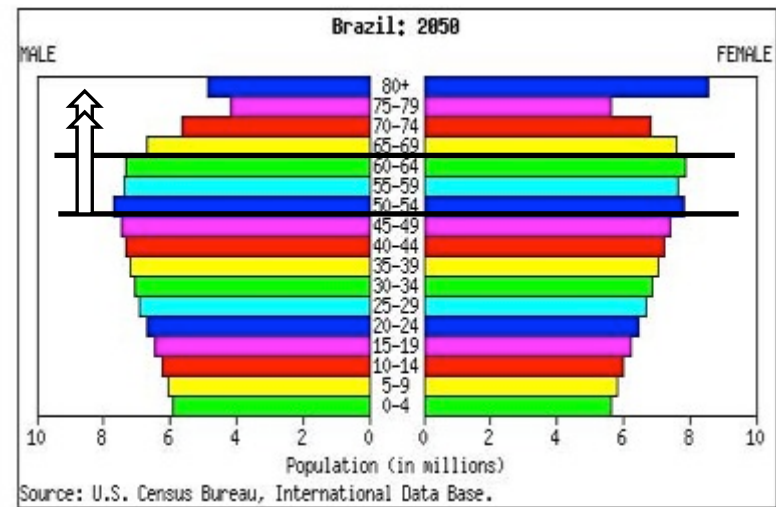
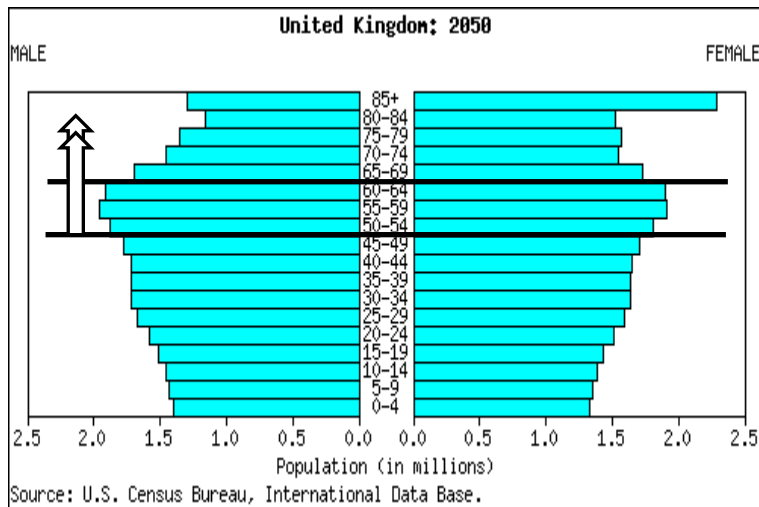
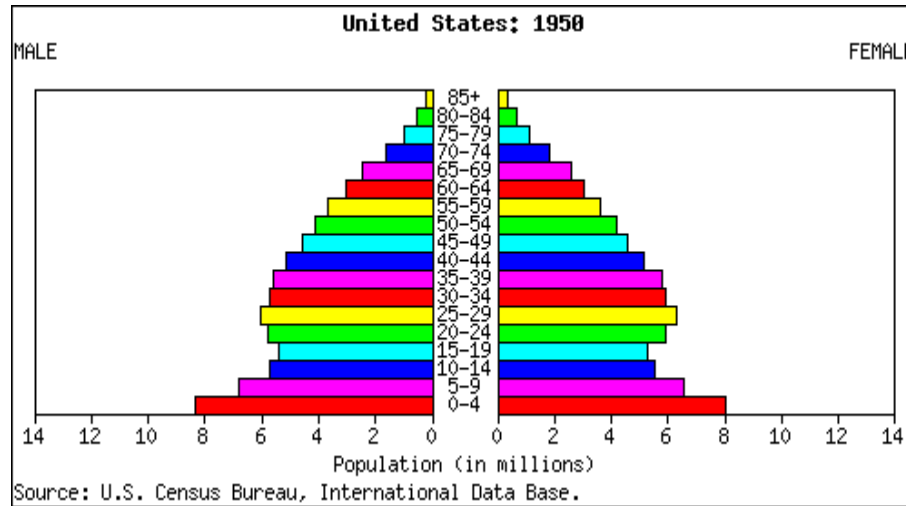
# **Time-course changes of molecular and physiological mechanisms during ageing in hypertensive and normotensive individuals: Effects of exercise training**

**Adriana Ruggeri, Lais Dellacqua, Charles Hindmarch, Vagner R. Antunes, Julian Paton, David Murphy, Lisete C. Michelini**

