

OXYTOCIN, VASOPRESSIN AND CHRONIC PAIN

**THE EVOLUTION OF MECHANISMS THROUGH WHICH
SOCIALITY AND LOVE
OVERCOME STRESS, FEAR AND PAIN**

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**Dedicated to a deeper understanding of the neurobiological basis
of love, sexuality, and wellness**

“Nothing is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.”

Marie Curie



But it is complicated....

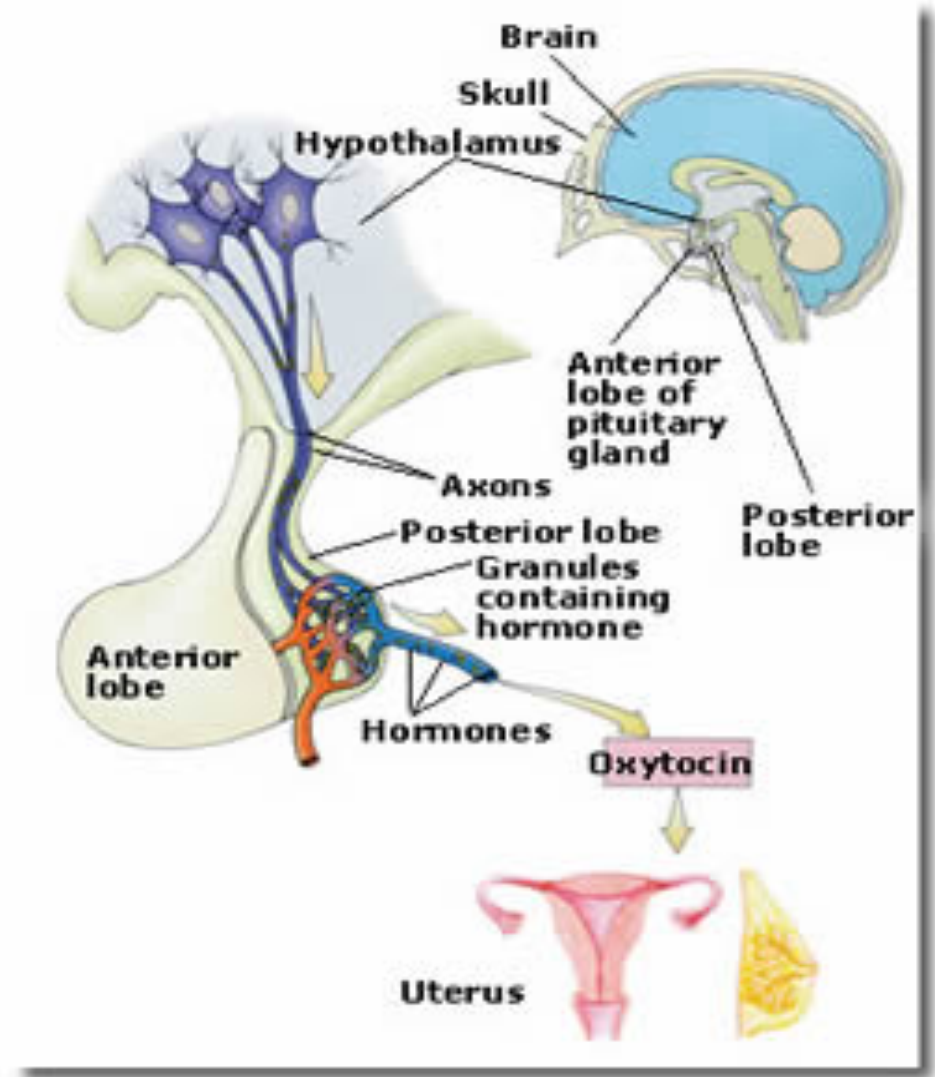
www.deism.com

What is oxytocin?

Oxytocin was classically viewed as a “FEMALE REPRODUCTIVE HORMONE,” acting primarily on the UTERUS and MAMMARY GLAND.

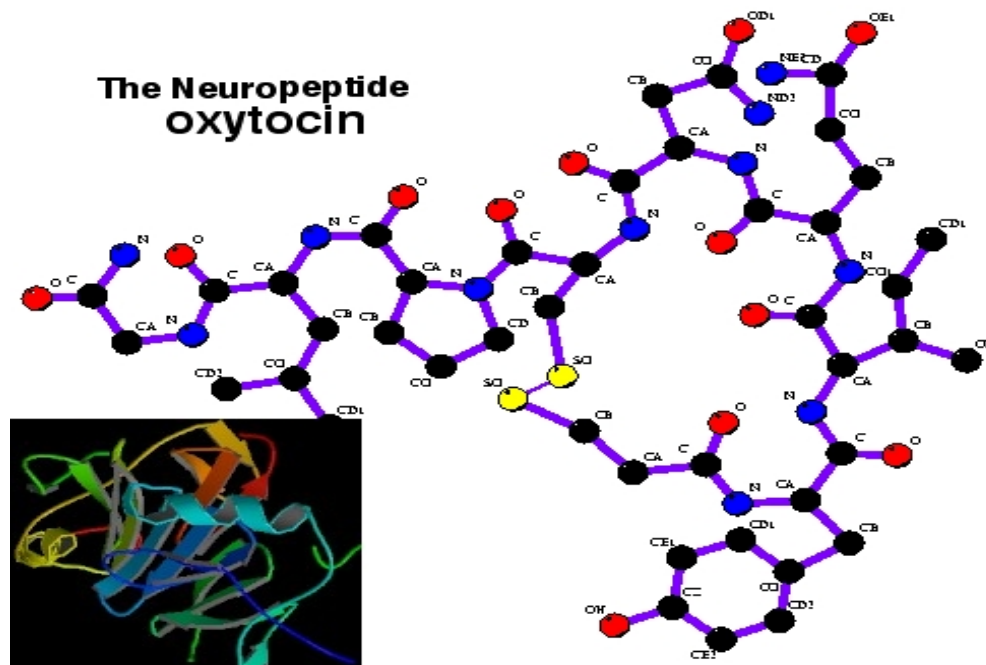
Of course, we now know that this is only part of the story!

OXYTOCIN HAS EFFECTS IN BOTH MALES & FEMALES THROUGHOUT THE BODY & BRAIN.

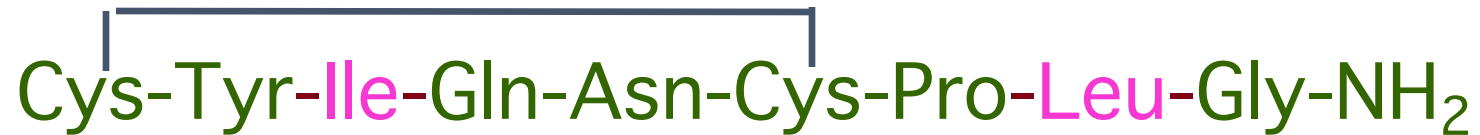


Oxytocin is a NEUROPEPTIDE MOLECULE with functions throughout the BRAIN and BODY.

**OXYTOCIN is central to the biology of
SAFETY & LOVE
OXYTOCIN AND LOVE OVERCOME TRAUMA**



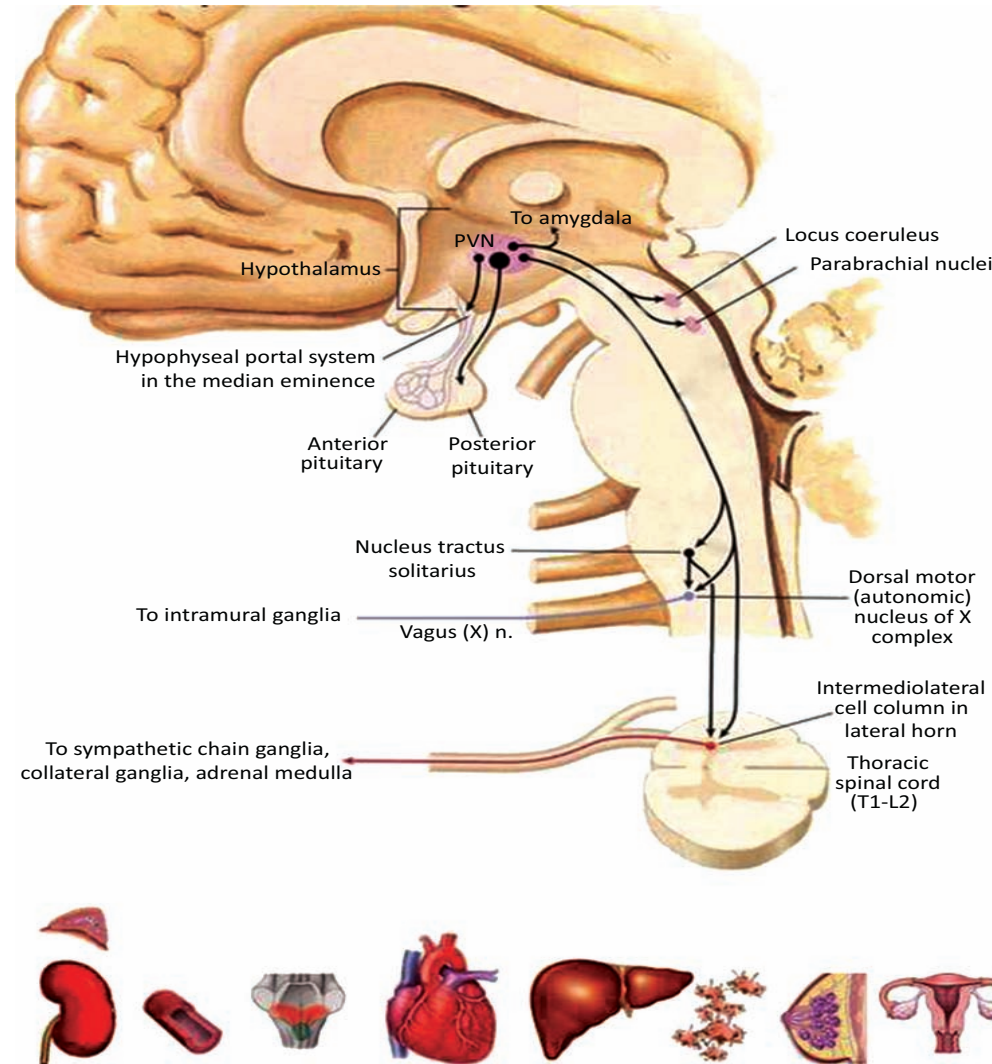
WHAT IS OXYTOCIN?



