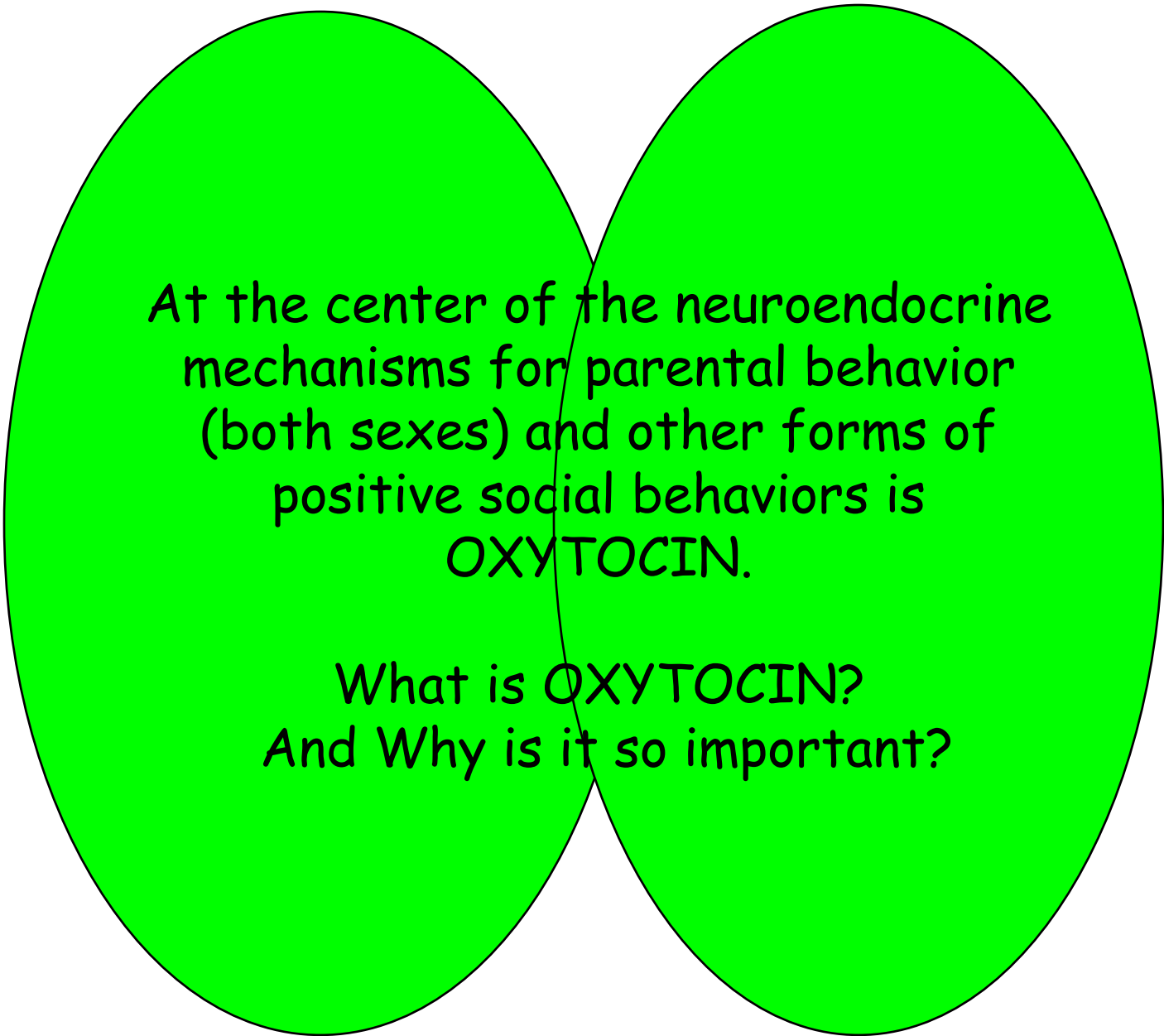


Oxytocin and Early Experience

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University of Illinois at Chicago



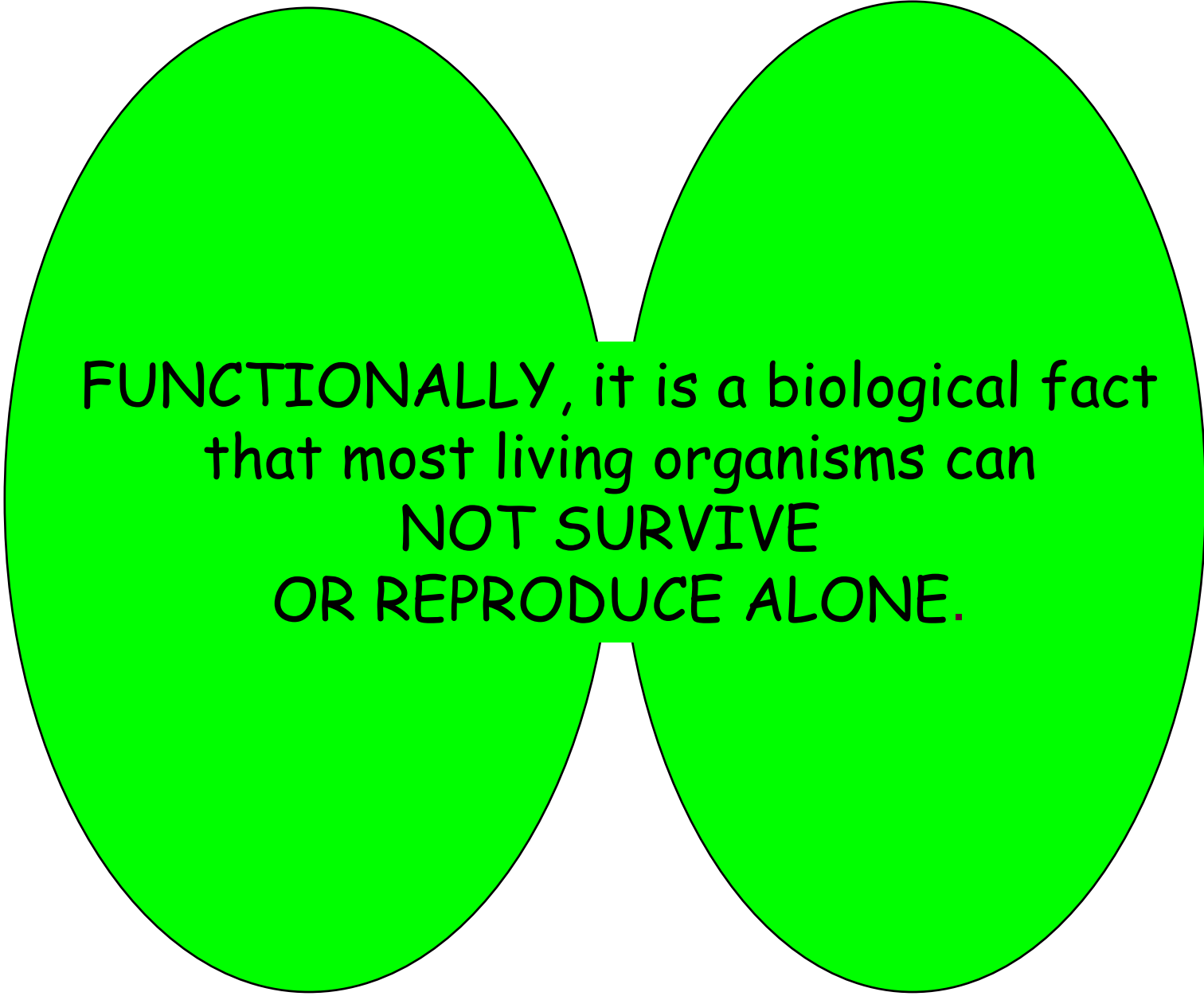
At the center of the neuroendocrine mechanisms for parental behavior (both sexes) and other forms of positive social behaviors is OXYTOCIN.

What is OXYTOCIN?
And Why is it so important?

