13 Jan 2022, Univ. Tokyo

Hormones and Behavior

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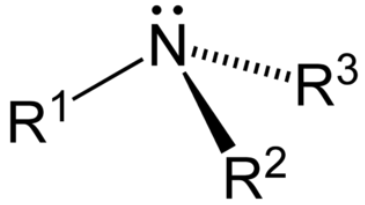
No COI to disclose

What are “hormones”?

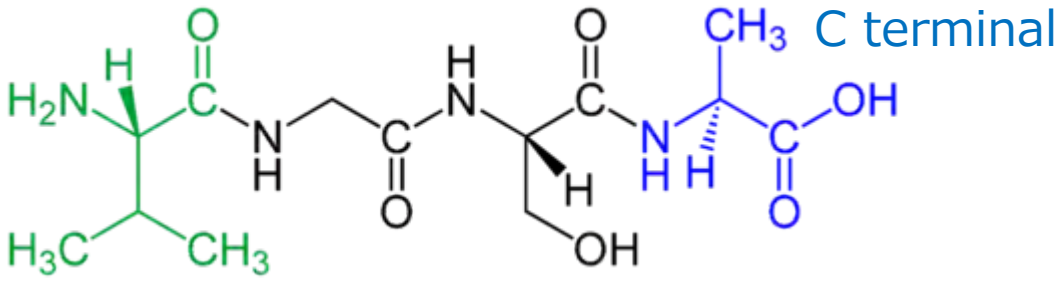
- Hormones are secreted by endocrine glands into the circulatory system. They are carried by circulation and bind the specific receptors in target organs to initiate a cellular response.
- Hormone receptors are on either cell surface or intracellular.
- Cell surface receptors for amine or peptides. Intracellular Receptor for steroids and thyroid hormones.

- Three classes of hormones based on their chemical nature:

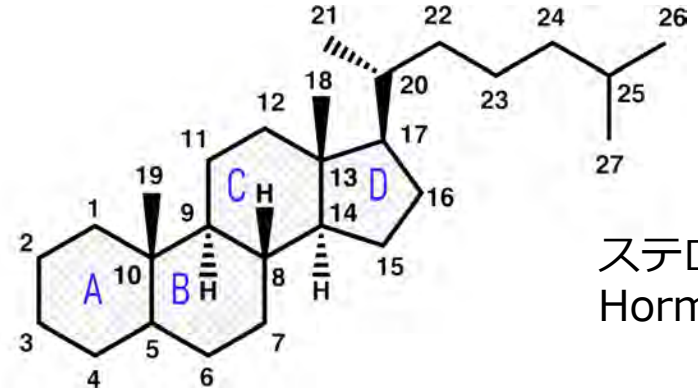
(1) amines; (2) peptides; (3) steroids



アンモニアの水素原子を炭化水素基または芳香族原子団で置換



4つのアミノ酸 (バリン-グリシン-セリン-アラニン) がペプチド結合でつながった tetrapeptide の一例



ステロイドの一例 Cholesterol (すべての steroid Hormone 合成の出発点)

In this lecture:

(1) we learn GnRH decapeptide, secreted by hypothamamic neurosecretory neurons, carried to anterior pituitary via pituitary portal circulation.