9 amino acids configured as a ring and a tail.

The ring in oxytocin is held together by sulfur bonds. These bonds allow oxytocin to have a high degree of biological activity and support positive social behaviors, stress buffering and good health.

Receptors for oxytocin are found in every cell in the body, and especially the brain.



- Kidney/adrenal
- Blood vessels
- Heart
- Liver
- Platelets
- Breast
- Uterine
- Bone
- Ovary
- Testicles
- Smooth muscle
- Cancer cells
- Autonomic Pathways
- BRAIN

Fig. (1). Extra-hypothalamic projections of PVN and targets of neurohypophyseal peptides: kidney, adrenal, blood vessel, area postrema, heart, liver, platelets, breast and uterus [adapted from 189].

Oxytocin supports
or
permits:

PREGNANCY
INFANT NUTRITION
MATERNAL BEHAVIOR
PATERNAL BEHAVIOR
ALLOPARENTAL BEHAVIOR
and
EXTENDED NURTURE
of the
immature
human offspring
And

ATTACHMENT
and LOVE



A photograph of an iceberg floating in the ocean. The visible tip of the iceberg is white and jagged, while the vast, dark blue submerged portion is hidden beneath the surface. A white rectangular box is superimposed over the top of the image, containing the text 'WHAT IS OXYTOCIN?'.

WHAT IS OXYTOCIN?

A PHYSIOLOGICAL
METAPHOR for SAFETY
AND LOVE??

Oxytocin - mediating cues of “safety” - helps to explain the biology and benefits of social support and co-regulation.



WHAT IS OXYTOCIN?

**THE TIP OF A PHYSIOLOGICAL “ICEBERG”.
CAPABLE OF CAUSING UTERINE
CONTRACTIONS AND LACTATION,
BUT ALSO SHIFTS IN
SOCIAL PERCEPTIONS, MOOD, EMOTION,
BRAIN DEVELOPMENT, HEALING AND MUCH
MORE**

Oxytocin does NOT act alone.
OXYTOCIN (OT) has a sibling hormone –
Arginine VASOPRESSIN (AVP) –
from which it differs by 2 (of 9) amino acids

OXYTOCIN (OT)



Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH₂

The diagram shows a horizontal line with vertical end caps, spanning the width of the peptide sequence above it, indicating a cyclic structure.

Arginine VASOPRESSIN (AVP)



Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH₂

The diagram shows a horizontal line with vertical end caps, spanning the width of the peptide sequence above it, indicating a cyclic structure.

Research in rodents suggests that

**BOTH
OXYTOCIN and
VASOPRESSIN
are involved in:**



**The EVOLUTION OF SOCIALITY AND LOVE involves:
A dynamic dance between Oxytocin and Vasopressin**

**Oxytocin facilitates a sense of SAFETY & SYNCHRONY,
as well as the capacity to RELAX AND RESTORE.**

Vasopressin permit ACTIVE DEFENSE and MOBILIZATION.

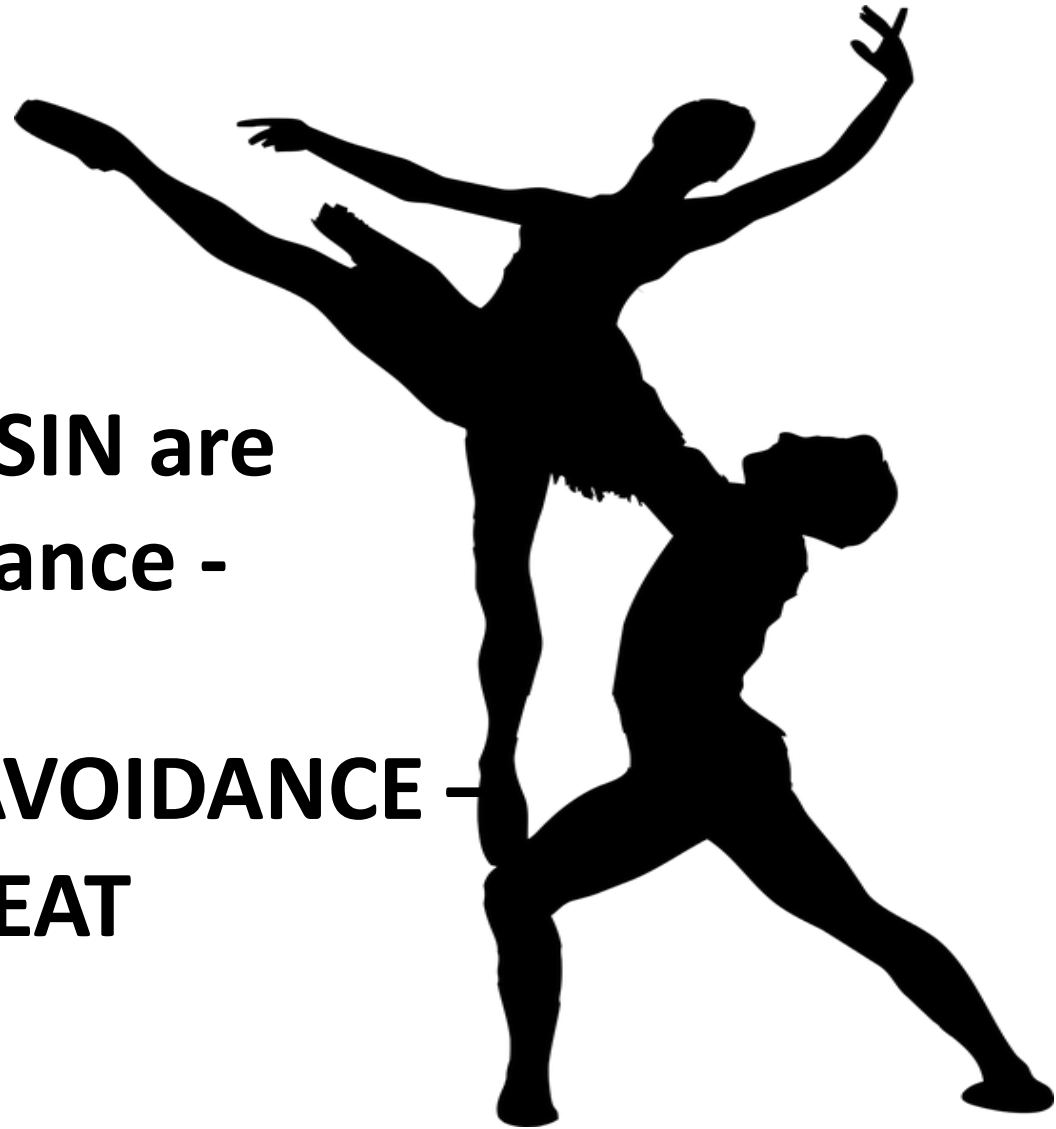


**OXYTOCIN AND VASOPRESSIN are
elements in the dynamic dance -**

between APPROACH and AVOIDANCE -

between SAFETY AND THREAT

between LOVE and FEAR



SMALL STRUCTURAL DIFFERENCES IN OXYTOCIN AND VASOPRESSIN ALLOW THEM TO INTERACT WITH EACH OTHERS' RECEPTORS.

STIMULATING OXYTOCIN RECEPTORS IS ASSOCIATED WITH PROSOCIALITY.

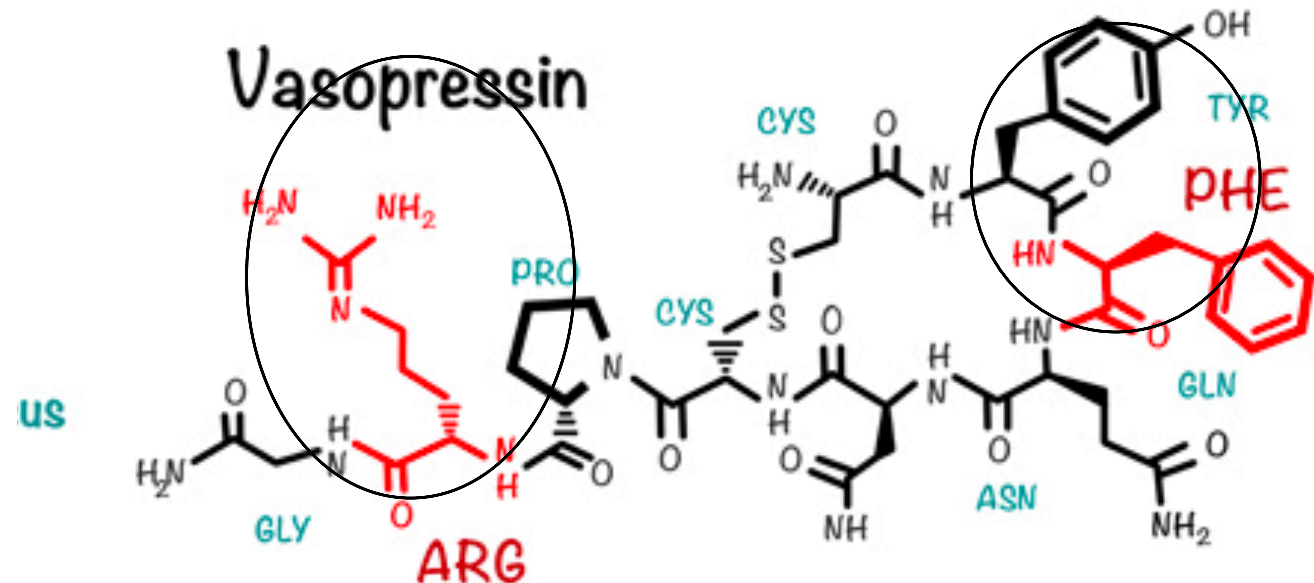
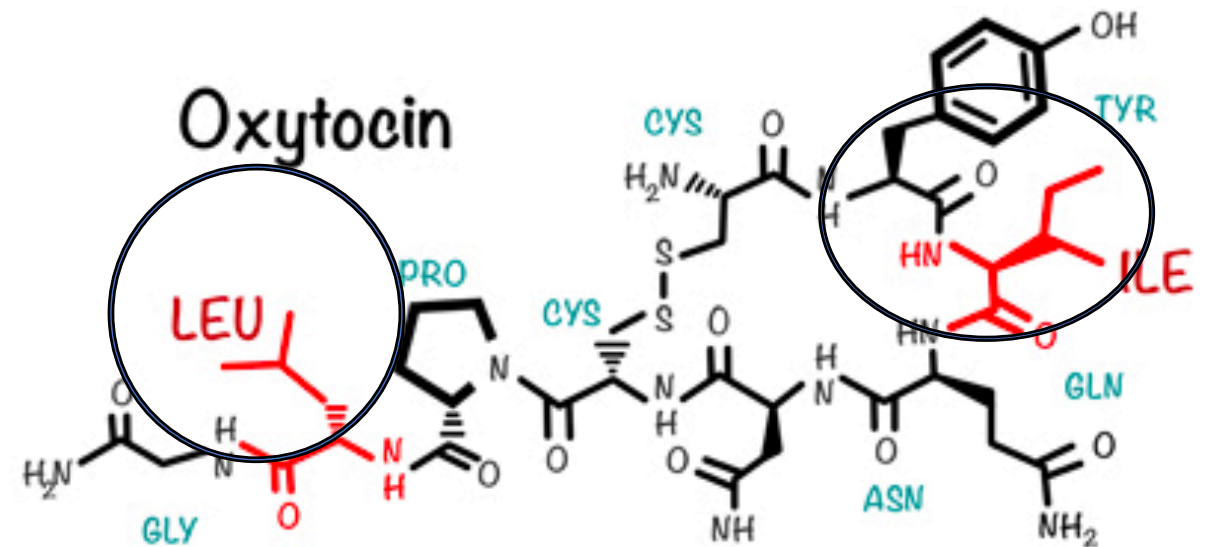
STIMULATING VASOPRESSIN RECEPTORS IS ASSOCIATED WITH DEFENSE.. But