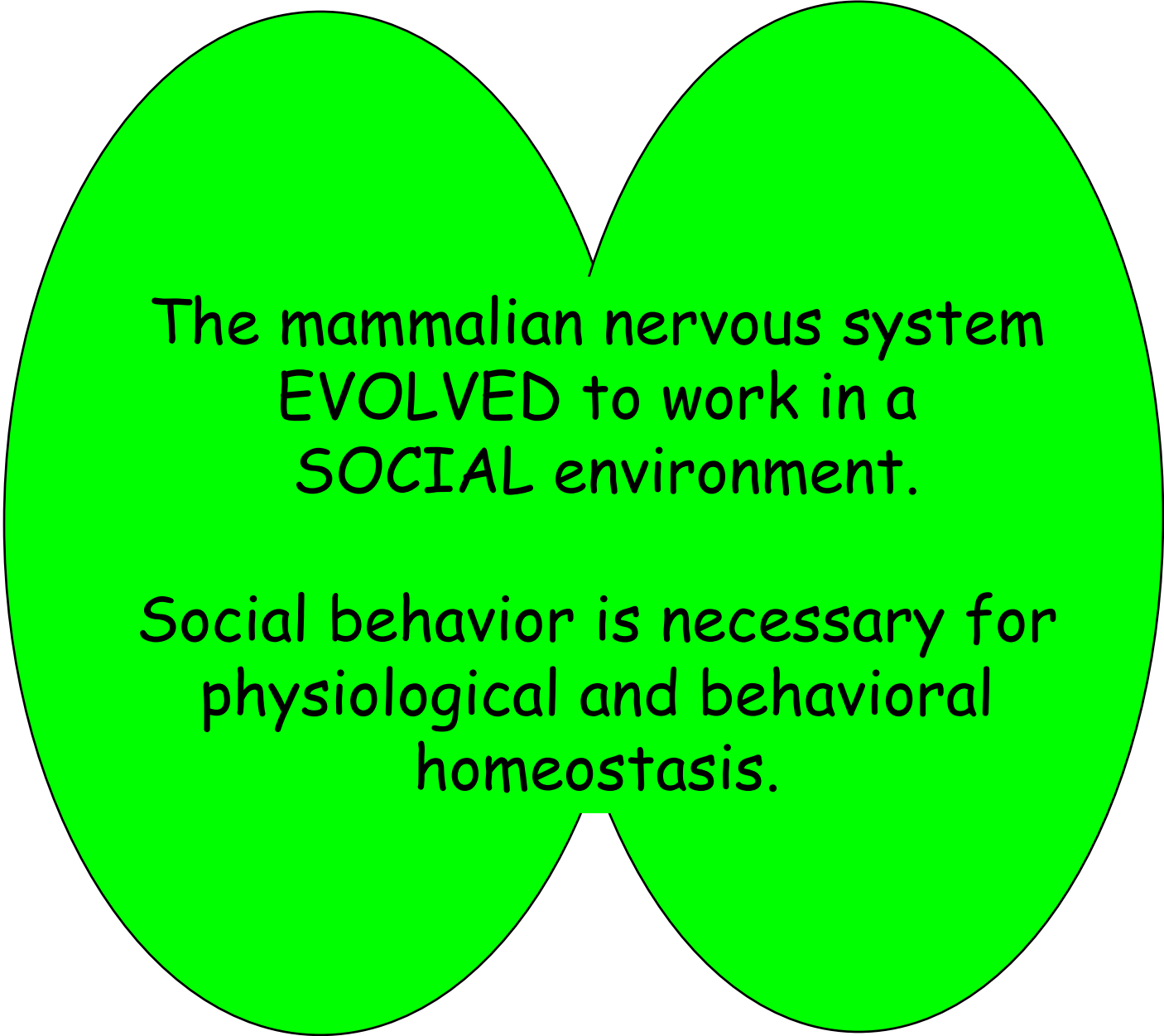
To understand Oxytocin -
HISTORICAL,
FUNCTIONAL,
EVOLUTIONARY
POINTS OF VIEW
ARE PROVING
HELPFUL



HISTORICALLY,
the most common
unit of analysis
and treatment
has been the
INDIVIDUAL.

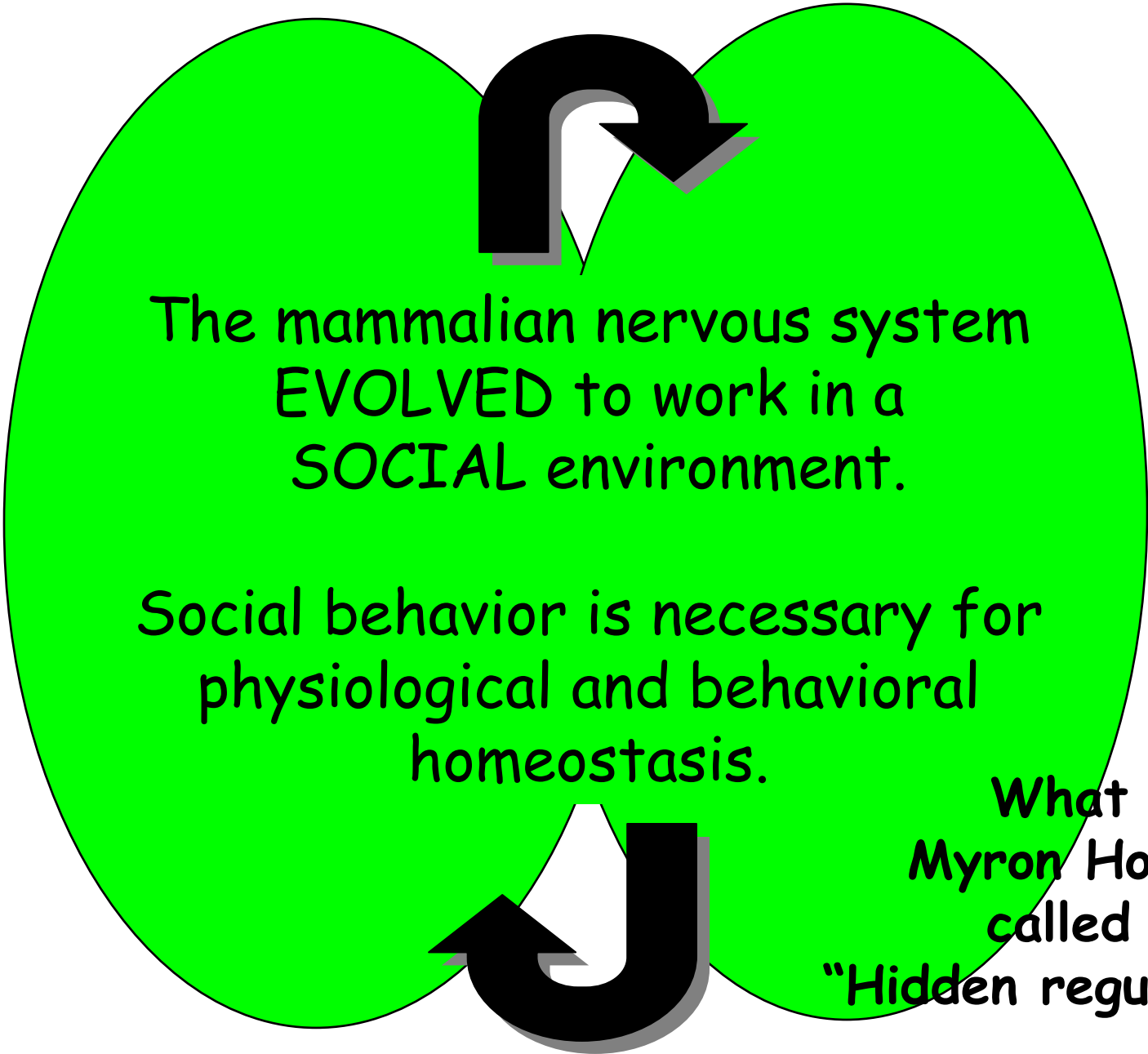


FUNCTIONALLY, it is a biological fact
that most living organisms can
NOT SURVIVE
OR REPRODUCE ALONE.



The mammalian nervous system
EVOLVED to work in a
SOCIAL environment.

Social behavior is necessary for
physiological and behavioral
homeostasis.



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What
Myron Hofer
called
"Hidden regulators"

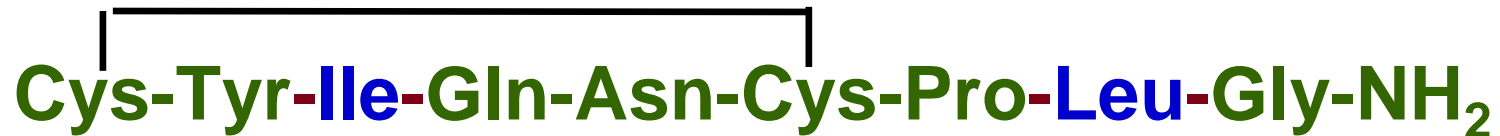
In the ABSENCE
of appropriate
social interactions
& social bonds
(i.e. ISOLATION)

-

Substitutions
May occur

Abuse of
Drugs
Food,
Mental
Dysfunction,
?