# The exponential increase of world population will be accompanied by fast growth of elder people in the next decades



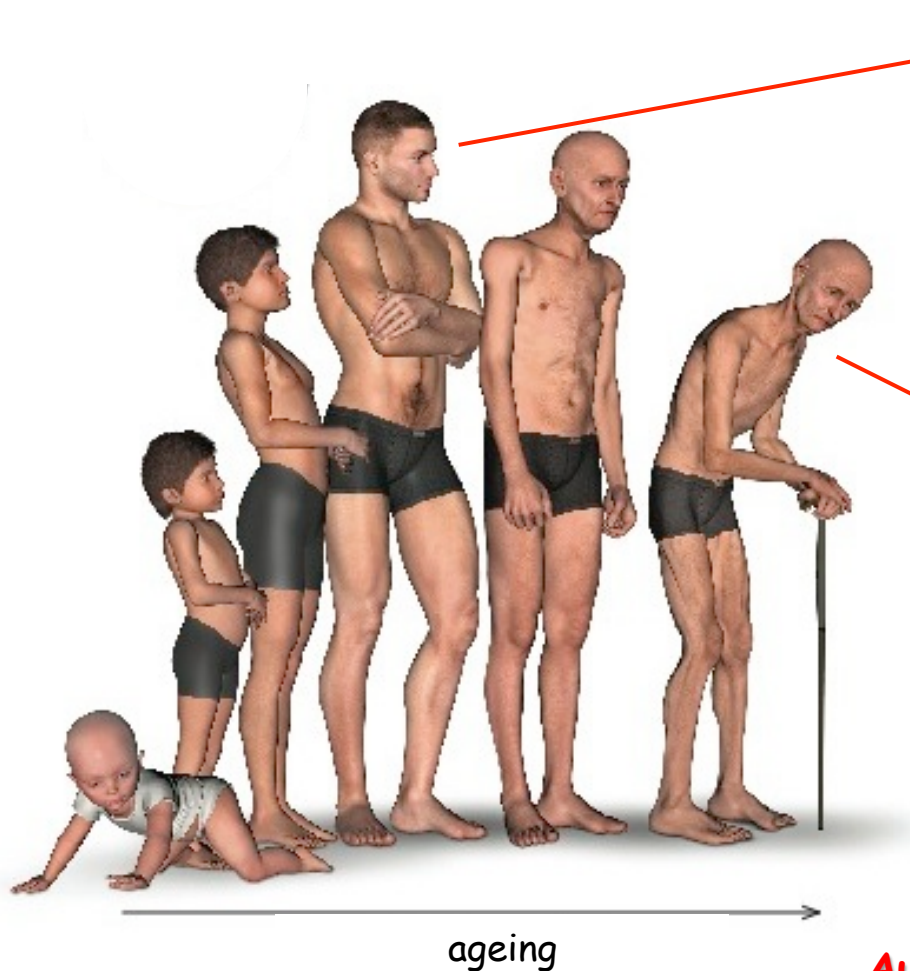
# The challenges of an ageing population



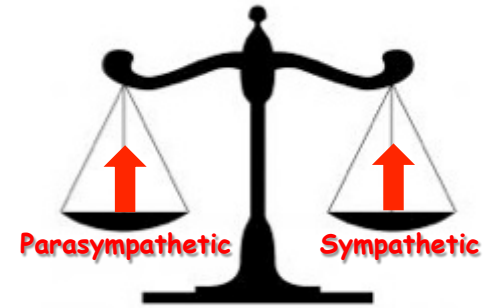
UK in 2050  $\Rightarrow$  40% over 50 years  
25% over 65 years

Brazil in 2050  $\Rightarrow$  37% over 50 years  
23% over 65 years

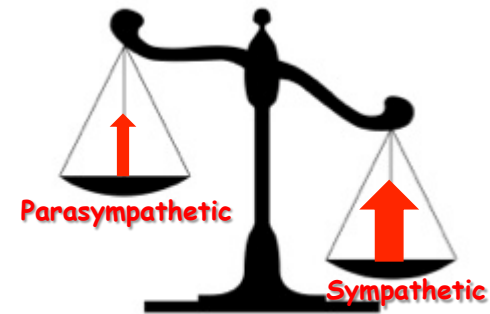
# Longevity is one of the most important medical advances in the last century



Autonomic Nervous System homeostasis



Homeostatic systems deteriorate in the elderly

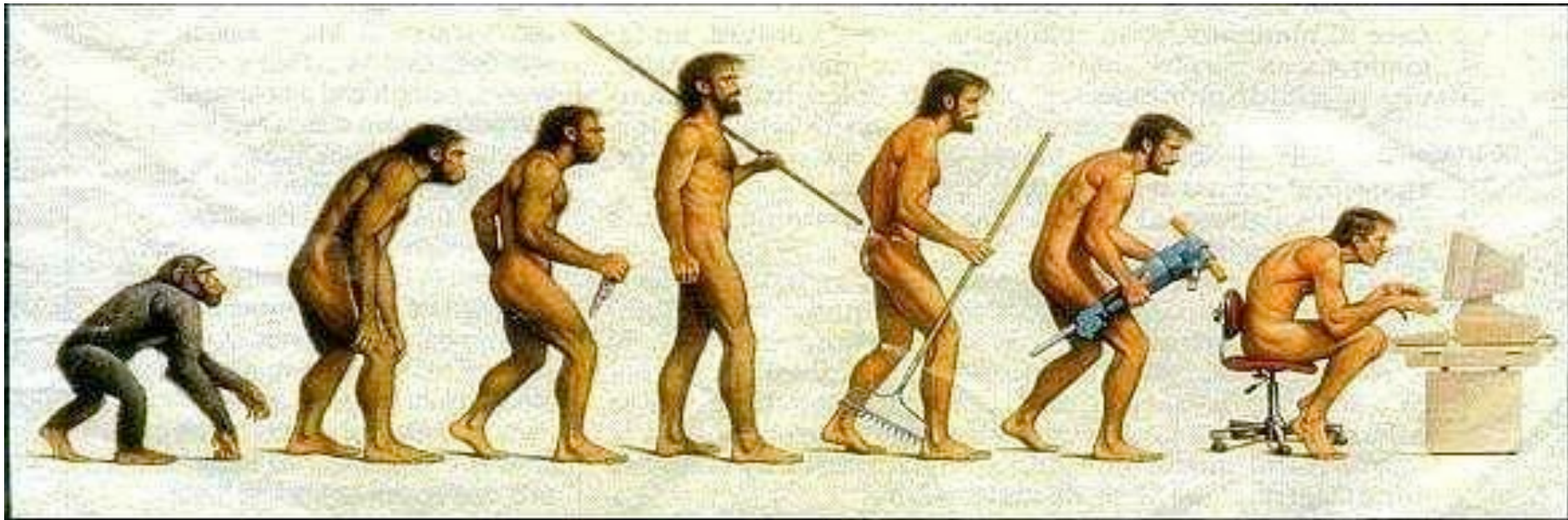


**Autonomic dysfunction** ⇒ **Chronic diseases**  
Hypertension, heart failure, stroke, diabetes, etc

**↑↑ Inactivity** ⇒ **aged people**

Lifespan augmentation has not been accompanied by an improvement in the quality of life of elder people

During evolution men improved their physical capacity...  
but in our modern sophisticated age...