THESE MOLECULES MAY STIMULATE EACH OTHERS' RECEPTORS.

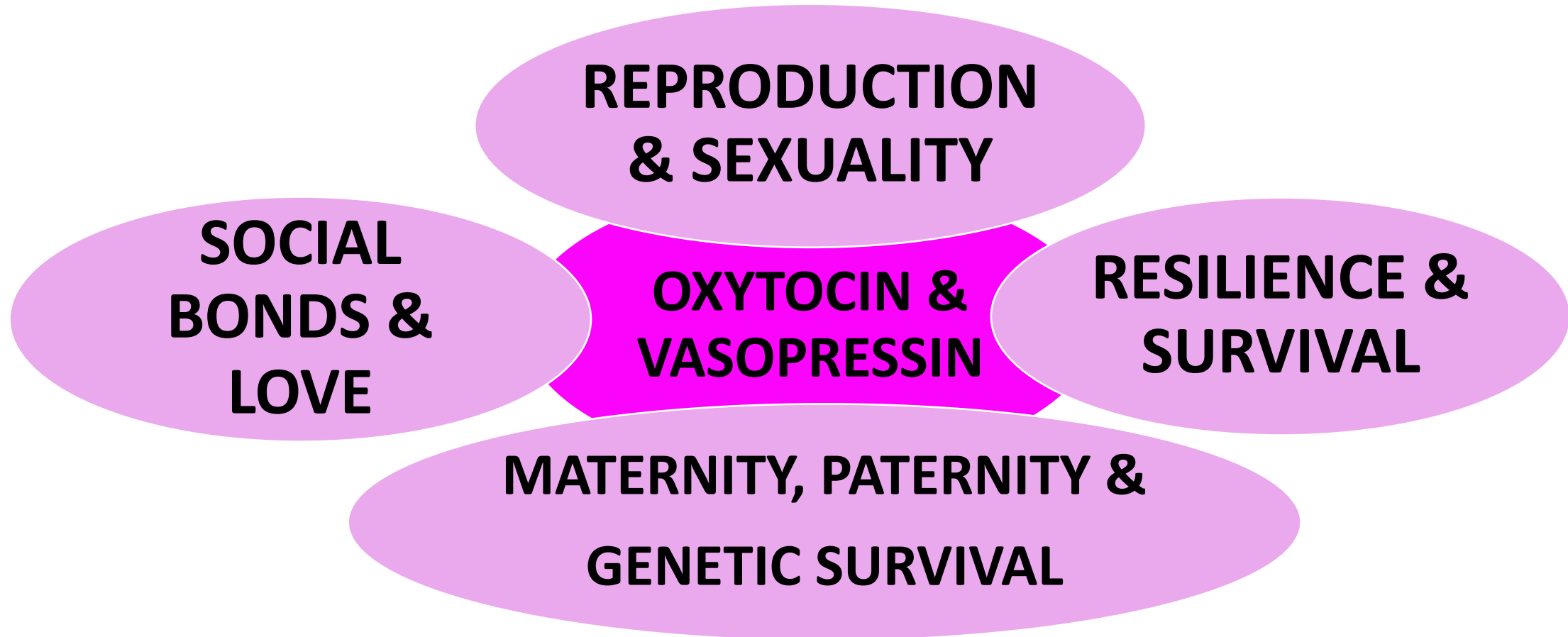
THEY MAY INHIBIT THE ACTIONS OF EACH OTHER.

THEY CAN HAVE DIFFERENT EFFECTS IN DIFFERENT CONTEXTS AND DIFFERENT BRAIN REGIONS, DEPENDING ON THE HISTORY OF THE INDIVIDUAL.

THIS ALLOWS MANY VARIATIONS OF ACTION FROM JUST TWO MOLECULES, AND SUPPORTS THE COMPLEXITY OF MAMMALIAN SURVIVAL AND REPRODUCTION.



**OXYTOCIN DOES NOT ACT ALONE.
OXYTOCIN PLUS VASOPRESSIN BOTH UNDERLIE CENTRAL FEATURES OF SOCIAL
BEHAVIOR ASSOCIATED WITH MAMMALIAN REPRODUCTION AND SURVIVAL**



**OXYTOCIN and VASOPRESSIN are similar in structure
but have different functions**

Vasopressin

**Fear/Defense
Territoriality**

**Vigilance, Arousal
Mobilization**

Sympathetic nervous system

PROTECTIVE

(active strategies)

More "primitive"

**Dominant during threat -
Extreme stress/ Trauma**

Oxytocin

**Prosociality/Approach
Sharing**

**Relaxation, Resilience
Immobilization without fear**

**Parasympathetic nervous
system (the vagus nerve)**

HEALING & RESTORATION

**(The healing power
of "love") More modern.**

**Dominant when there
Is a sense of SAFETY.**

**OXYTOCIN AS AN ANALGESIC: EXAMPLES OF MECHANISMS
FACILITATING SOCIAL CONNECTION AND SAFETY - which also may involve -**

OXYTOCIN MOLECULE: DIRECT INTERACTIONS WITH RECEPTORS INCLUDING -

OXYTOCIN RECEPTORS (many other consequences)

VASOPRESSIN RECEPTORS

OPIOID RECEPTORS (u opioid)

TRPV1 RECEPTORS (inhibiting pain sensations)

GABA_A (inhibiting anxiety)

FRAGMENTS OF THE OXYTOCIN MOLECULE ARE ANALGESIC

Acts on the MESOLIMBIC systems (mPFC-Amy-NAcc) implicated in emotional learning

ANTI-INFLAMMATION (for example)

INTERACTIONS WITH VASOPRESSIN – generally inhibiting effects of vasopressin

REGULATION OF THE AUTONOMIC NERVOUS SYSTEM - inc. VAGAL TONE

REGULATION OF THE HPA AXIS – “stress coping” – adaptively inhibiting -

VASOPRESSIN (Oxytocin inhibits effects of vasopressin)

CRF (inhibiting effects of CRF)

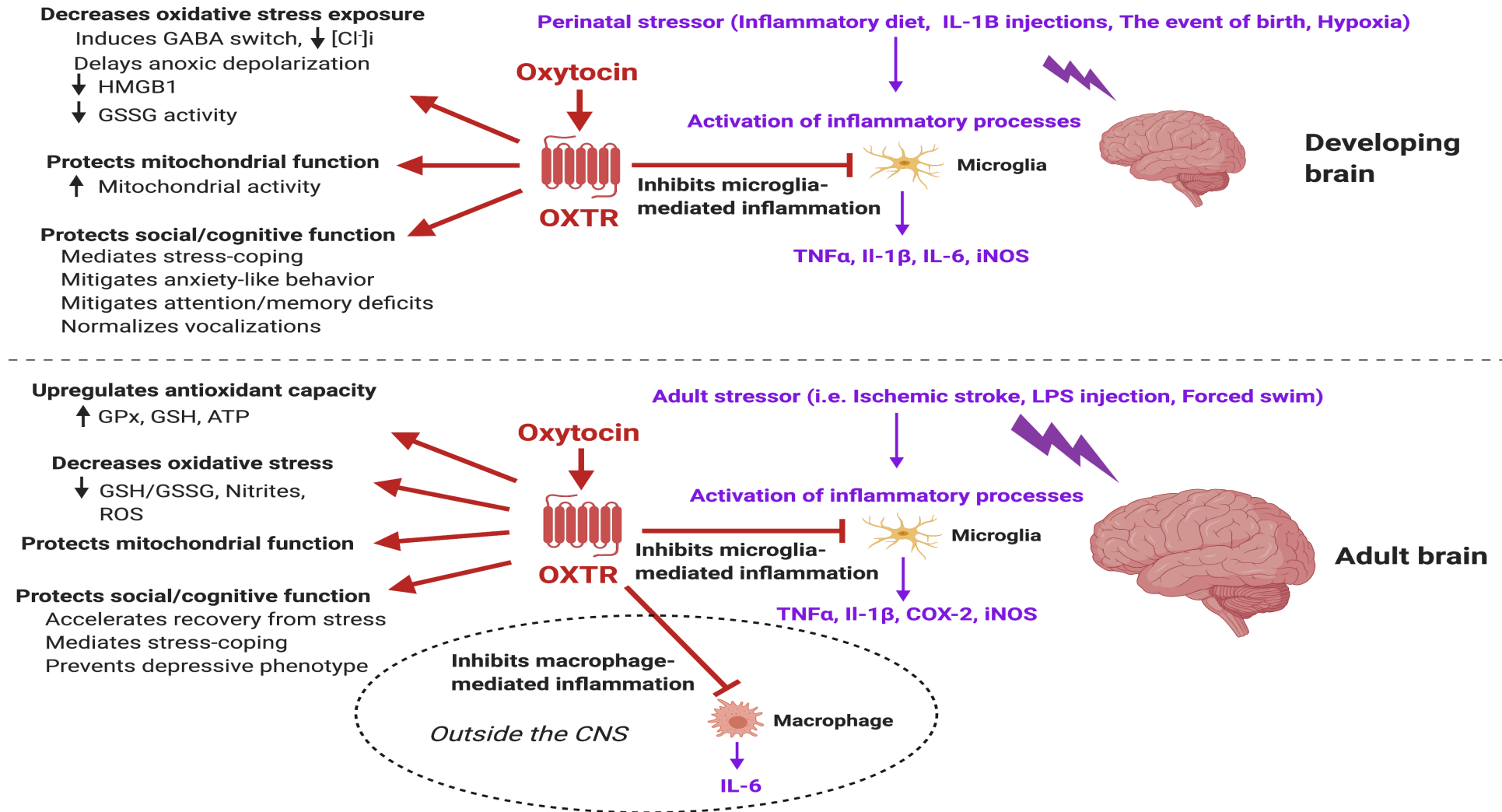
Vasopressin (AVP) and
hormones of the stress axis (HPA AXIS including CRF)
are primarily pro-inflammatory - fast strategies of defense.