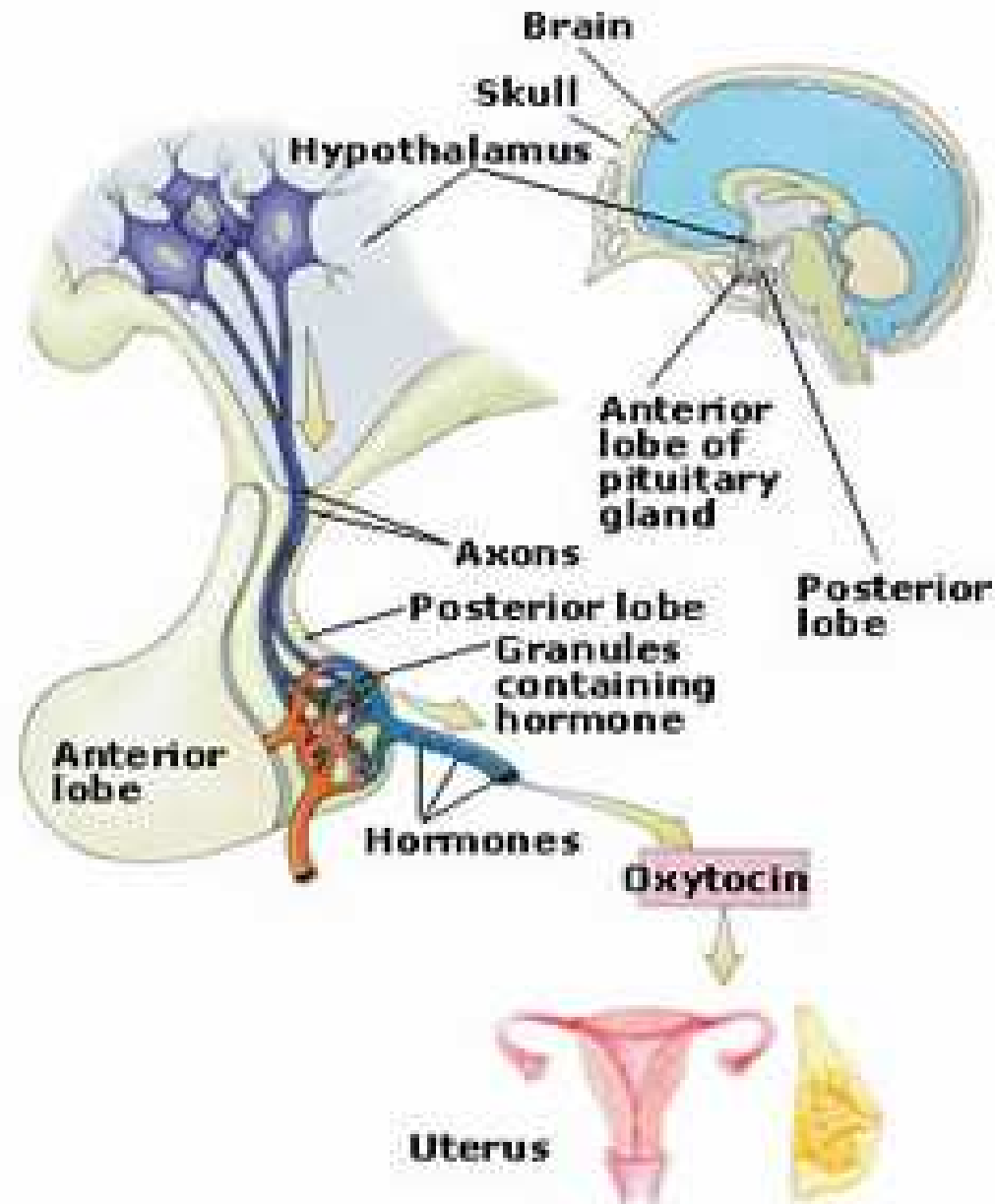
OXYTOCIN



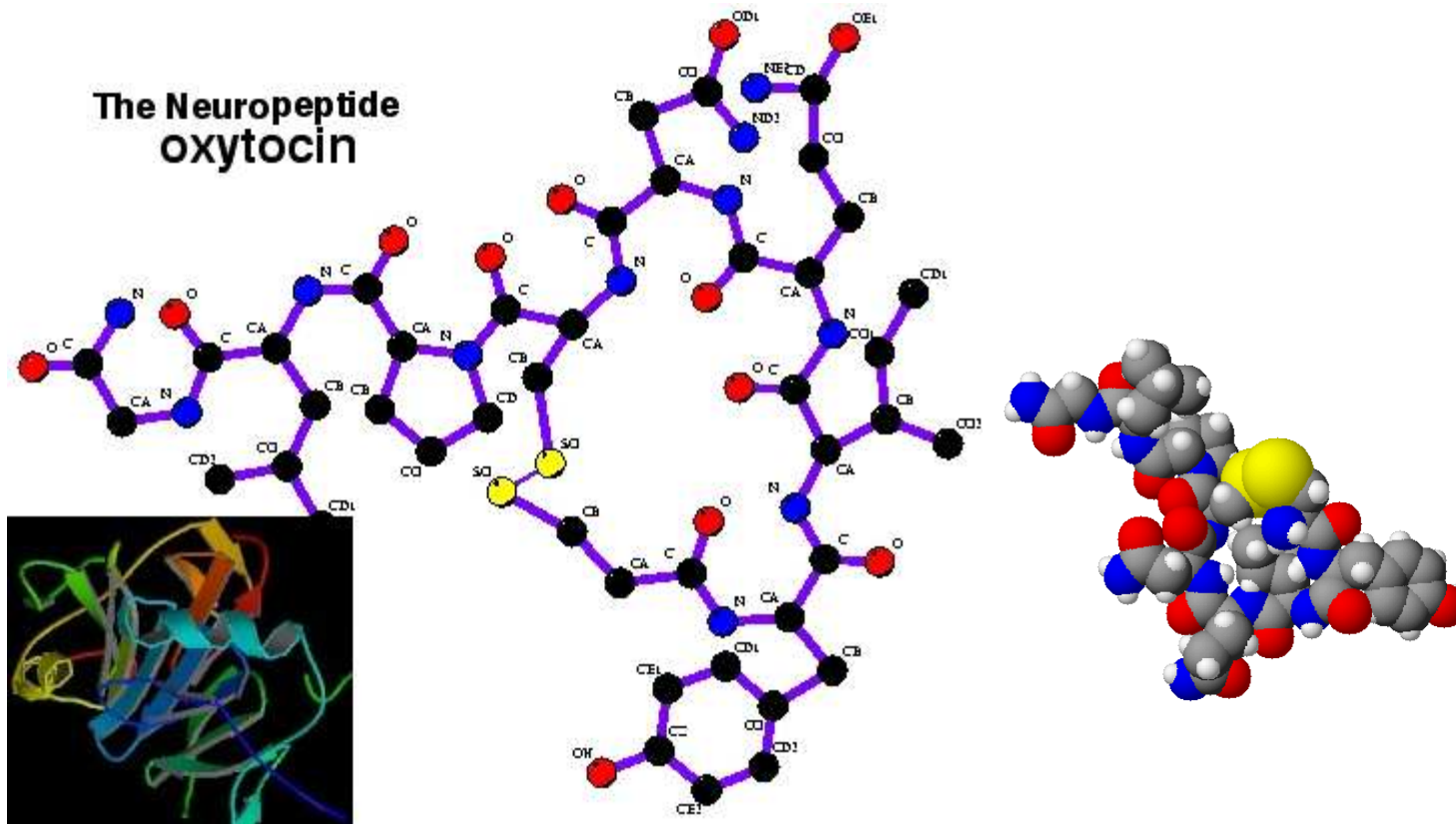
9 amino acids configured as a ring and a tail

Oxytocin was classically viewed as a "FEMALE REPRODUCTIVE" Hormone, Acting primarily On the UTERUS And MAMMARY GLAND.

This is only part of the story!



Oxytocin is also central to understanding the biology of social behavior, social bonds and social support, and sexual behavior.



Oxytocin does not act alone - for example,
OXYTOCIN has a sibling hormone -
VASOPRESSIN - from which it
differs by 2 (of 9) amino acids

OXYTOCIN (OT)

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

Arginine VASOPRESSIN (AVP)

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

Lactation is an important natural model for understanding the neurobiology of social bonding, and other forms of "love," as well as the biology of oxytocin

During the postpartum period
modern women may elect to

EITHER LACTATE OR NOT...

Lactating women experience many changes in the
MATERNAL BRAIN and other aspects of maternal
physiology and behavior.

Women who do not lactate (bottle-feeding) are
exposed to **LOWER** amounts of **OXYTOCIN**, as well as
changes in a host of other hormones.

Lactation, mediated in part by **OXYTOCIN**, may allow a new mother to manage stress more effectively.

Buffer between the physiological state of pregnancy & the postpartum period - possibly in part through effects of **OXYTOCIN**.

During lactation women are generally less reactive to many types of stressors, including exercise and psychosocial stressors.

ENDOGENOUS OXYTOCIN is

1. made primarily in the brain (hypothalamus) & released into the blood supply at the posterior pituitary from which it acts on the uterus (birth) and Mammary tissue (milk ejection)

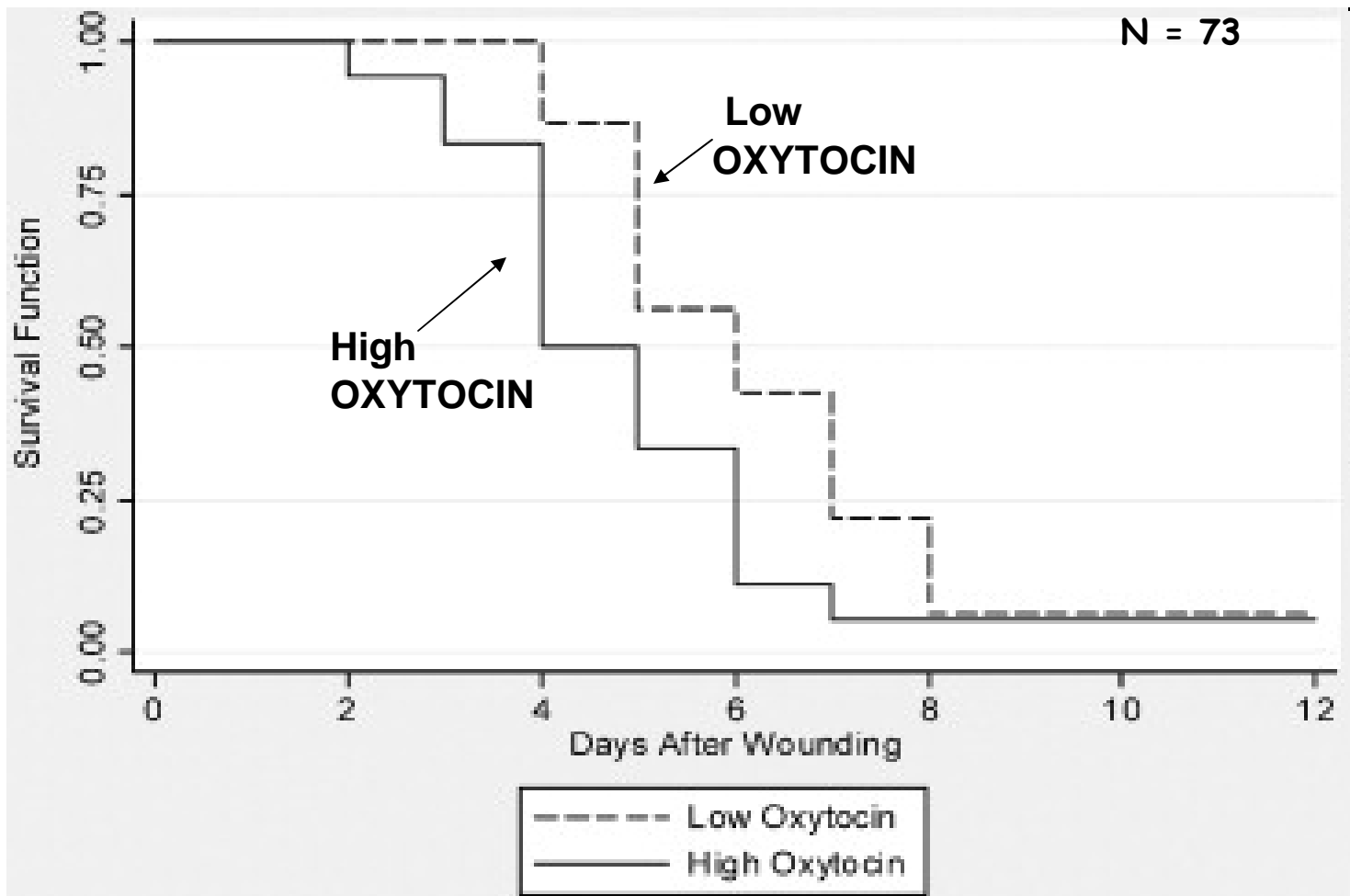
2. also released into the brain & spinal cord where it binds to OXYTOCIN receptors (OTRs) to influence behavior & physiology