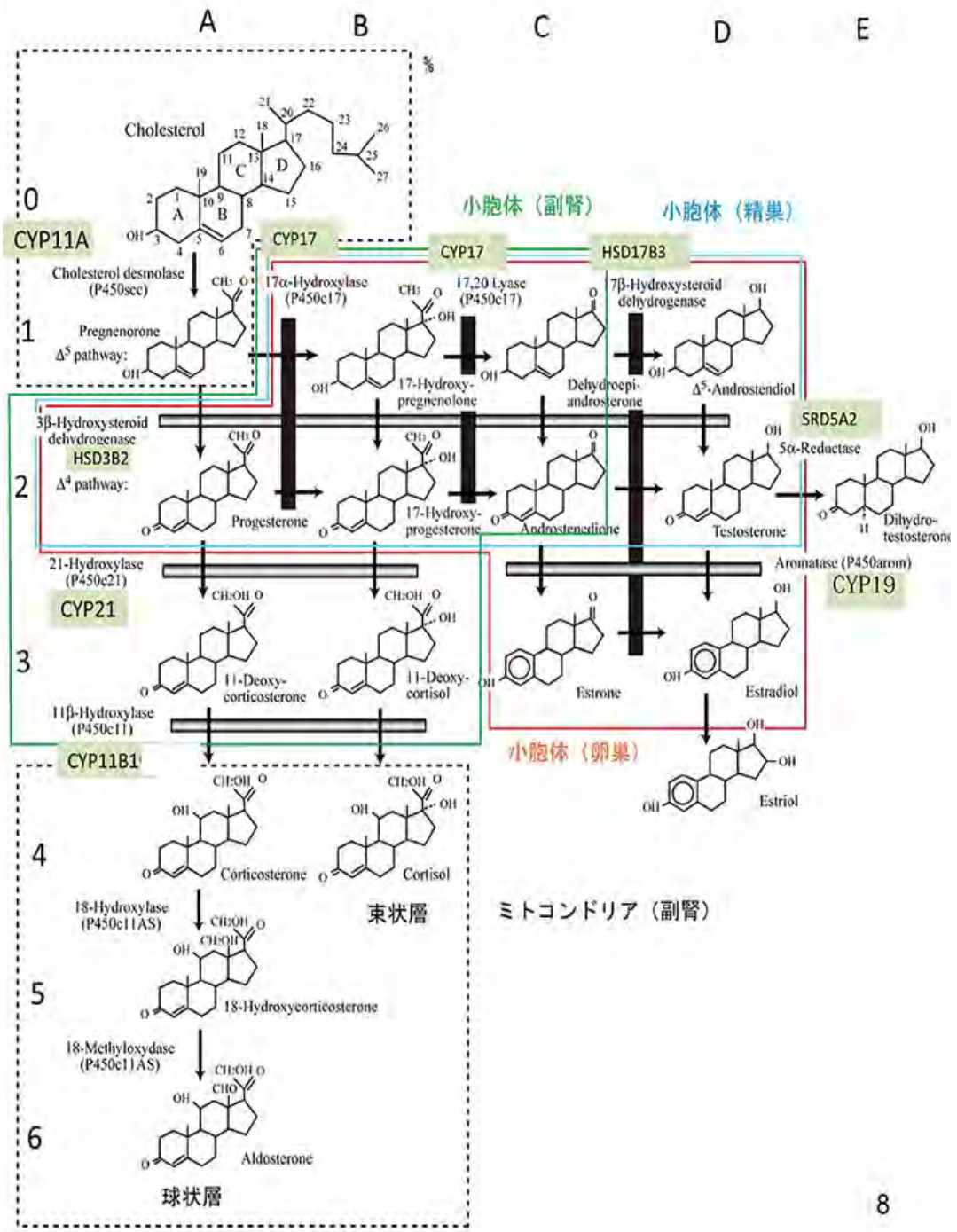
(2) Actions of estrogen and other steroid hormones on the morphogenesis of the brain, generation of male-female difference.

(3) Neurophysiology of GnRH neurons (patch-clamp studies).

(4) Patch-clamp analysis of neural actions of estrogen.

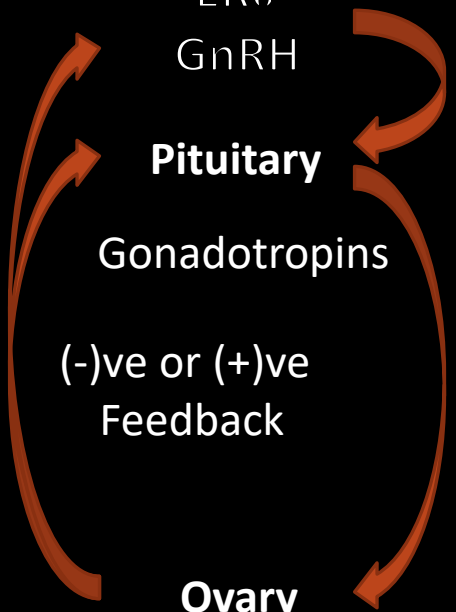
(5) Role of oxytocin (a nanopeptide) on dog-owner bond and social attachment and trust.