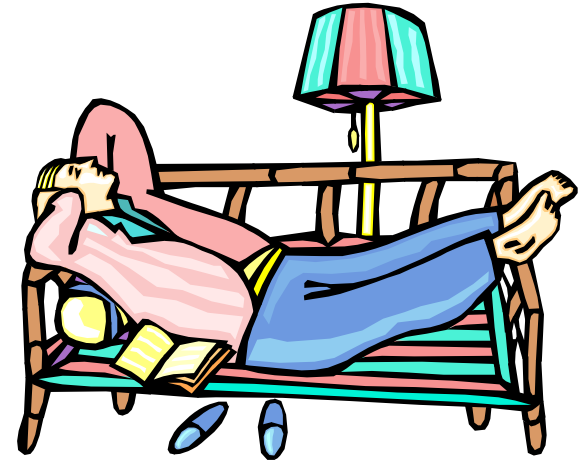


... inactivity had replaced the active life, with  
deleterious consequences, mainly for the old people

# Inactivity in the elderly (and young) men

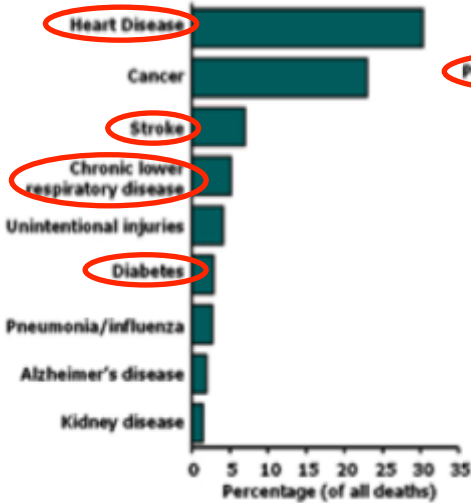
increases the risk of over 30 disease states including:

- ✓ hypertension
- ✓ congestive heart failure
- ✓ arrhythmias
- ✓ peripheral vascular disease
- ✓ stroke (hemorrhagic & ischemic)
- ✓ coronary artery disease
- ✓ diabetes
- ✓ obesity
- ✓ inflammation
- ✓ depression
- ✓ cancer
- ✓ Alzheimer's and Parkinson's (↓ memory & cognition)
- ✓ other diseases