3. possibly a major factor in the body's capacity to PROTECT or HEAL in the face of either emotional or physical challenge/stress.

4. capable of healing - partial list
injured skin (burns),
heart (cardiac infarct)
breast cancer
bone (osteoporosis)
intestines (intestinal bowel disease)
brain (stroke)
mental disorders (anxiety, depression
autism, schizophrenia)

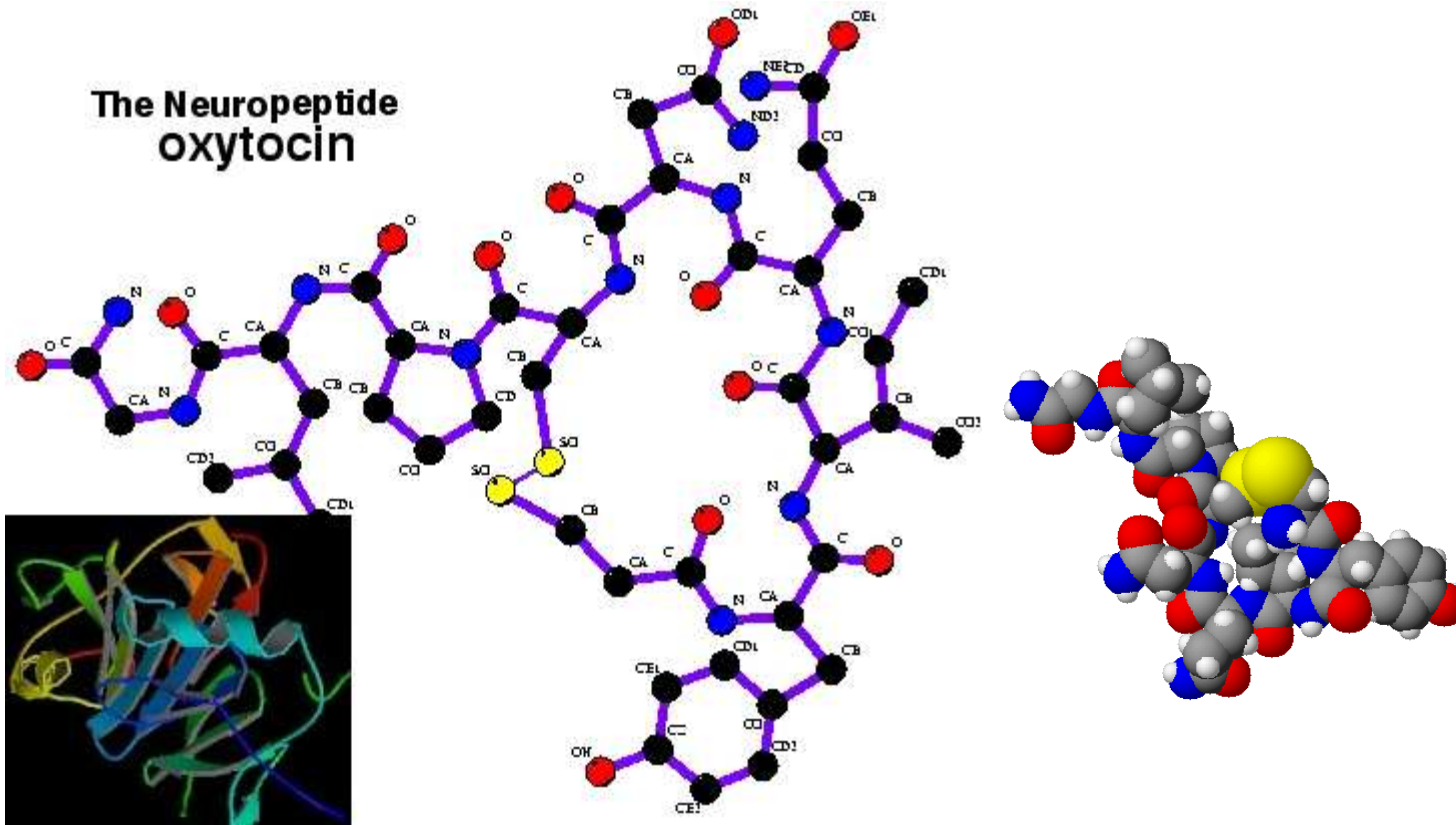
5. Oxytocin is an anti-inflammatory and anti-oxidant

WOUND HEALING of small blisters
was faster in individuals with
HIGH levels of **ENDOGENOUS OXYTOCIN**.
(Gouin, Carter, Kiecolt-Glaser, et al., 2010, PNEC)

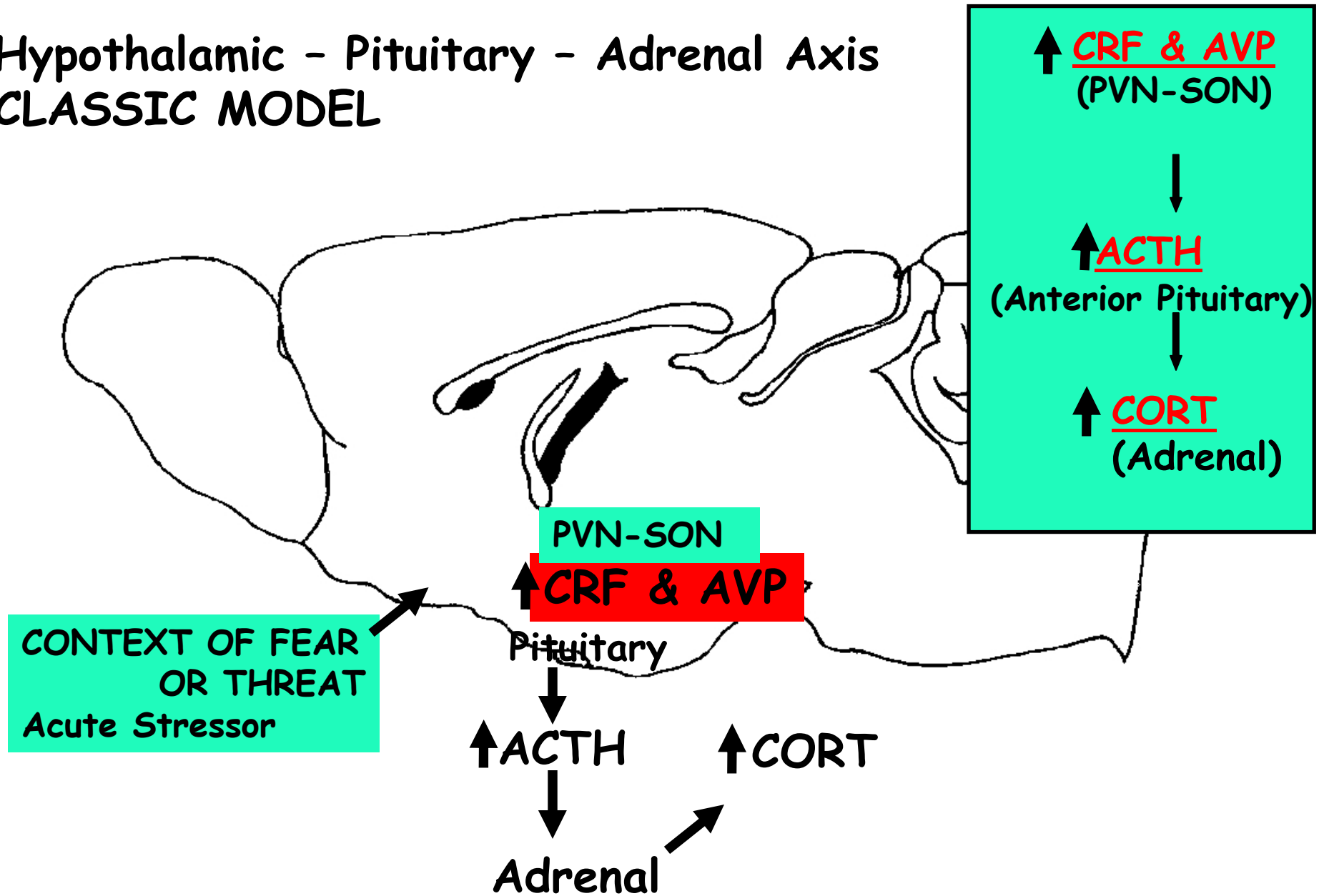


WHAT ARE THE MECHANISMS and NEURAL SYSTEMS THROUGH WHICH OXYTOCIN WORKS?