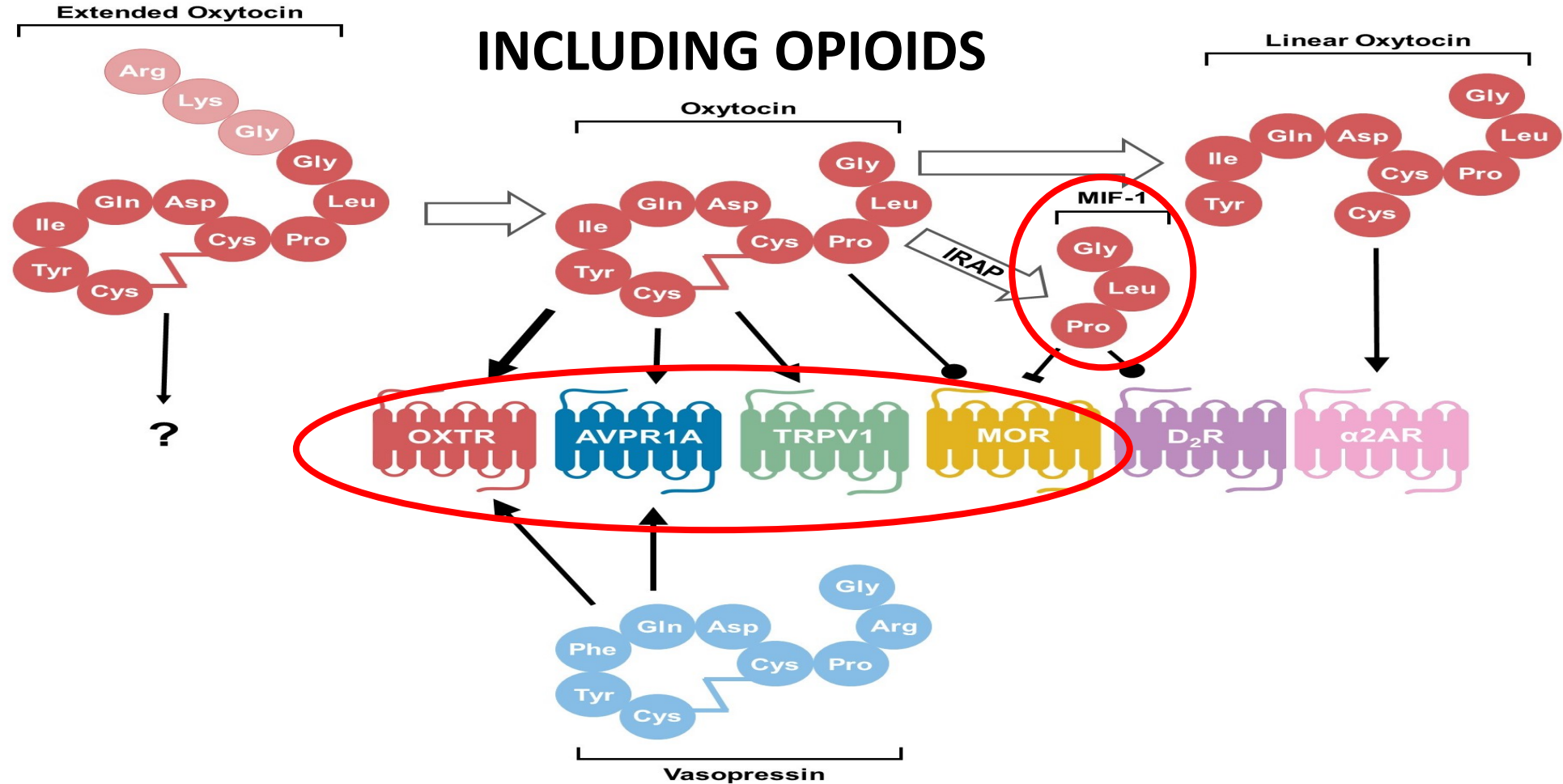
Oxytocin works like a fire extinguisher...
Acting as an anti-inflammatory and anti-oxidant.



Oxytocin inhibits inflammation both during perinatal development and in adulthood.



ANALGESIC EFFECTS OF OXYTOCIN ALSO MAY EXIST BECAUSE OXYTOCIN ITSELF BINDS TO RECEPTORS FOR OTHER MOLECULES INCLUDING OPIOIDS

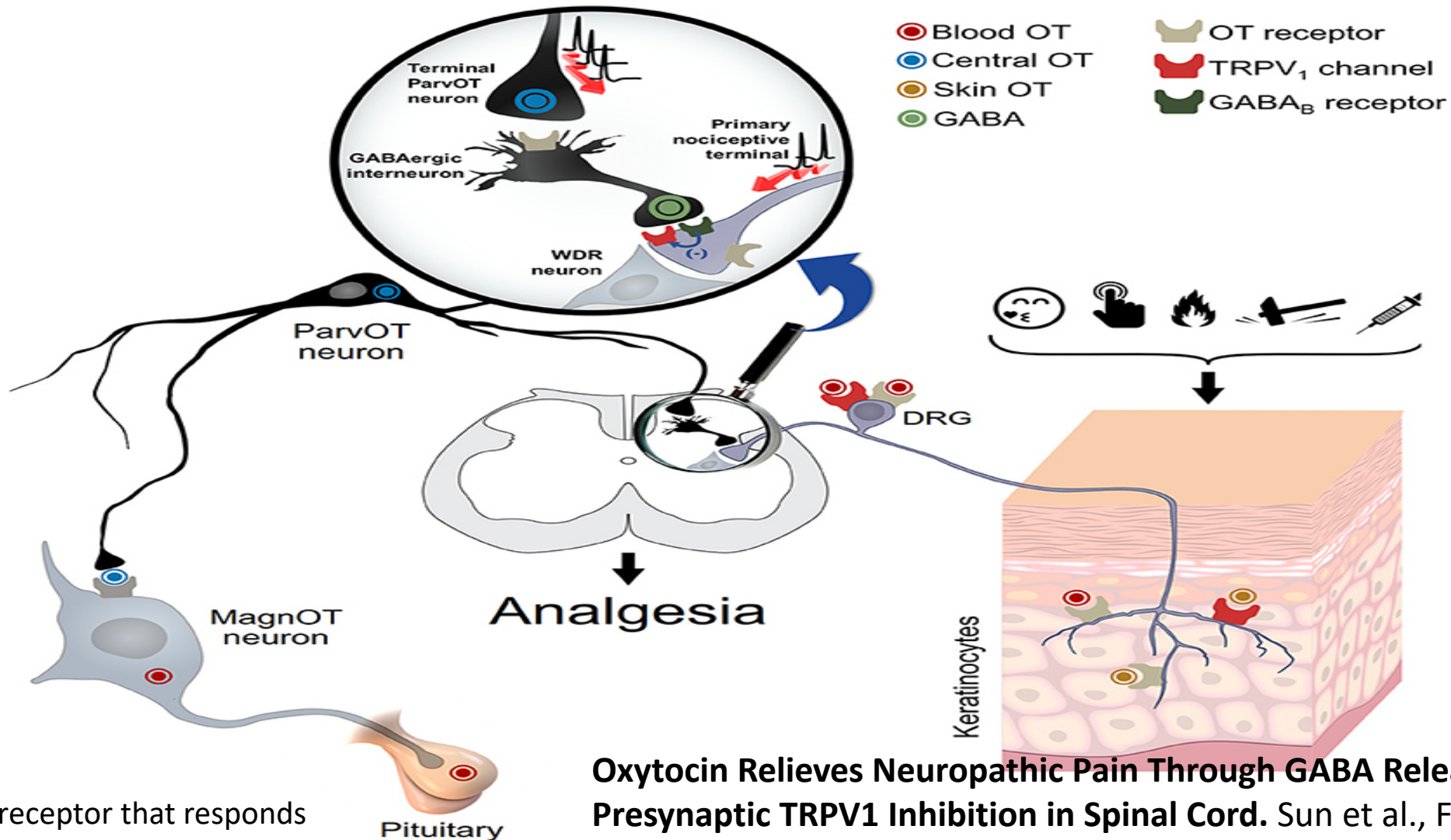


THE LAST 3 AMINO ACIDS OF OXYTOCIN (PLG aka MIF-I) HAVE ANALGESIC PROPERTIES.

OXYTOCIN BINDS TO SEVERAL RECEPTORS including OXTR, AVPR1A, TRPV1, MOR = u opioid receptor.
(all of which have a role in pain).