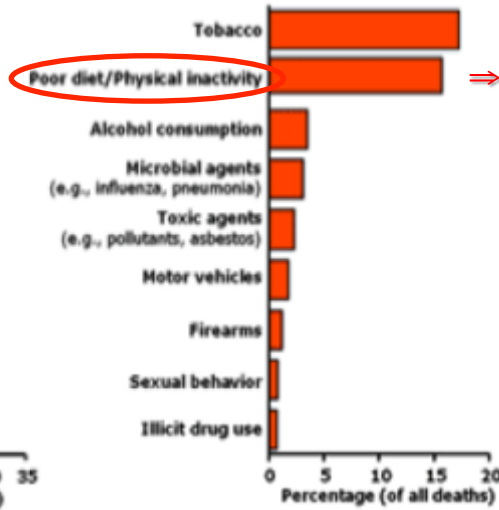


# Inactivity has serious consequences

Leading Causes of Death  
United States, 1980-2002



Associated preventable behaviors and exposure



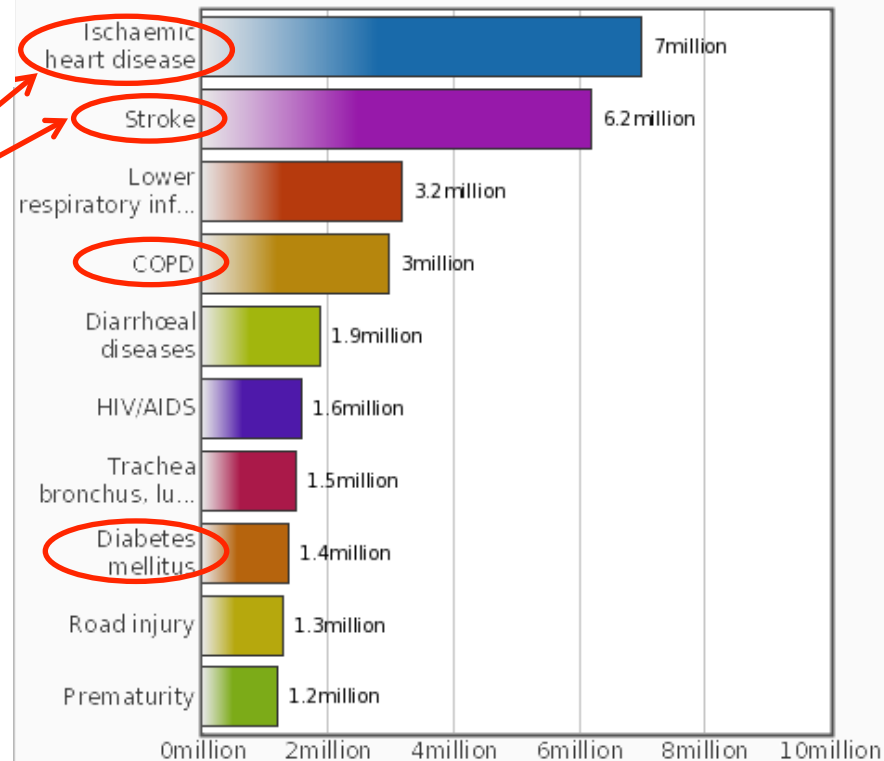
⇒ leading associated cause of death

*Mokdad et al, JAMA 291:1238, 2004*

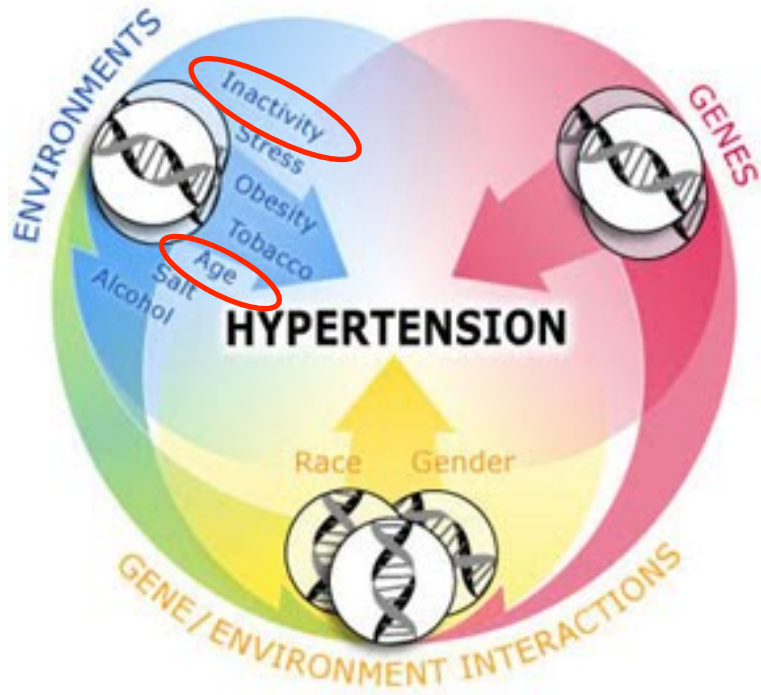
**Chronic Hypertension**  
(>50% in old people)

Modifiable behavioral risk factors such as inactivity still is a leading cause of mortality in the world.

The 10 leading causes of death in the world  
2011



# Hypertension = gene/environmental interactions



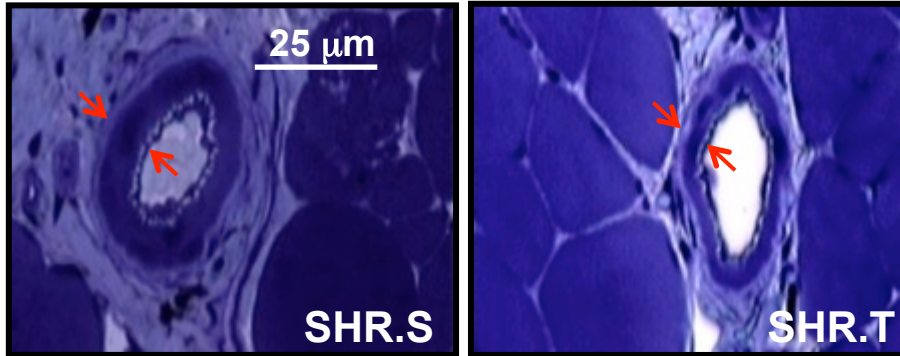
Are there beneficial effects of exercise training on hypertension and ageing?



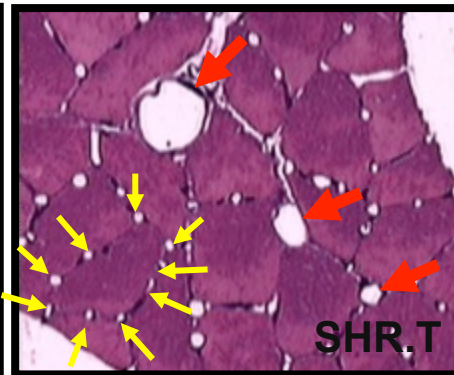
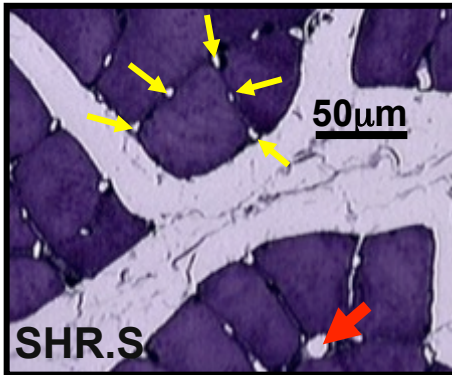
# Beneficial effects of exercise training in adult hypertensive rats (SHR)



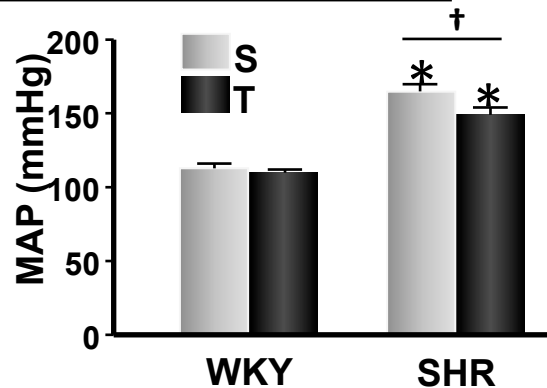
## Cardiovascular System



↓ arterioles wall/lumen ratio  
↓ resistance to blood flow



↑ capillary density  
↑ venule density  
↑ tissue conductance ⇒ ↑ blood flow  
↓ probability of end-organ damage