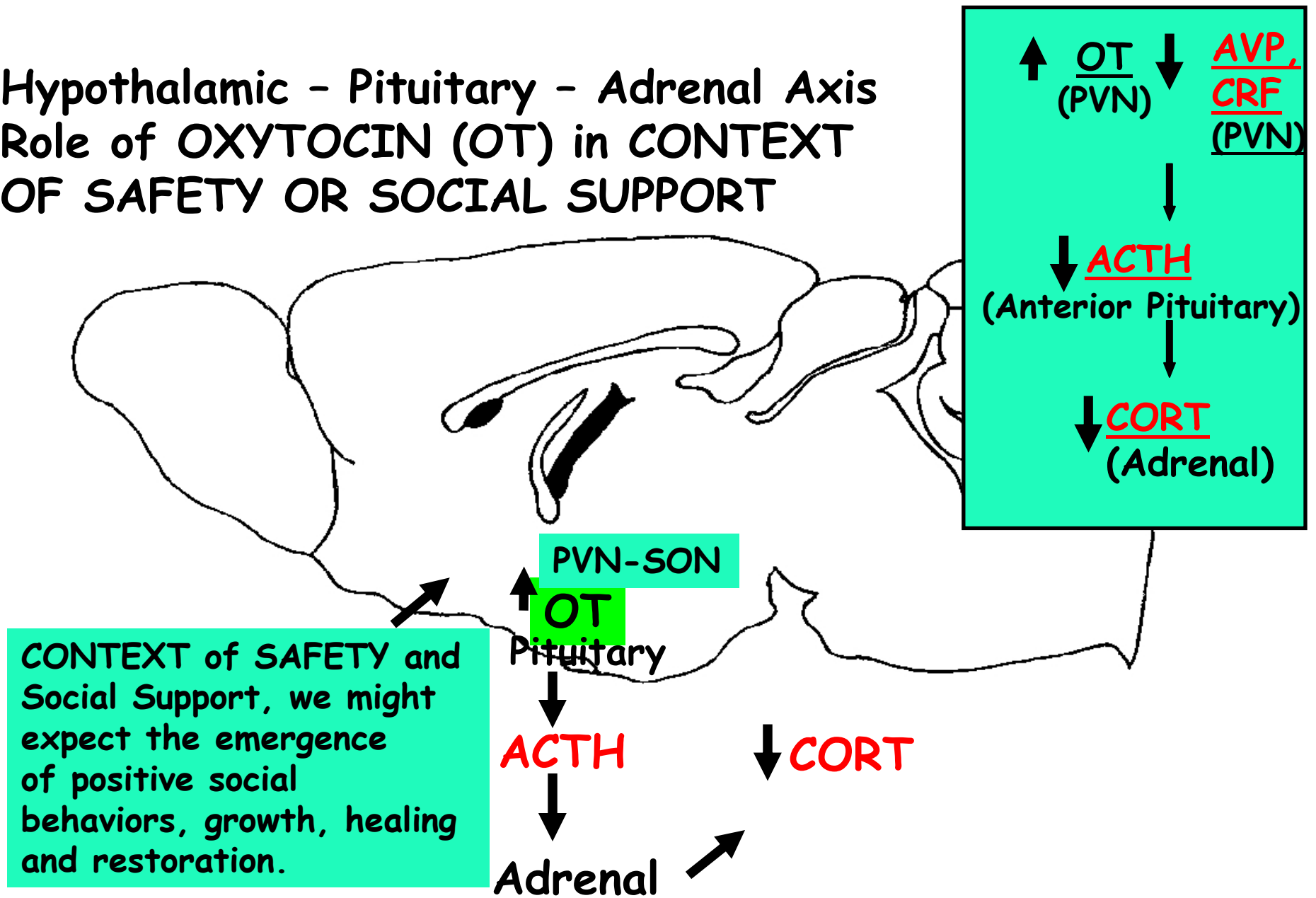
The Neuropeptide
oxytocin



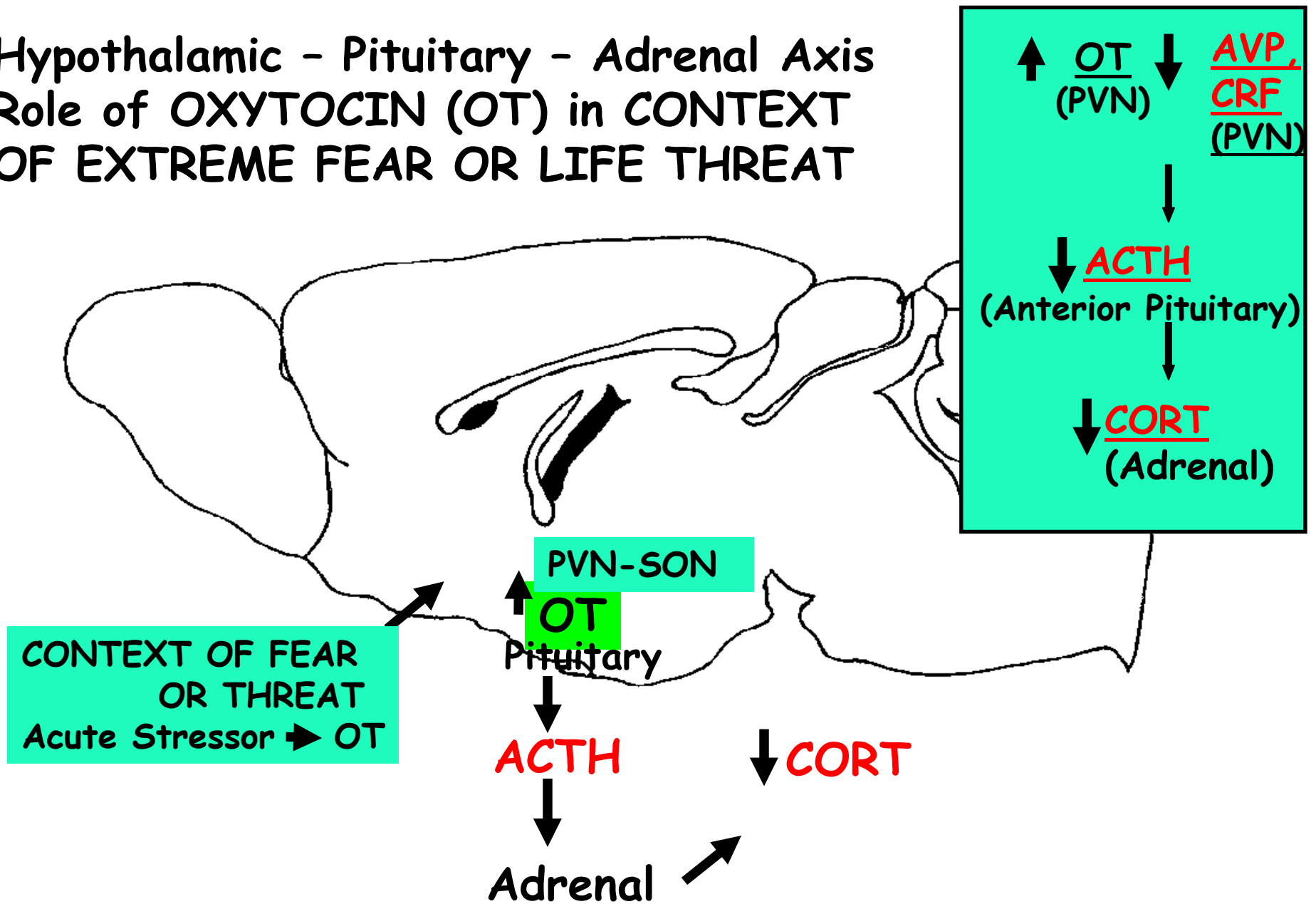
Hypothalamic - Pituitary - Adrenal Axis CLASSIC MODEL



Hypothalamic - Pituitary - Adrenal Axis Role of OXYTOCIN (OT) in CONTEXT OF SAFETY OR SOCIAL SUPPORT



Hypothalamic - Pituitary - Adrenal Axis Role of OXYTOCIN (OT) in CONTEXT OF EXTREME FEAR OR LIFE THREAT



Inherent in the concept of
MONOGAMY or at least
SOCIAL MONOGAMY is

**Selective and Long-lasting Social
Behavior usually between
one male and one female - or in
other words SOCIAL BONDS**

WHAT IS MONOGAMY???

A SOCIAL SYSTEM, including the capacity of individuals to form SOCIAL BONDS.

Inherent in the concept of monogamy are selective social behaviors, social bonds as well as biparental care (i.e. both parents care for young).

SEXUAL EXCLUSIVITY?

Seen in some but not all individuals. There is not much evidence for this at the species level.