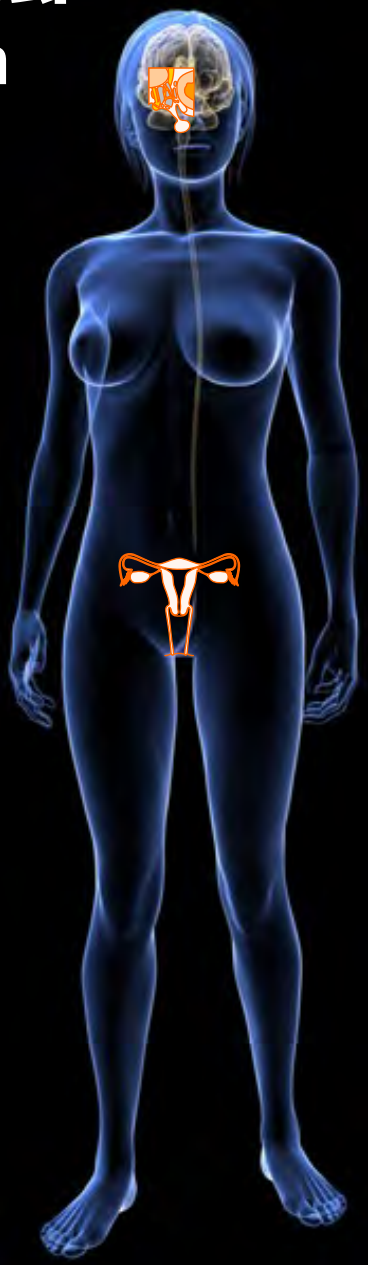
Synthesis of ovarian, testicular, and adrenal steroid hormones



フィードバック調節
Feedback regulation

Hypothalamo-Pituitary-Gonadal Axis





GnRH neurons …Reproductive neuroendocrinology

ERα-positive neurons …Sex difference

Estrogen production in ovary

- Negative (-) feedback throughout ovarian cycle
- Positive (+) feedback at the time of ovulation
- No (+) feedback in males