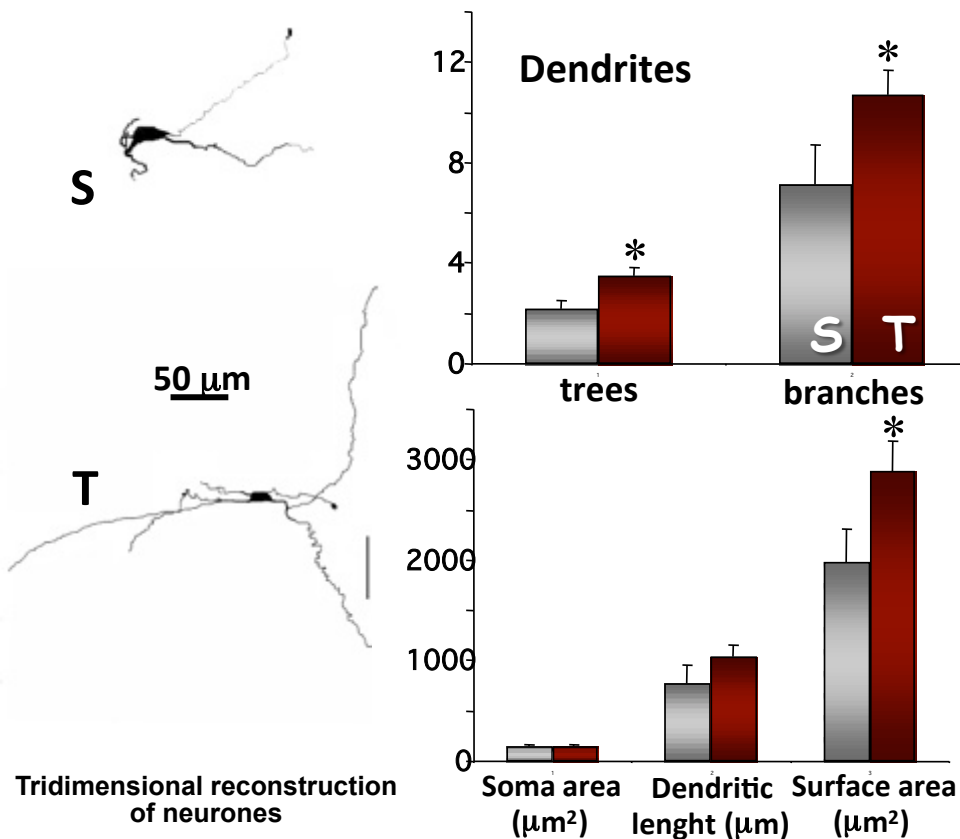


↓ Arterial Pressure

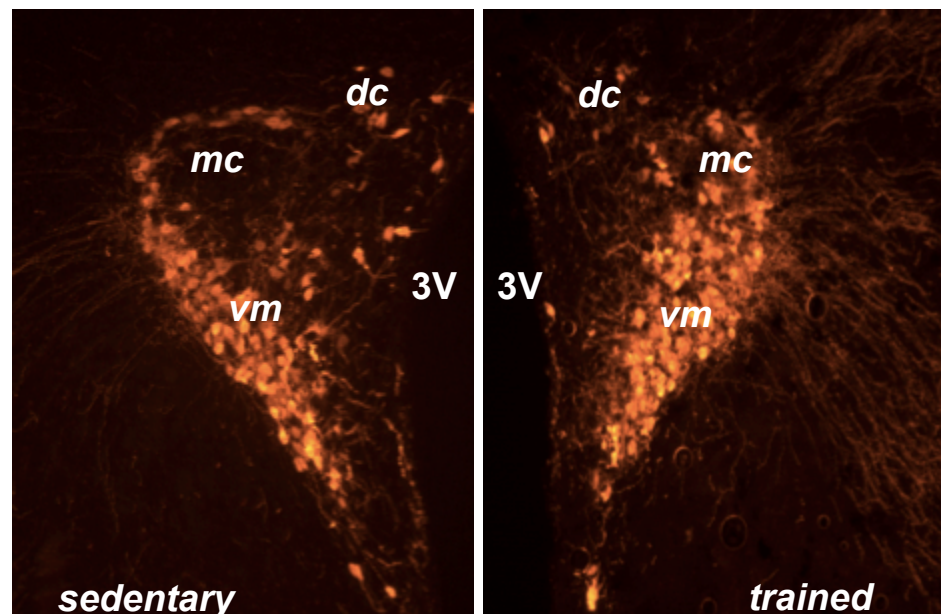
# Beneficial effects of exercise training in the CNS of adult hypertensive rats (SHR)



## Neuronal plasticity in Hypothalamus



Training causes morphological remodeling in preautonomic hypothalamic neurones projecting to parasympathetic and sympathetic pathways to heart and vessels