FEATURES OF PRAIRIE VOLE BEHAVIORAL BIOLOGY (SOCIAL MONOGAMY)

HIGH LEVELS OF SOCIAL CONTACT and
DEPENDENCE ON SOCIAL INTERACTION

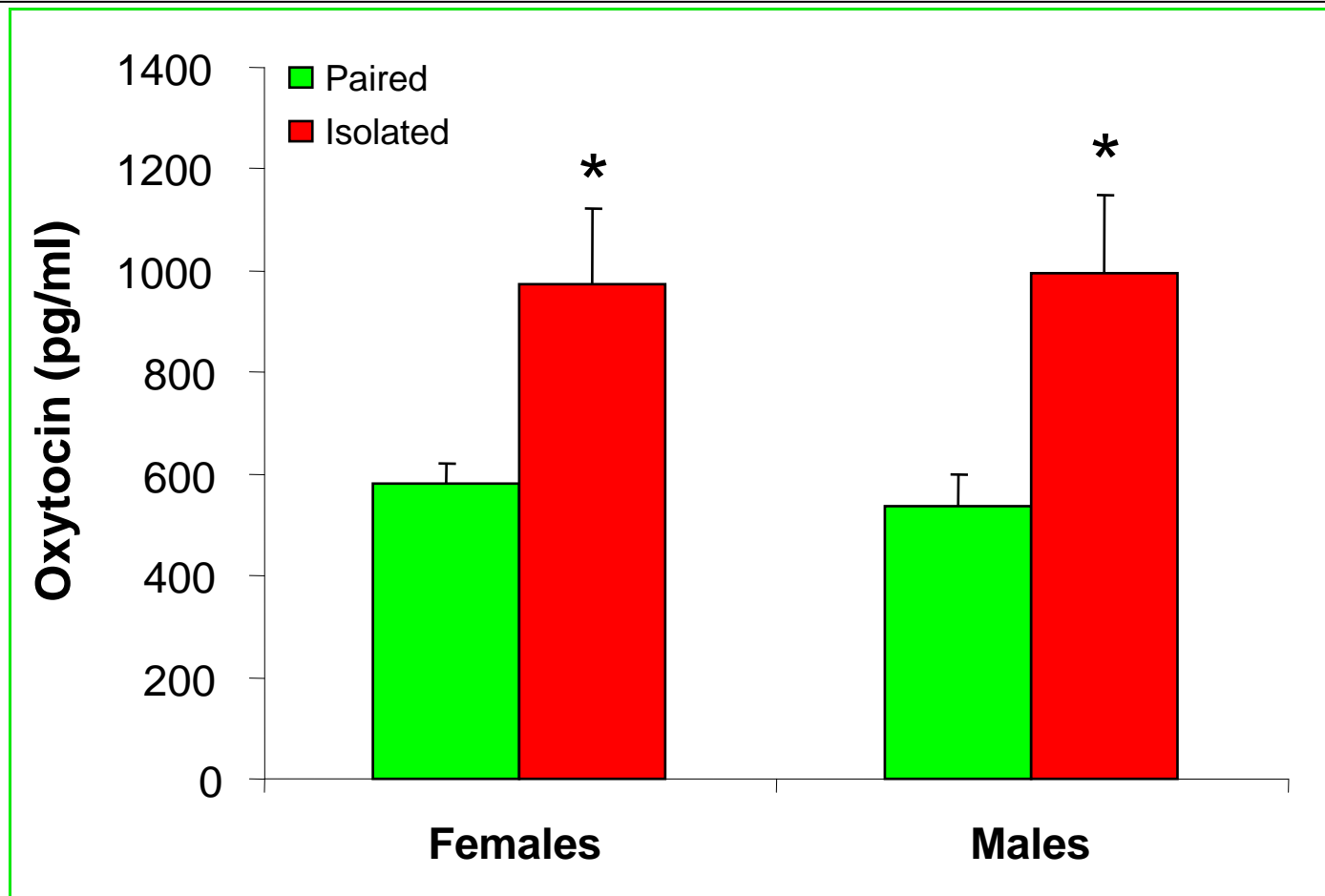
PAIR BONDING (male-female)

BIPARENTAL CARE OF YOUNG and
ALLOPARENTING (baby sitting)

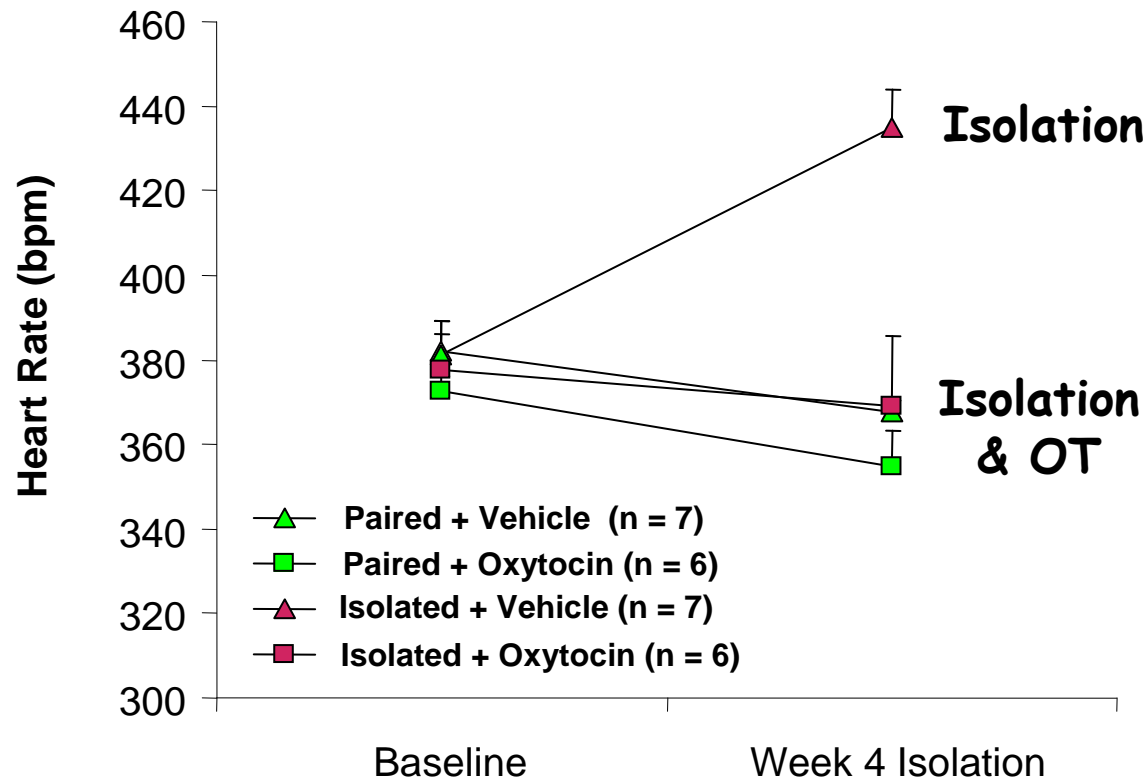
HIGH LEVELS OF OXYTOCIN

HUMAN-LIKE AUTONOMIC NERVOUS SYSTEM,
WITH HIGH LEVELS OF VAGAL TONE
(Parasympathetic activity- helping to explain in part why
social interactions and social bonds play a critical role in
emotional regulation)

Under stressful conditions oxytocin may be released.
Probably providing stress buffering, including
physiological and emotional compensation against the
effects of the stressor.



Oxytocin treatment (14 days, sc) reversed or prevented the adverse effects of isolation on heart rate (also on measures of anxiety and "depression")



ADVERSITY IN EARLY LIFE, including NEGLECT

Early Experience/
Handling

Behavior in Later Life

Excessive
Manipulation
/Stimulation
Of Parent
Or Offspring

Reduced
Parental
Stimulation

Increased
Anxiety
In, esp
MALE
Offspring

Reduced
Alloparental
Or Other
Social
Behaviors
Esp in
MALES

Endogenous OXYTOCIN (esp in FEMALES)
May allow females to adapt using a
passive strategy

Endogenous VASOPRESSIN (esp in MALE)
May allow males to adapt using a more
ACTIVE strategy

As a starting point in the study of the possible developmental effects of OXYTOCIN we used the prairie vole model...

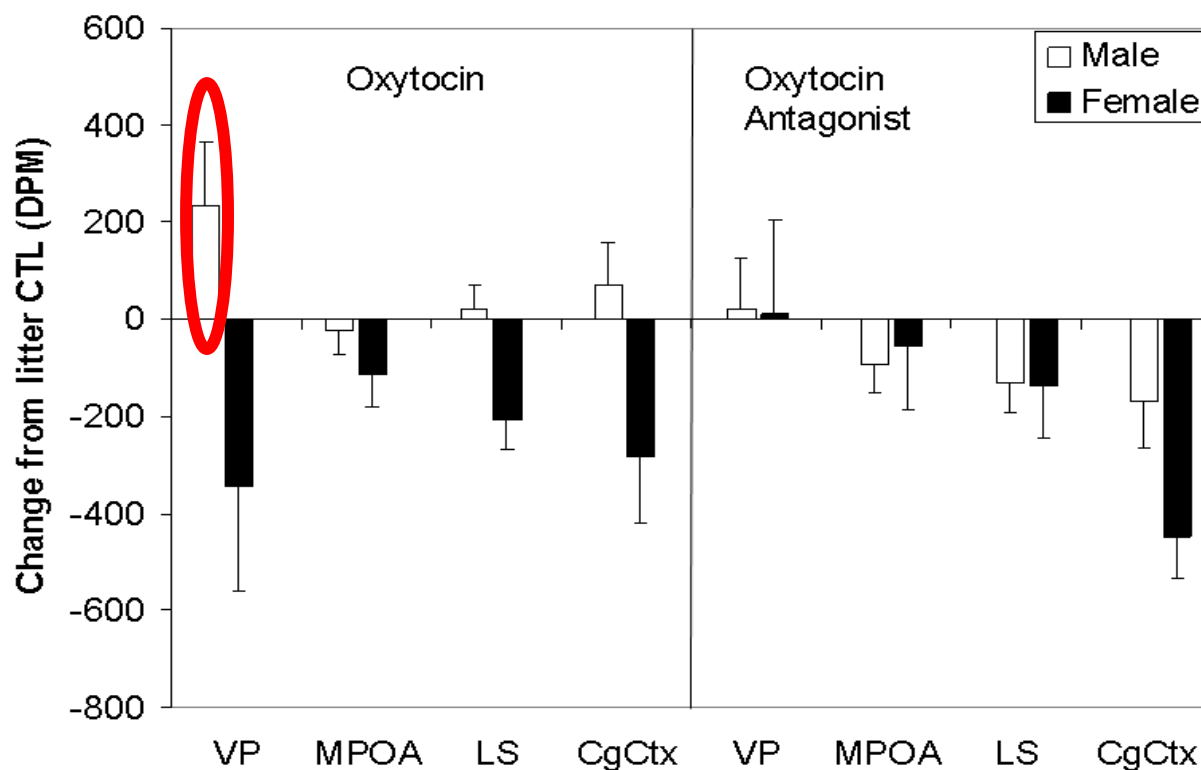
We focused on the effects on newborn infants of direct exposure to OXYTOCIN (injecting pups).