REVIEWED CARTER, KENKEL ...KINGSBURY, PHARM REV 2020

One hypothesis from an acute peripheral pain model suggests that **OXYTOCIN BLOCKS PAIN, by increasing GABA, inhibiting TRPV1 pain receptors, thus decreasing PAIN.** *Oxytocin, GABA, and TRPV1, the Analgesic Triad?* Gonzalez-Hernandez and Charlet. Front. Mol. Neurosci. 2018



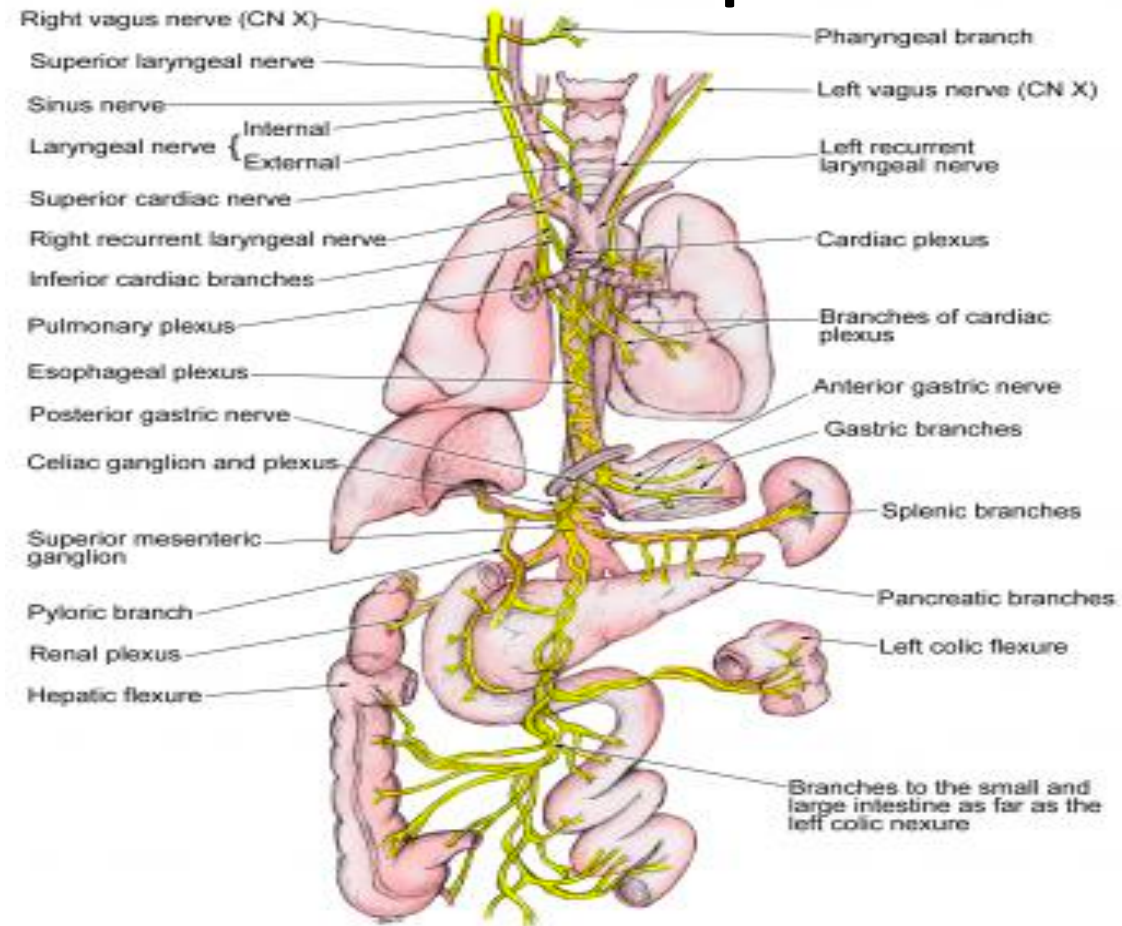
Oxytocin Relieves Neuropathic Pain Through GABA Release and Presynaptic TRPV1 Inhibition in Spinal Cord. Sun et al., Front. Mol. Neurosci. 2018

TRPV1 – pain receptor that responds to capsaicin and inflammation.

Of particular importance to understanding Oxytocin and Vasopressin - as well as the HEALING POWER of SAFETY AND SOCIAL CONNECTION - is the fact that these hormones act on the AUTONOMIC NERVOUS SYSTEM and regulate the VAGUS NERVE – with various consequences for PAIN

THE VAGUS (10TH CRANIAL NERVE), SHOWN HERE, LINKS THE BODY TO THE BRAIN, AND IS CRITICAL TO EXPLAINING THE HEALTH BENEFITS OF FEELING SAFE AND THE HEALTH RISKS OF FEAR AND ANXIETY.

OXYTOCIN & VASOPRESSIN BOTH REGULATE THE ADAPTIVE FUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM AS WELL AS REGULATING INFLAMMATION AND HEALING.

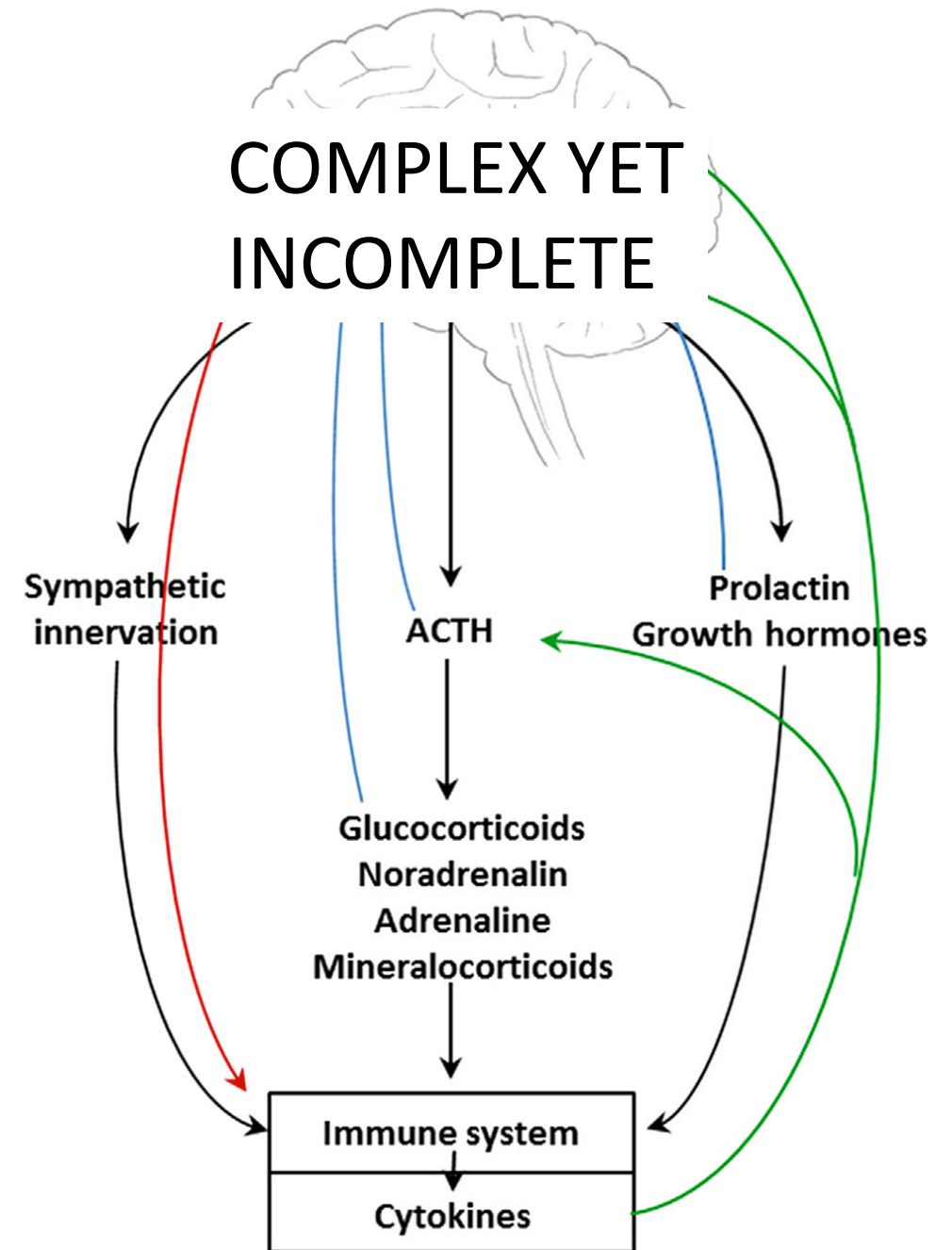


THE HPA AXIS, IMMUNE SYSTEM AND CYTOKINES HAVE ALL BEEN IMPLICATED IN CHRONIC PAIN.

BOTH STRESS AND IMMUNE SYSTEMS CAN ACTIVATE OXIDATIVE STRESS, ESP IN THE BRAIN. OXIDATIVE STRESS IN TURN CAN AFFECT THE RELEASE OF CRF AND ACTH AND INCREASE SYMPATHETIC AROUSAL.

FROM KALINICHENKO, ET AL. FRONTIERS IN NEUROENDOCRINOLOGY 2019.

The vicious circle of co-activation of pathways of stress system, immune system, and oxidative system under conditions of emotional stress or isolation – which can lead to CHRONIC PAIN



Classic stress models often omit these -

EVOLUTION: Different ways of coping with THREAT vs SAFETY

The origins of the HPA axis and SOCIAL STRATEGIES

Social context and the importance of ADAPTATION to context

Dealing with both THREAT and SAFETY

EXPERIENCE ACROSS THE LIFE CYCLE

Both NEGATIVE and POSITIVE experiences matter

SEX DIFFERENCES – GONADAL Steroids

ACUTE VS CHRONIC Stress: require different physiology

SYSTEMS BEYOND THE CLASSIC SYMPATHO-ADRENAL MODELS

INFLAMMATION AND IMMUNE RESPONSES

AUTONOMICS, esp. Parasympathetic nervous system

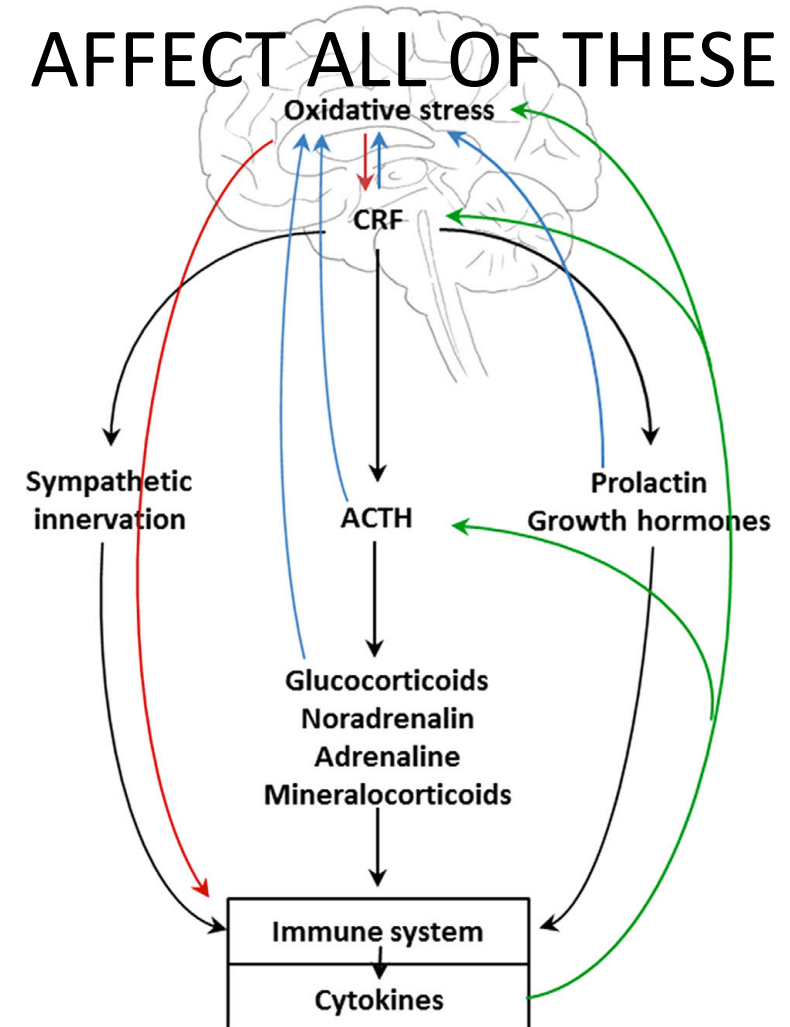
ENDOCRINE MODULATORS - Hormones & receptors mediate and moderate reactions to challenge and are affected by experience:

OXYTOCIN – MODERN: INTEGRATES SOCIALITY with “stress responses”

Stress-COPING; adaptive decreases in shut-down

Vasopressin – increases in both acute and chronic stress (esp in MALES)

LOVE AND OXYTOCIN AFFECT ALL OF THESE



CLASSIC STRESS-PAIN MODELS

CLASSIC hypothalamic-pituitary-adrenal (HPA) axis model for ACUTE STRESS shown with negative feedback of cortisol on Anterior Pituitary and Hypothalamus.

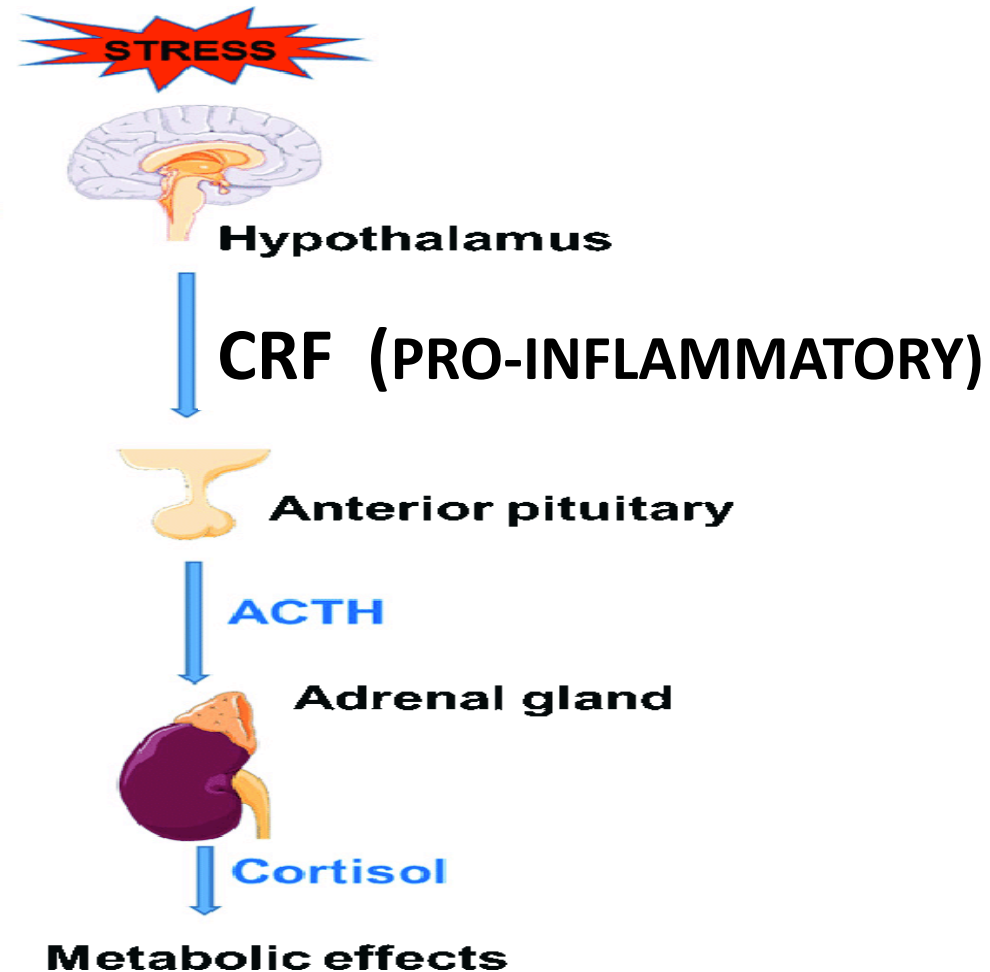
Factors releasing ACTH

CRF = CORTICOTROPIN RELEASING FACTOR

ACTH (Adrenocorticotropin hormone)
From the Anterior Pituitary releases

CORTISOL (a glucocorticoid =GC)
From the Adrenal Cortex - INC ENERGY

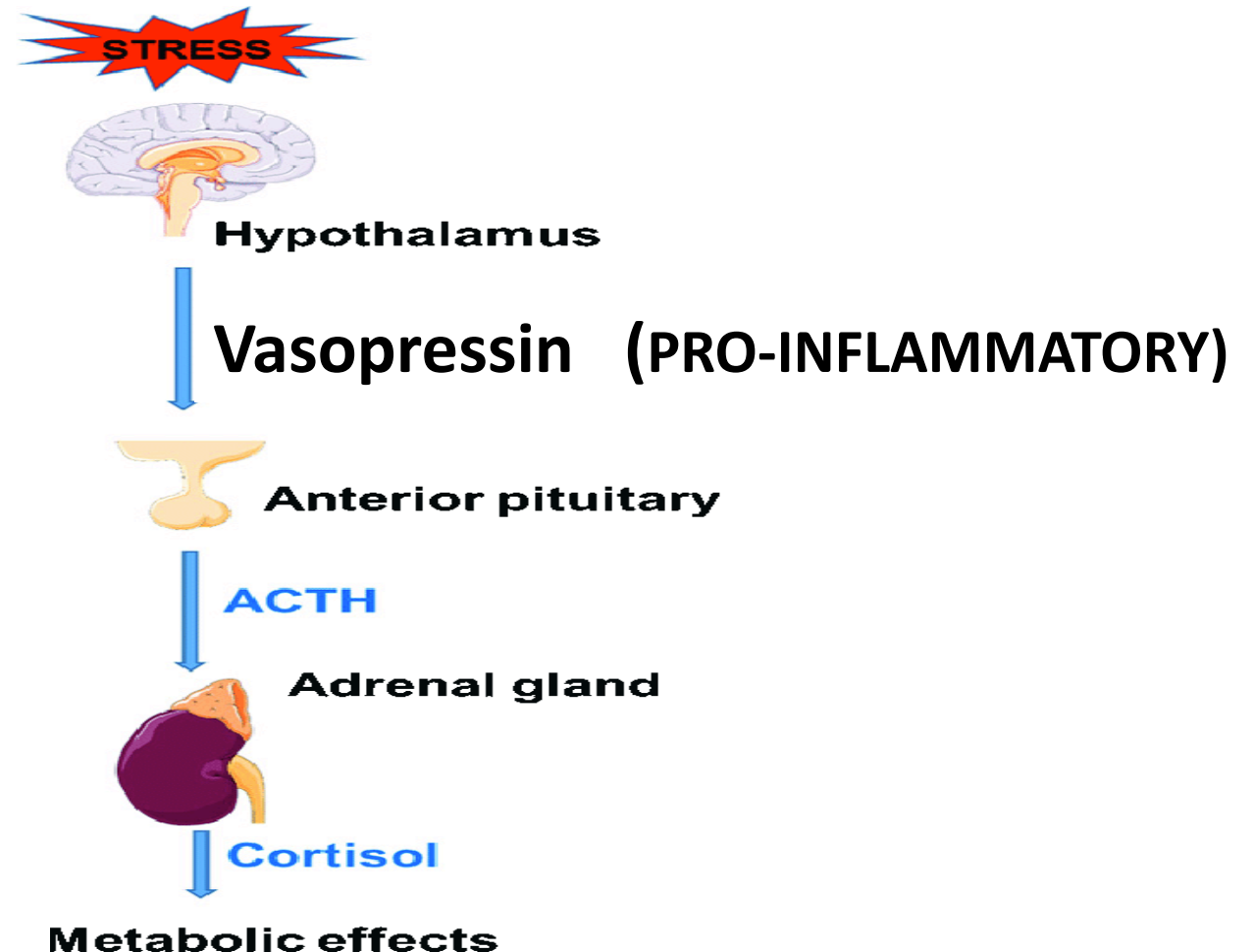
In CHRONIC stress GC receptors in the brain downregulate the release of CRF. In addition, Urocortins (similar to CRF) also can downregulate the HPA axis, allowing recovery after a stressor.



In **MALES** during **CHRONIC STRESS**, **vasopressin** may dominate the HPA response allowing new stressors to be managed like an acute stressor -
(Permitting fight and flight vs shut-down?)