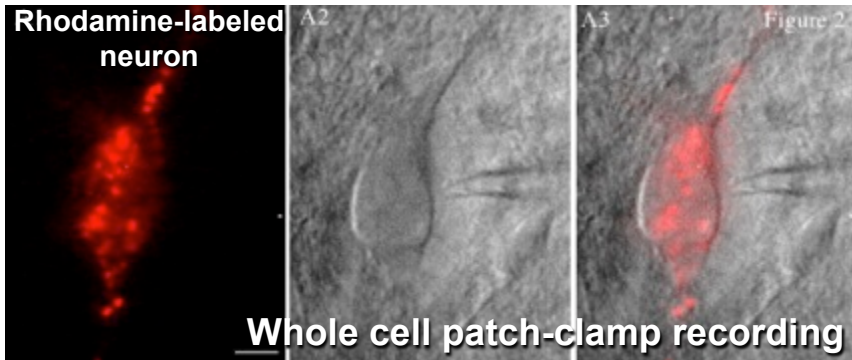
Michelini & Stern, *Exp Physiol* 2009

Cavalleri et al, *AJP.Regul*, 2011

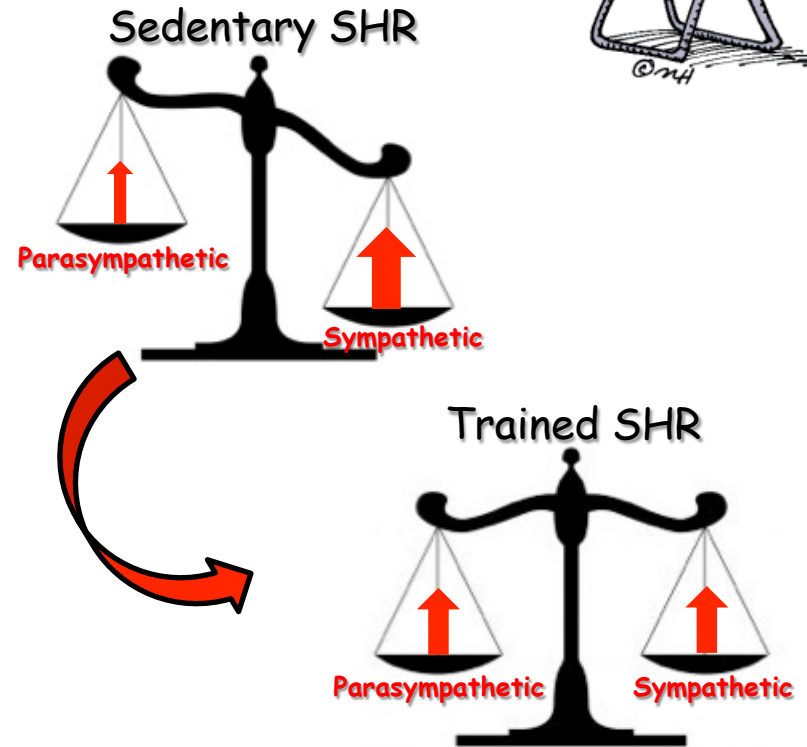
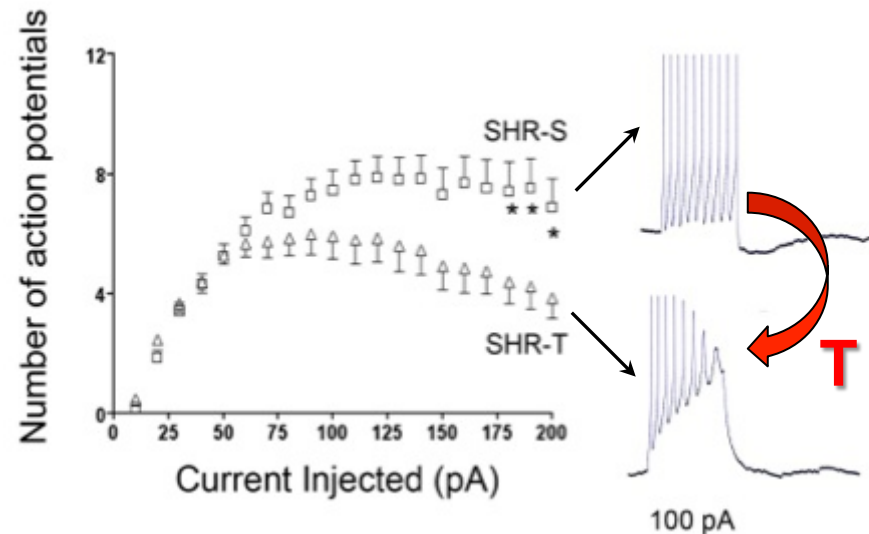
# Beneficial effects of training on neuronal activity of adult hypertensive rats (SHR)



## Hypothalamic Neuronal excitability



Stern et al, *J Neurophysiol*, 2012



By reducing excitability of SHR's preautonomic hypothalamic neurones, training abrogates the increased sympathetic outflow to heart and vessels, improving homeostasis

# Beneficial effects of exercise training in adult hypertensive rats (SHR)



## Reflex control of the circulation

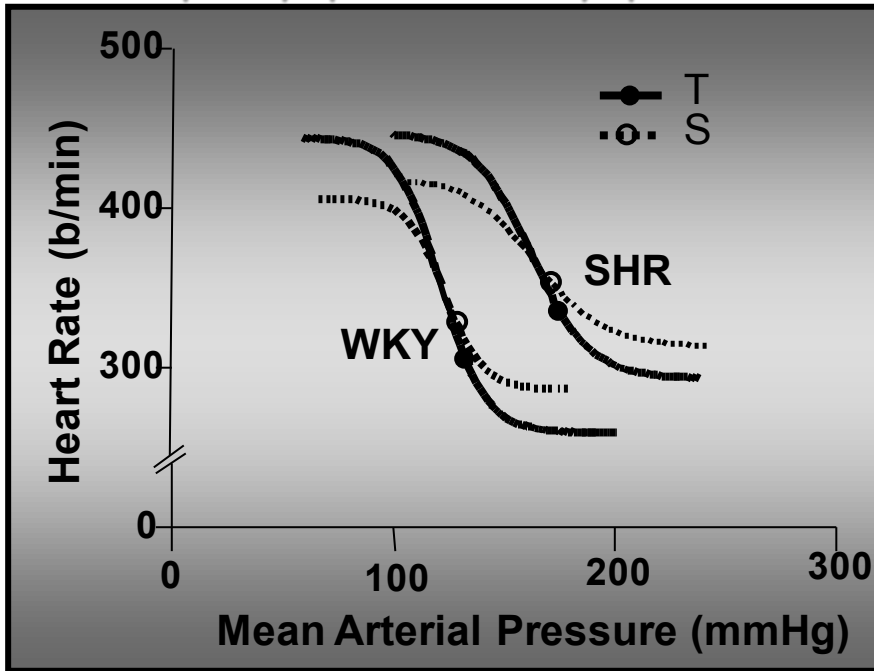
(governed by **parasympathetic** and **sympathetic** outflow to heart/vessels)

Training (SHR & WKY):