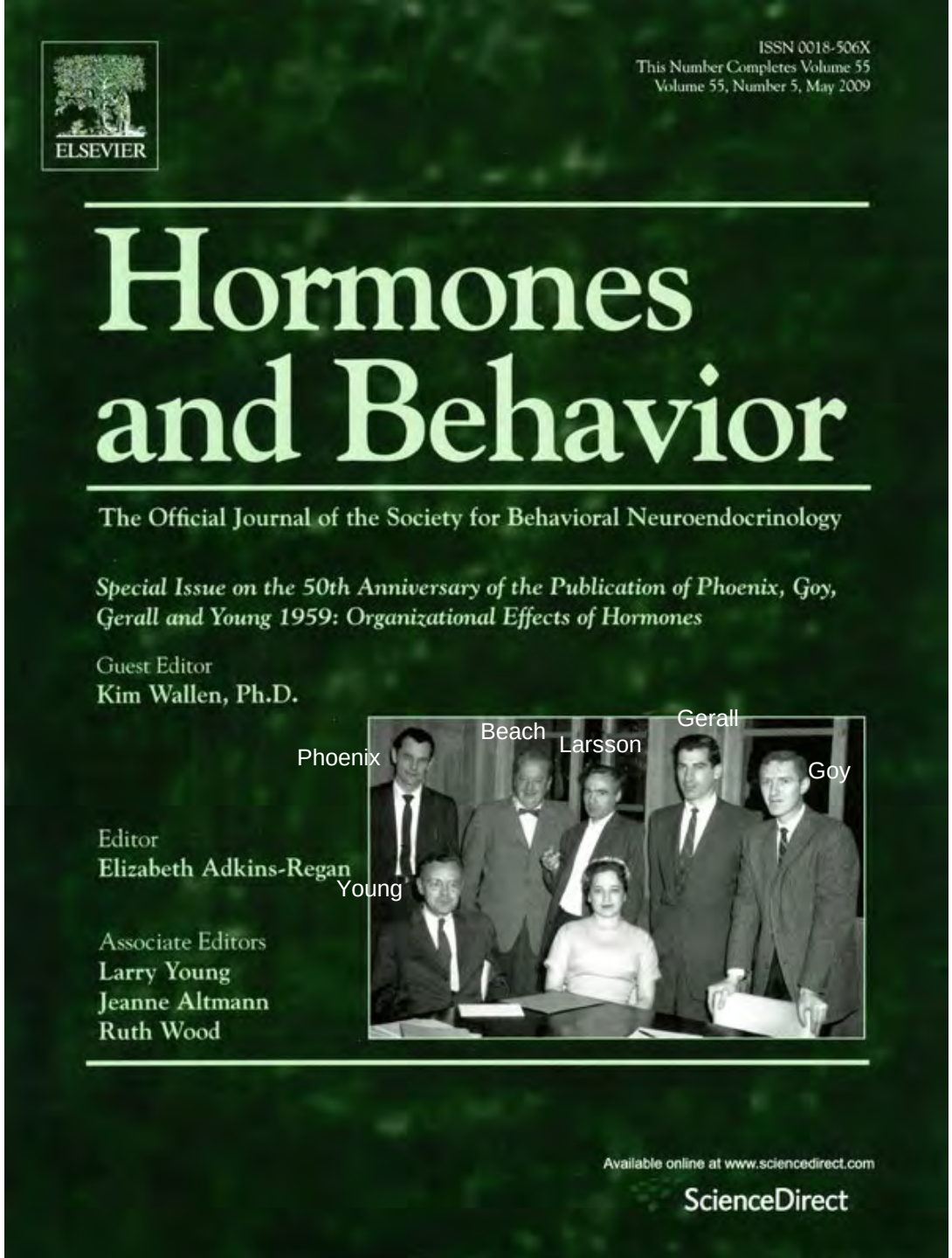
Organizational & Activational Actions of Gonadal Steroids

Organizational Actions

- Effective only during the critical period in the ontogeny
- Irreversible
  In rodents, masculinizes the brain both morphologically & functionally

Activational Actions

- Depends on the circulating titer of steroids after puberty
- Reproductive endocrinology & behavior



Phoenix CH, Goy RW, Gerall AA, Young WC: Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology* **65**: 369-382, Sept 1959

Organizational effects of sex steroids

Activational effects of sex steroids

Kawakami M, Sawyer CH: Induction of behavioral and electroencephalographic changes in the rabbit by hormone administration or brain stimulation. *Endocrinology* **65**: 631-643, October 1959

Organizational Actions of Sex Steroids

Masculinization: Lack of Estrous Cyclicity
Behavioral Masculinization
(Territorial, Mounting)

Testicular
or
Exogenous
Androgen

Presence of Androgen during Perinatal Period

Lack of Androgen during Perinatal Period

Female
or
Neonatal
Castration

Feminization: Estrous Cyclicity
Feminine Behavior
(Proceptivity, Receptivity)

Organizational & Activational Actions of Gonadal Steroids

Organizational Actions

- Effective only during the critical period in the ontogeny
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Activational Actions

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Masculinization of rodent brain via estrogen receptor α

Aromatase Hypothesis

dehydrogenase (HSD3B) activity. Δ^5-Androstendiol is the final product

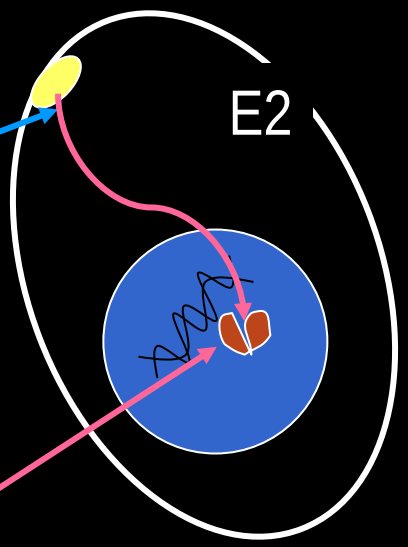
♂ Fetal testes secrete large amount of testosterone autonomously