On postnatal day 1 animals female prairie voles were treated with a single injection (ip) of SALINE or OXYTOCIN at 3, 6, 12, or 24 ug

And tested for the capacity to show selective social behavior (for pair bonds) in ADULTHOOD

The effects of NEONATAL exposure to a single OXYTOCIN treatment were dose-dependent.

Changes in V1aR following postnatal OT (3ug) or OTA (0.3ug) were **sexually dimorphic** and brain region specific.



Bales, et al., Neuroscience, 2007

Conclusions:

OXYTOCIN EXPOSURE PROGRAMS THE DEVELOPING NERVOUS SYSTEM and SUBSEQUENT BEHAVIOR with EFFECTS that are:

**Sexually dimorphic and
Dose dependent**

MALES - extra OT (at low doses) facilitated later social behavior (possibly through enhancement of vasopressin receptor binding in areas such as VENTRAL PALLIDUM)

FEMALES - extra OT (low doses) facilitated later social behavior (possibly by reducing vasopressin binding in areas implicated in anxiety and fear)

HIGH DOSES OF OT were also DISRUPTIVE to PAIR BOND formation. WHY?? To be continued.

Hypothesis:

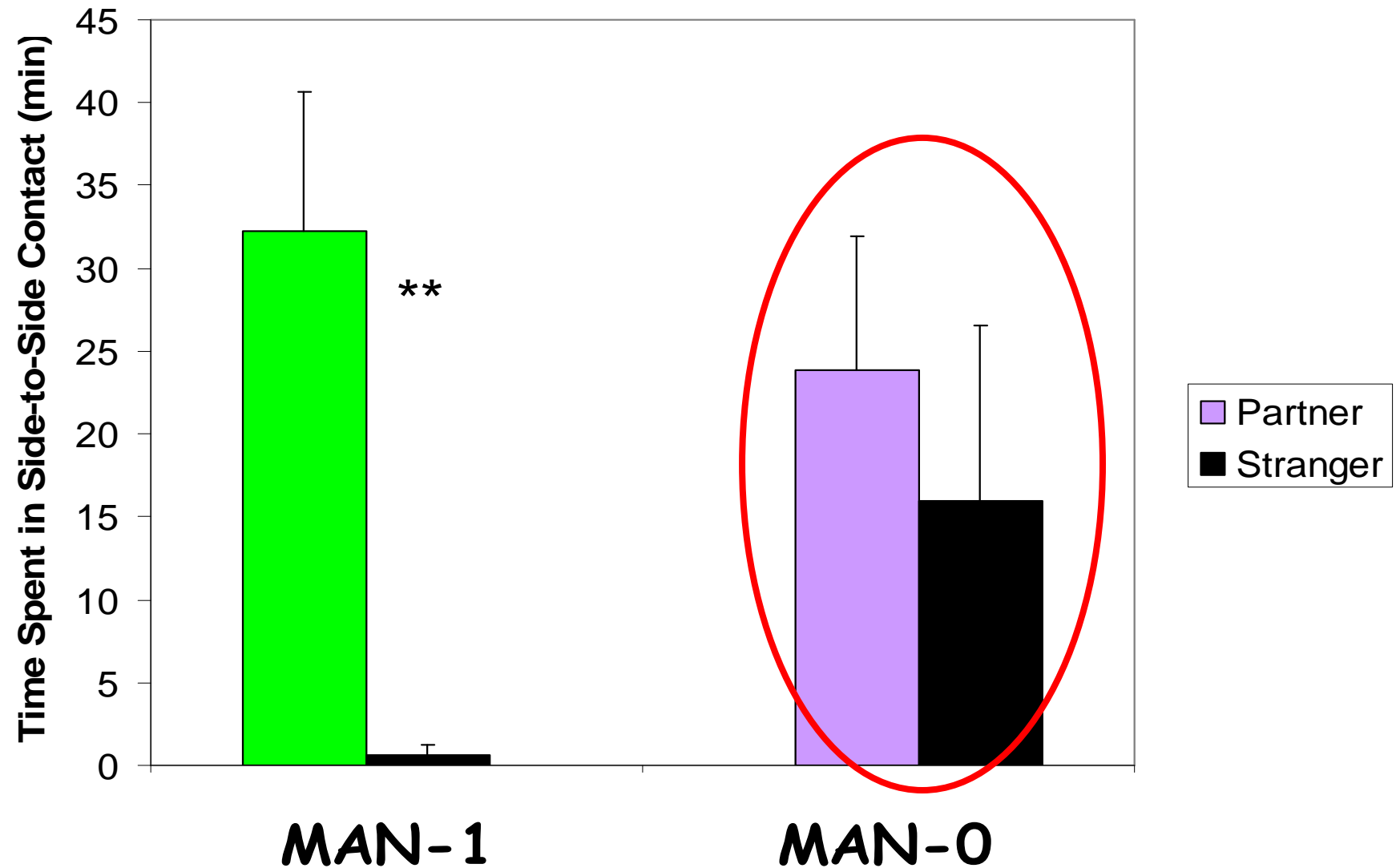
EARLY EXPERIENCE also may program the developing nervous system, possibly also through effects on systems that involve
OXYTOCIN and
VASOPRESSIN

This hypothesis is being examined in prairie voles, that receive varying amounts of early handling during the first few days of life.

Prairie Vole Handling Studies

- VERY simple paradigm - version #1
- During normal cage-cleaning, parents either picked up by hand ("MAN 1") or transferred in a cup ("MAN 0")
- NO OTHER MANIPULATION until after weaning (21 days)
- **Measures:**
 - Alloparental behavior (postweaning),
 - Pair bonding (partner preference behavior, adult),
 - Anxiety (indexed by the elevated plus maze)
 - Measures of various receptors
 - VASOPRESSIN - V1a
 - Oxytocin - OTR
 - Dopamine (D2)

Unmanipulated (MAN-0) **FEMALES** FAILED to develop pair bonds (as indexed by partner preferences)



(Bales, et al. Devel Psychobiol., 2007)

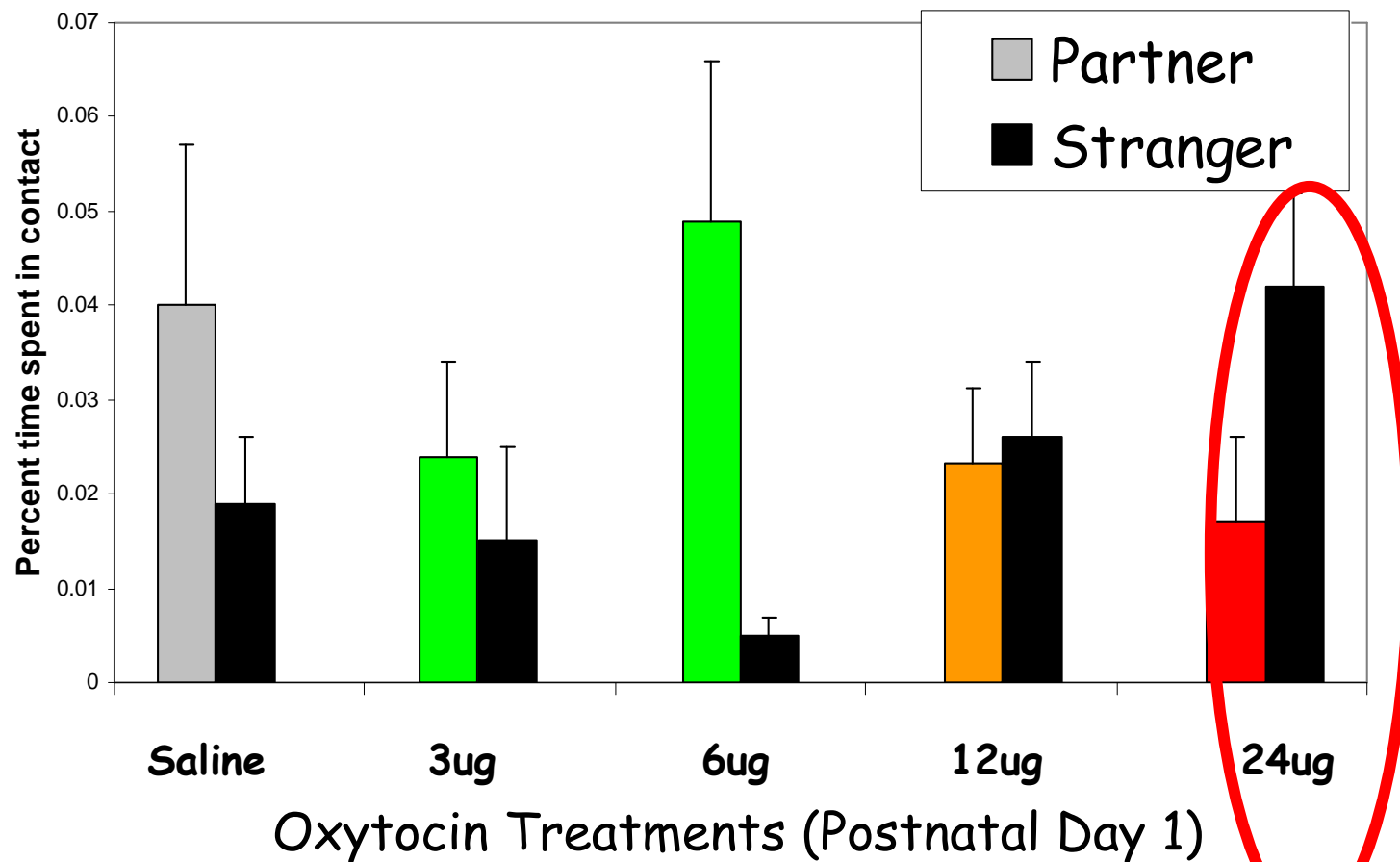
Behavioral and Cellular Mechanisms of Early Experience??