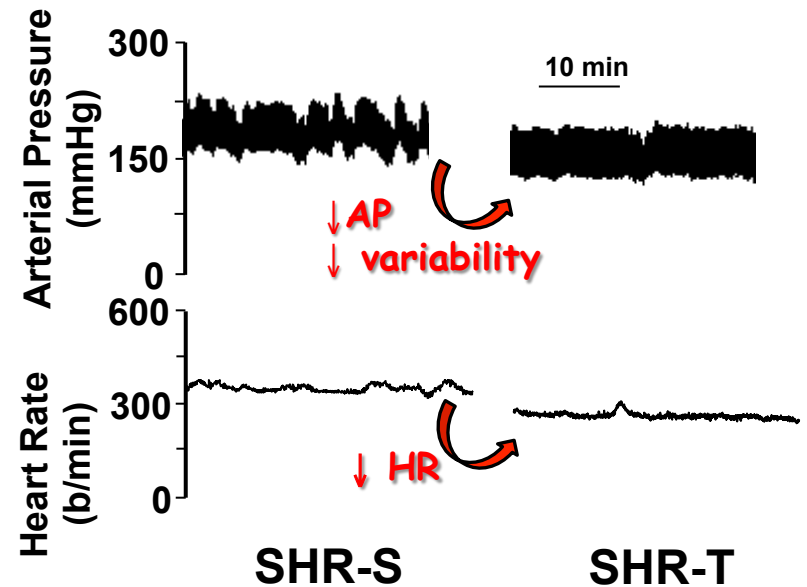
- improves reflex gain (↑ slope)
- ↑ operational range of the reflex



better control of Heart Rate  
better control of vasoconstriction  
(arteries/arterioles & veins/venules)

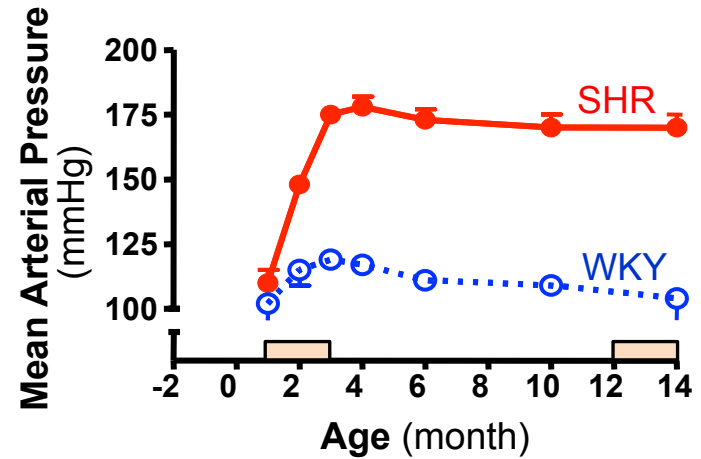
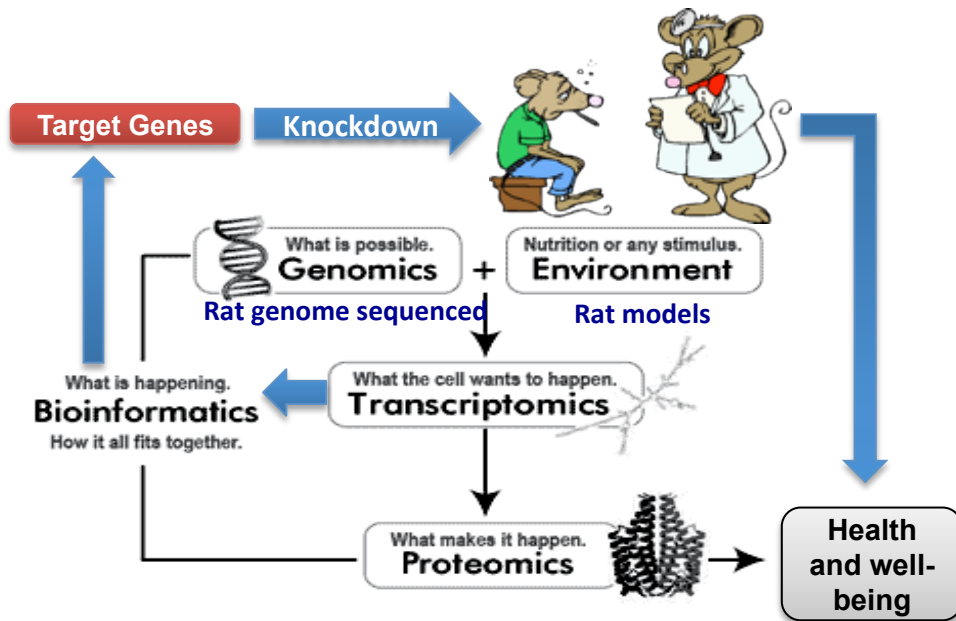
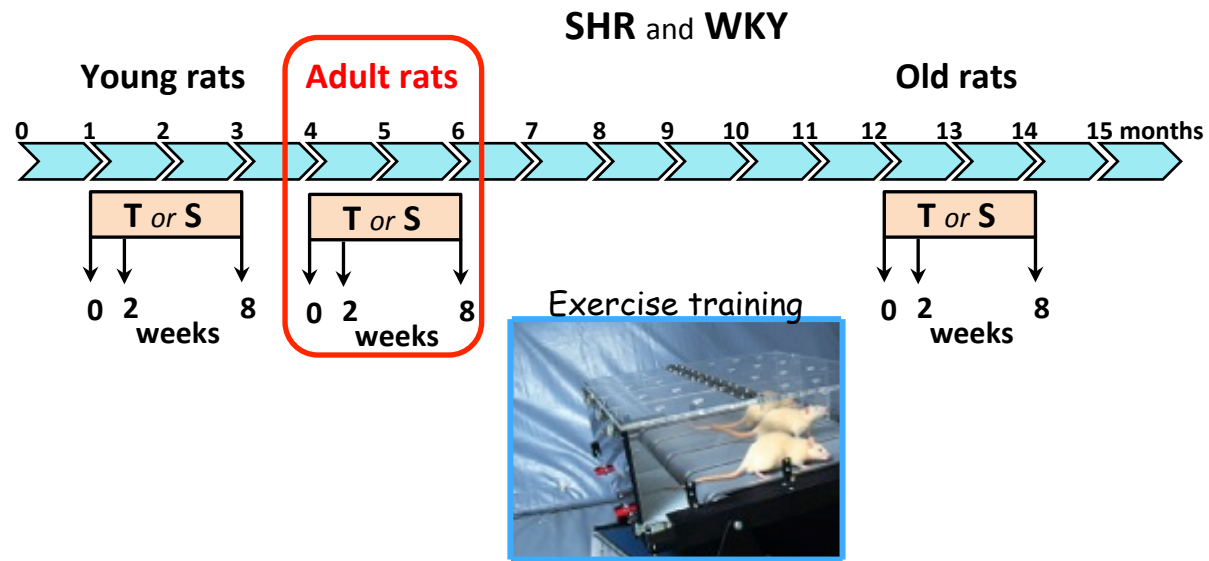
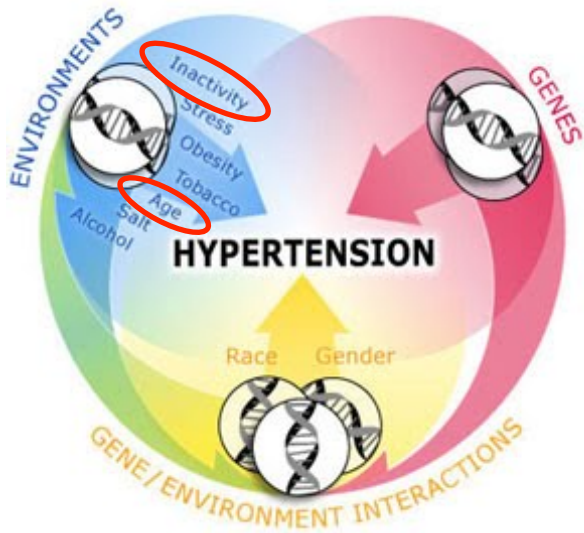