VASOPRESSIN

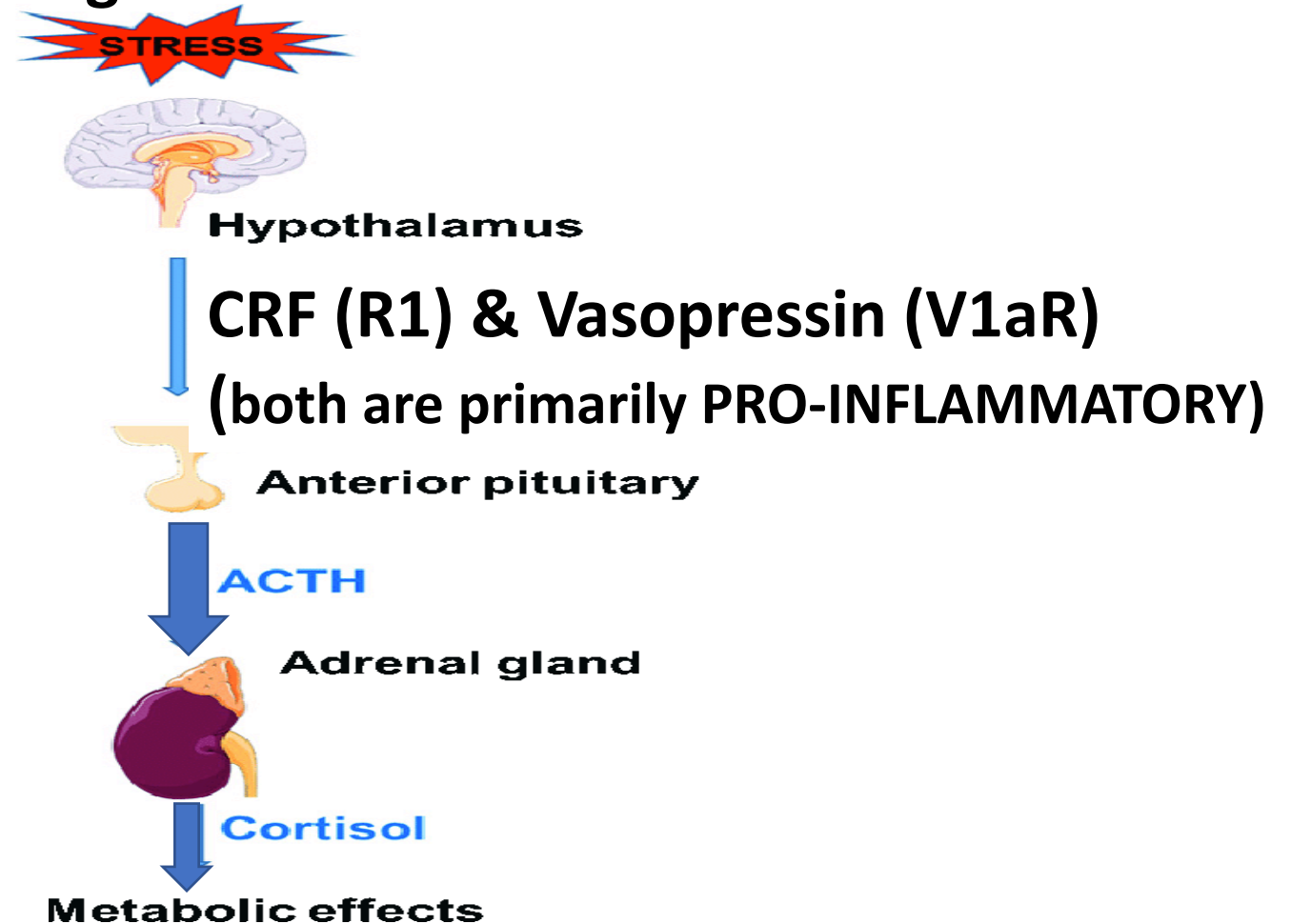
- May increase **CHRONIC PAIN??**
- A neuropeptide produced in the Hypothalamus.
- Is associated with **MOBILIZATION, ANXIETY** and **DEFENSIVE AGGRESSION**
- **ACTIVATES** the **SYMPATHETIC NERVOUS SYSTEM**
- **PRO-INFLAMMATORY**
- Is androgen-dependent in hypothalamus



VASOPRESSIN can amplify the effects of CRF, and may be of particular relevance to **SOCIAL** stress and allowing **ACUTE** responses even during chronic stress?

It is possible that the amplifying effects of vasopressin on CRF are of greater consequence in males, but the combination could contribute to **CHRONIC PAIN**?

OXYTOCIN may inhibit the effects of CRF & vasopressin in both males and females, allowing Cues of **SOCIAL SAFETY** to **INHIBIT FEAR, INFLAMMATION AND PAIN**??



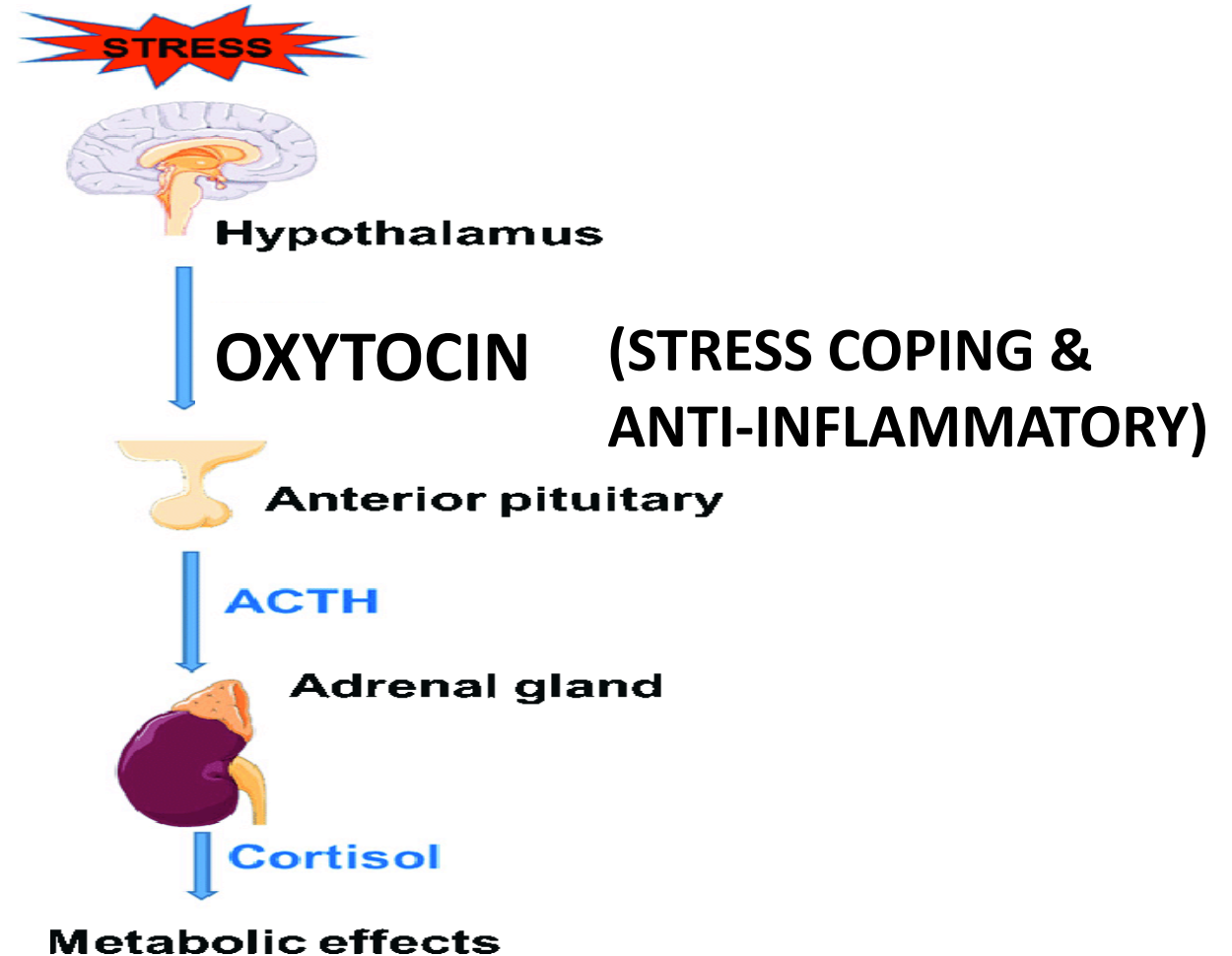
In **FEMALES** during **ACUTE or CHRONIC STRESS**,
OXYTOCIN is released and may moderate the effects of stress.
(CRF is NOT inhibited by negative feedback in females.)

OXYTOCIN (OT) is associated with:

- Perceived **SOCIAL SAFETY**.
- Increased **SOCIAL ENGAGEMENT** incl.
- Activation of the **VAGUS** nerve
- **ANALGESIA** (Reduced pain)
- **ANTI-INFLAMMATION**
- Increases **GABA_A** activation

ESTROGEN, esp **ER β** (inc effects of OT)

- Increases **OT synthesis**
- Increases **OT receptors expression**



HPA axis model for COPING with CHRONIC STRESS

(May be more powerful in FEMALES)

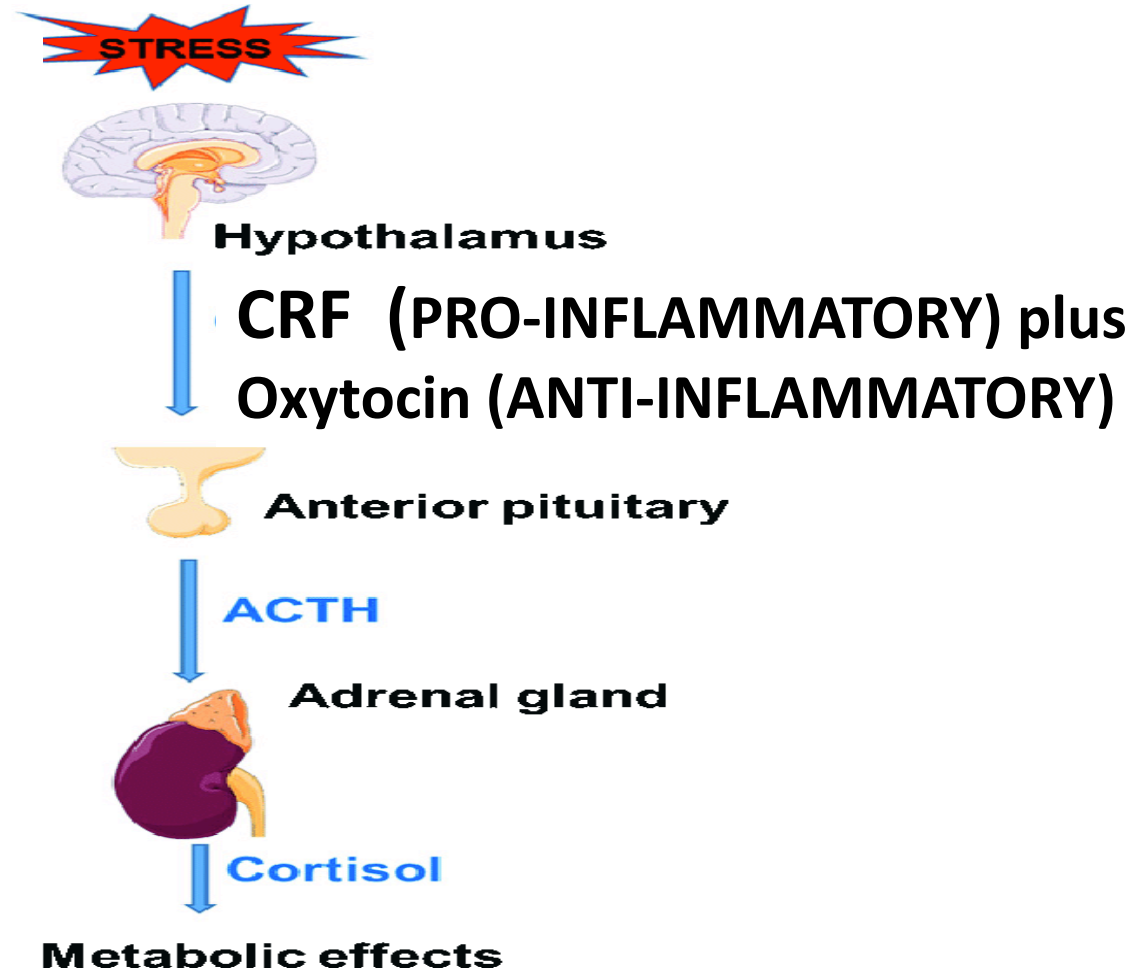
CRF = CORTICOTROPIN RELEASING FACTOR
and
OXYTOCIN (stress-coping)