Testicular testosterone

Excessive dose of estrogens
Non-steroidal estrogenic compounds
(e.g., endocrine disruptors like DES, diethylstilbestrol)

od Brain Barrier

$P450_{arom}$/CYP19

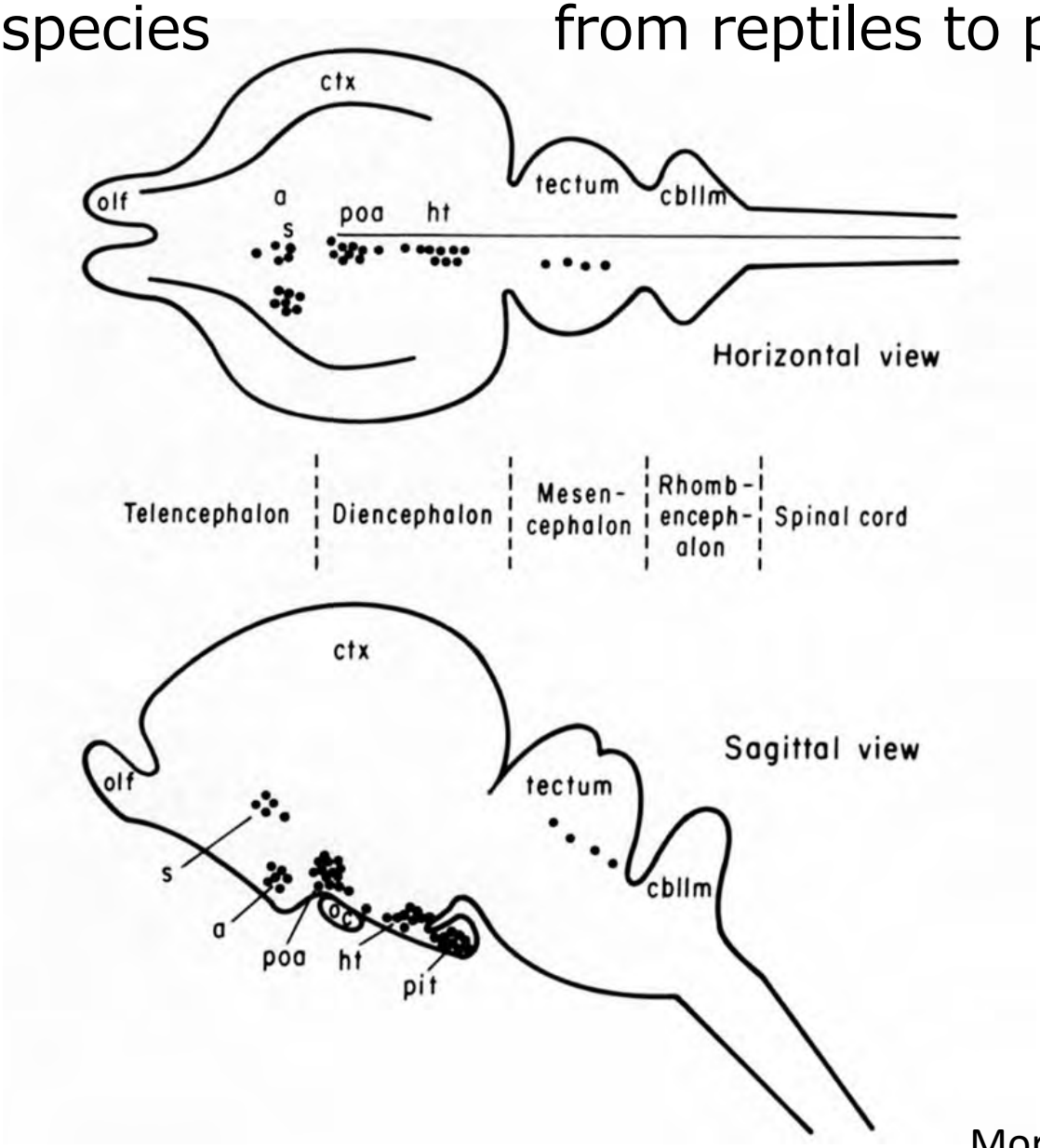


Lordosis Reflex: A major estrogen-dependent component of female rat sexual behavior