Ceroni et al, *Exp Physiol*, 2009



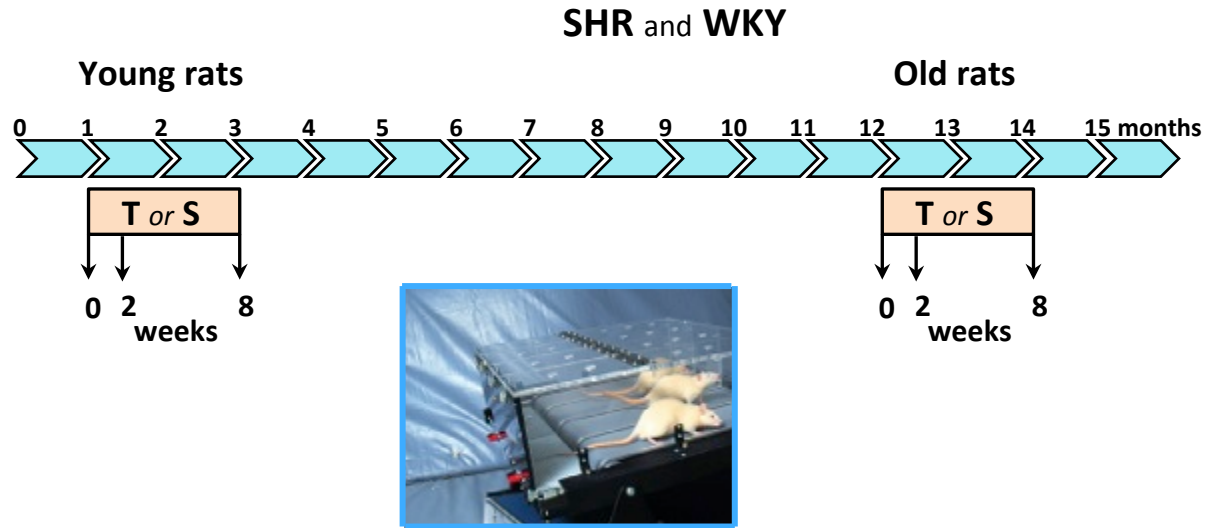
Does training have beneficial effects in old hypertensive individuals?  
And in elder normotensive people?

# Knowing that



It is our hypothesis...

# Hypothesis...

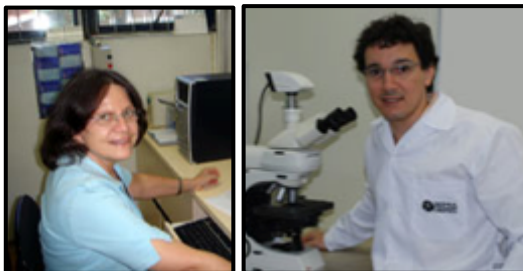


- ✓ The development and/or maintenance of autonomic imbalance in ageing SHR is associated with changes in the expression of a large number of genes in the brain (one or more functional networks) that, through their activity, deteriorate the homeostatic systems and lead to increased morbidity and mortality.
- ✓ It is also our hypothesis that lifestyle changes such as improved physical activity can ameliorate the autonomic imbalance in hypertensive young and elder subjects.

# Amelioration of autonomic imbalances in hypertension and old age with exercise: Exploring the molecular and physiological mechanisms



- To perform detailed physiological analysis (eg. arterial blood pressure, heart rate, baroreceptor reflex gain, sympathetic and parasympathetic tone to heart and vessels) in young and old, trained and sedentary, SHR and age-matched WKY rats
- To identify, by carrying out detailed and comprehensive transcriptome analysis, putative gene networks on brain regions involved in the regulation of autonomic outflow.
- To examine the interaction of hypertension, ageing and training on both gene expression changes and sympathetic and parasympathetic outflow to heart and vessels.
- To test whether identified nodal genes are physiologically important by altering their expression using *in vivo* somatic gene transfer approaches



*Thank you!*