1. REDUCTIONS IN FEAR IN LATER LIFE allowing INCREASED SOCIALITY to emerge? MAN1 rearing
2. Increased Oxytocin receptors -
Nucleus Accumbens- shell (MAN0) FEMALES
BNST (MAN-1) BOTH MALES AND FEMALES
3. Increased Oxytocin peptide esp MAN1(x3)FEMALES
(May explain by MAN1(x3) females are less affected)
4. Vasopressin & V1a receptors - in progress...
- to be continued

WHAT HAPPENS TO PAIR BONDING IN FEMALE PRAIRIE VOLES EXPOSED TO NEONATAL OXYTOCIN?

Oxytocin Exposure on Postnatal Day 1 has a Dose-Dependent Effect on Partner Preference Formation in Adulthood.

(Moderate doses facilitate; High doses inhibit preference for the familiar partner and may even render the partner aversive?)



**EARLY EXPERIENCE AFFECTS
SOCIAL BEHAVIOR, ANXIETY,
OXYTOCIN PEPTIDE, &
EXPRESSION OF THE OXYTOCIN RECEPTOR
& THE ESTROGEN RECEPTOR**

For example, Early handling (moderate)

**Increases social behavior & pair bonding, but
Decreases OTR in the Nucleus accumbens (NAcc)
Decreases methylation of the OTR in NAcc
(possibly accounting for Decreased OTR)**

SEX DIFFERENCES ARE OFTEN NOT IDENTIFIED IN THE ABSENCE OF STRESSORS.

- * Male and female prairie voles do NOT usually differ in the distribution of either oxytocin or vasopressin receptors.
- * Also under optimal conditions BASAL OT is typically similar in males and females.

However,.... In the face of challenges or stressors..

MALES AND FEMALES DIFFER in their RESPONSES including to:

- * Manipulations of OT/AVP during early life.
- * Effects of early experience (handling, etc)
- * Chronic stressors, such as isolation

- * FEMALES protected by the synthesis and release of OT??

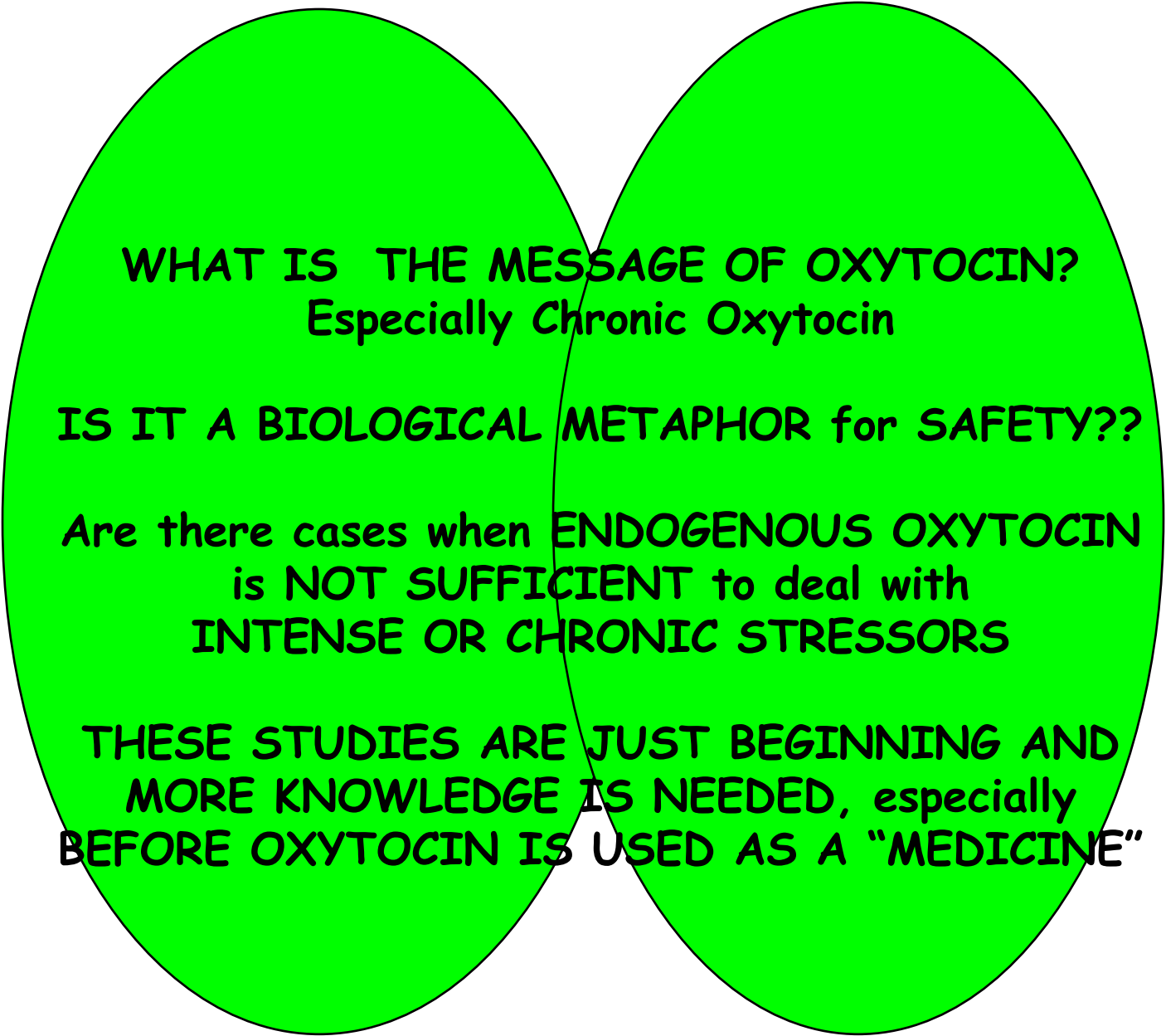
- * MALES also may be normally protected by OT and/or AVP, but may be especially dependent on and vulnerable to disruptions of OT or AVP, especially in early life - which may leave them more "anxious" and less capable of managing social challenges, modeled here by responses to infants (alloparenting).

WHAT IS OXYTOCIN??

A METAPHOR for SAFETY or SOCIAL SUPPORT, with HEALING PROPERTIES??

A component of compensatory responses including regulation of the parasympathetic nervous system, but also...

A compound widely used in Obstetrics to Facilitate or Induce labor and Prevent prevent bleeding



**WHAT IS THE MESSAGE OF OXYTOCIN?
Especially Chronic Oxytocin**

IS IT A BIOLOGICAL METAPHOR for SAFETY??

**Are there cases when ENDOGENOUS OXYTOCIN
is NOT SUFFICIENT to deal with
INTENSE OR CHRONIC STRESSORS**

**THESE STUDIES ARE JUST BEGINNING AND
MORE KNOWLEDGE IS NEEDED, especially
BEFORE OXYTOCIN IS USED AS A "MEDICINE"**

By understanding the causes and consequences of mammalian sociality and the "social nervous system," we are gaining a deeper understanding of the biology of human emotion, and natural factors, such as "social support" or "love" that contribute to human health and well being.

Because of the fundamental role of sociality in human behavior, concepts like "social support" or "social bonds" translate into to a sense of **SAFETY**. A concept that is at the heart of enduring relationships and most successful therapies - of all kinds. A perceived sense of safety is necessary to allow the body to grow, heal and restore itself in the face of the "stress of life".

SHOULD OXYTOCIN BE A MEDICINE??

Oxytocin is already available on the internet as an intranasal spray. It is NOT a controlled substance. It has NOT been evaluated by the FDA. We have NO information about the CHRONIC effects of exogenous oxytocin. (Chronic elevations in OT were associated with a down-regulation of OT receptors... Will this happen if OT is chronically used as a "medicine?" Probably!!)

However, used wisely it may have a role in medicine. Several drug companies are testing OT-based compounds for the treatment of autism, schizophrenia and other disorders.

Oxytocin (Pitocin) is routinely used during birth and in the postpartum period. We know essentially NOTHING about the consequences for the child or mother of these treatments.

OXYTOCIN IS ONE COMPONENT OF A COMPLEX NEUROENDOCRINE-AUTONOMIC SYSTEM. We must have a deeper knowledge of the natural regulation of this system, especially in early life.

Knowledge of ENDOGENOUS oxytocin may serve as a metaphorical Rosetta Stone for understanding natural healing.

I suggest we start there.