Lordosis reflex: frequency or strength of arching

- Lordosis quotient (LQ) = lordosis/mount (%)
- Lordosis score (LS) = 1-3

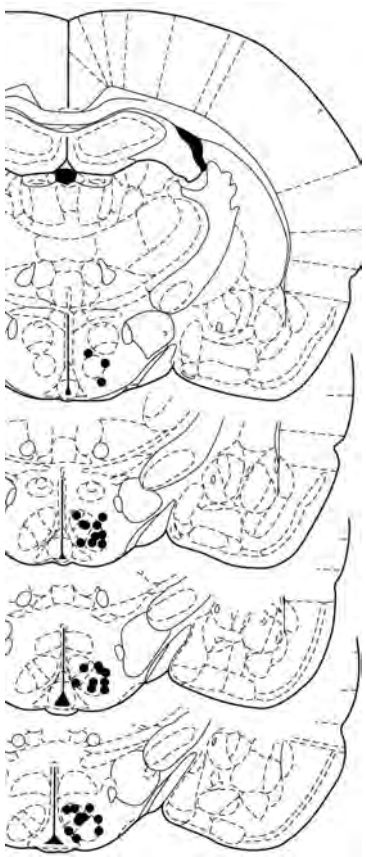
Common pattern of estrogen-concentrating cells across species from reptiles to primates

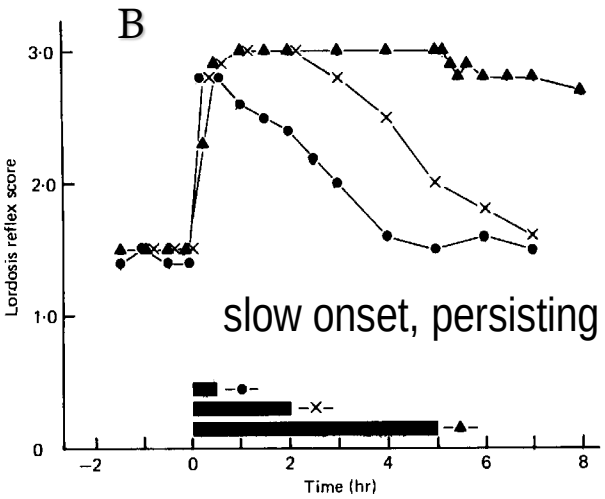


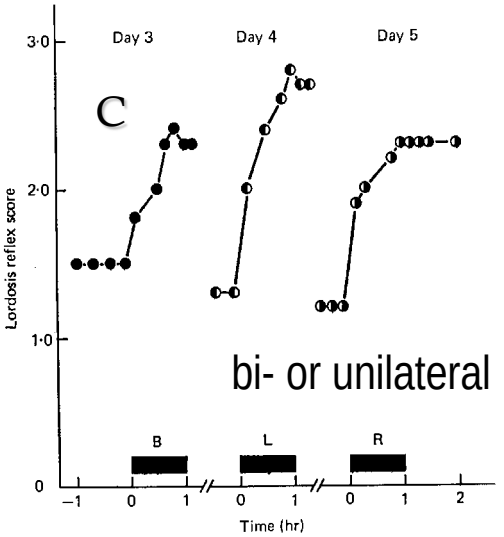
Morrell & Pfaff, 1977

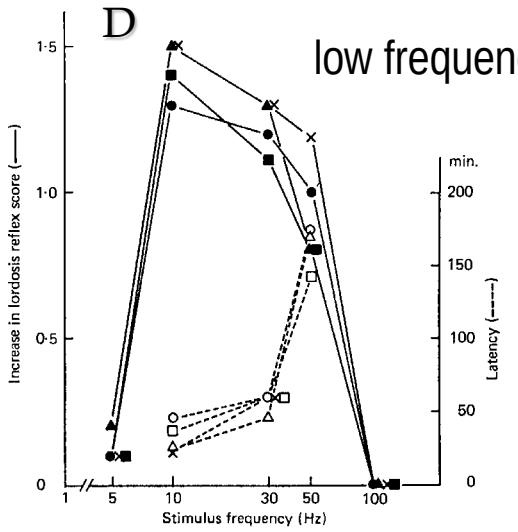
Facilitation of the lordosis reflex of female rats from the ventromedial nucleus of the hypothalamus