OXYTOCIN (OT) is associated with:

- Perceived SOCIAL SAFETY.
- Increased SOCIALITY
- Activation of the VAGUS nerve
- ANALGESIA (Reduced pain)
- ANTI-INFLAMMATION
- Increases GABA_A activation

ESTROGEN (inc effects of OT – dec stress rx)

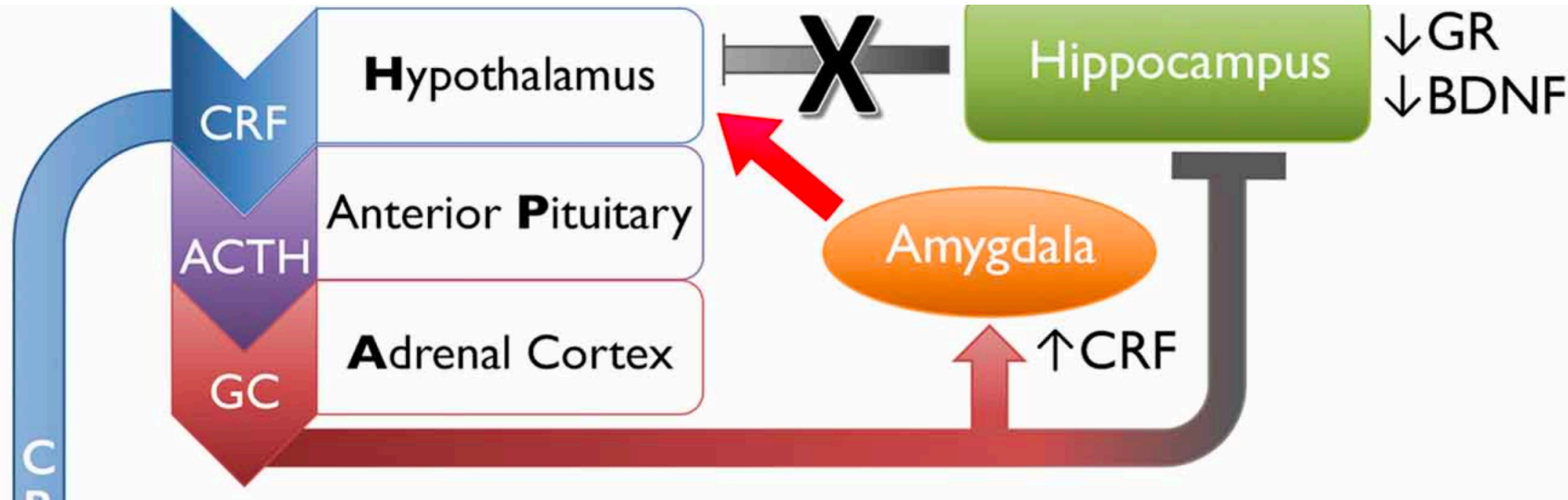
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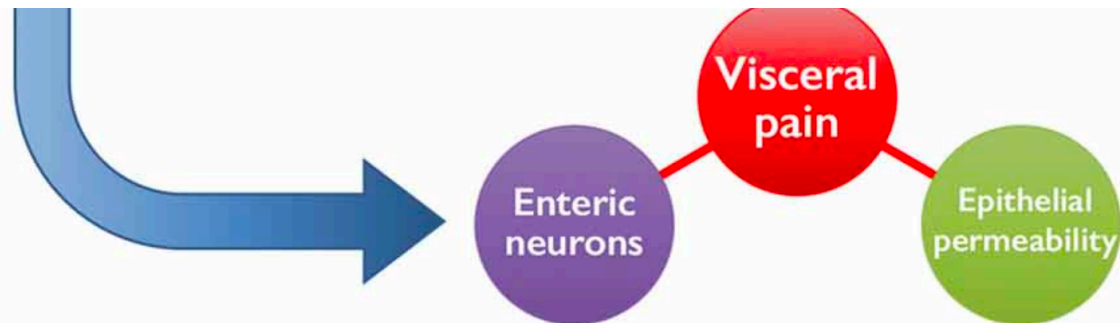
CORTICOTROPIN RELEASING FACTOR MAY MEDIATE THE EFFECTS OF CHRONIC STRESS ON VISCERAL PAIN

From Fuentes and Christianson, Frontiers in Systems Neuroscience 2018

Influence of early life experience on visceral pain



**EARLY LIFE ADVERSITY CREATES VULNERABILITY TO LATER CHRONIC PAIN,
DOWN-REGULATES THE OXYTOCIN SYSTEM
AND UPREGULATES THE VASOPRESSIN AND CRF SYSTEMS.
THIS IS A PLAUSIBLE SOURCE OF INDIVIDUAL AND SEX DIFFERENCES.**

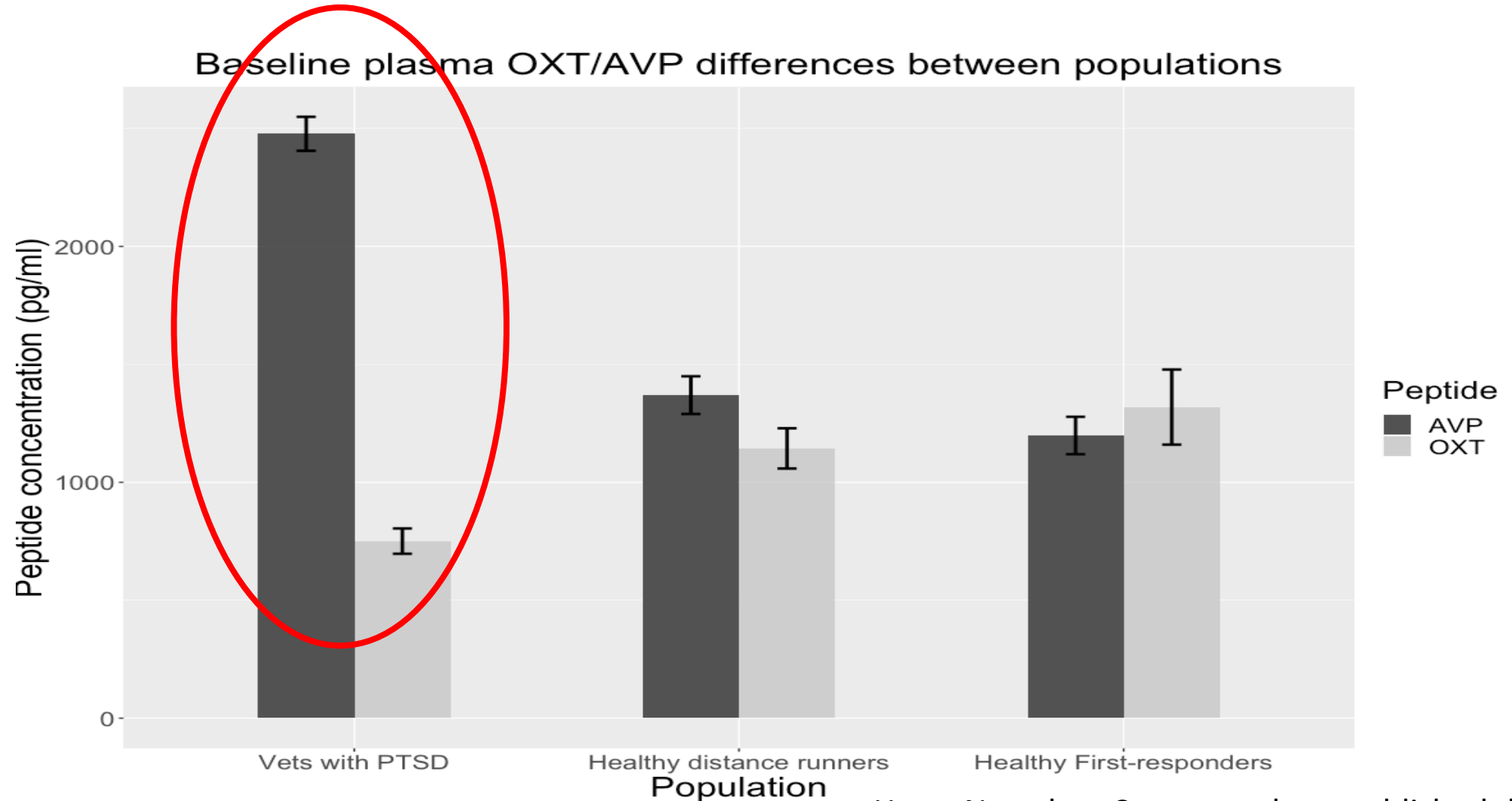


One example:

PTSD patients (vets) had LOW OXYTOCIN AND HIGH VASOPRESSIN (in plasma).

Non-patients (first responders in SWAT training) or

Healthy runners doing an Ultramarathon did not show this pattern, even under extreme acute stress.



Horn, Nazarloo, Carter, et al., unpublished data 2020

“Nothing is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.”

Marie Curie