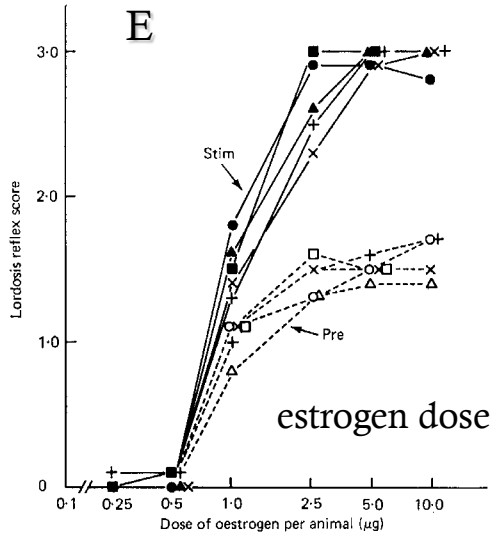
A stimulation sites





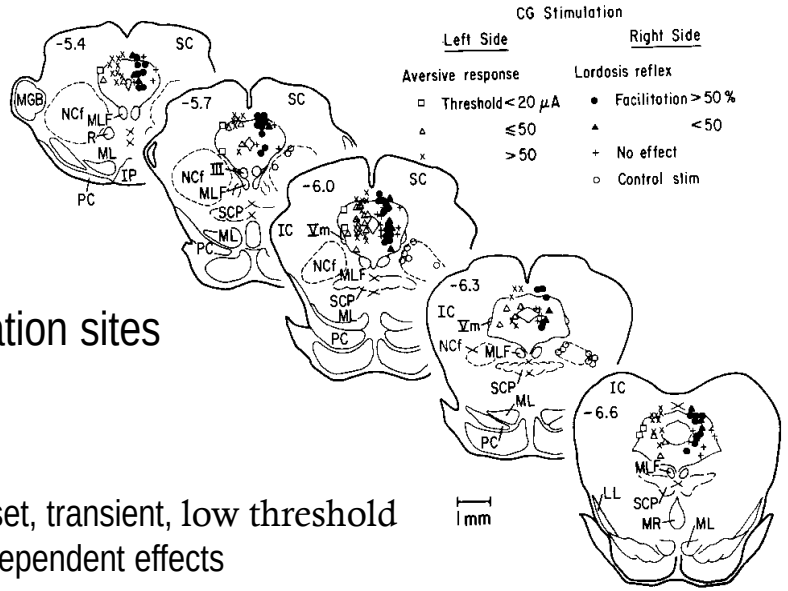






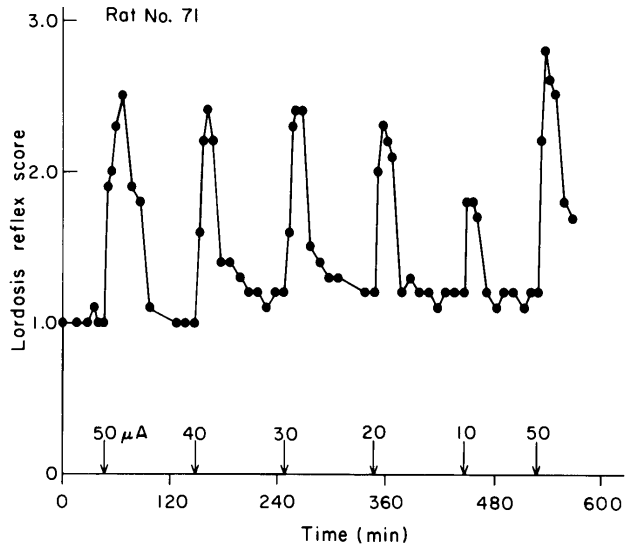
J Physiol (Lond) , 1979

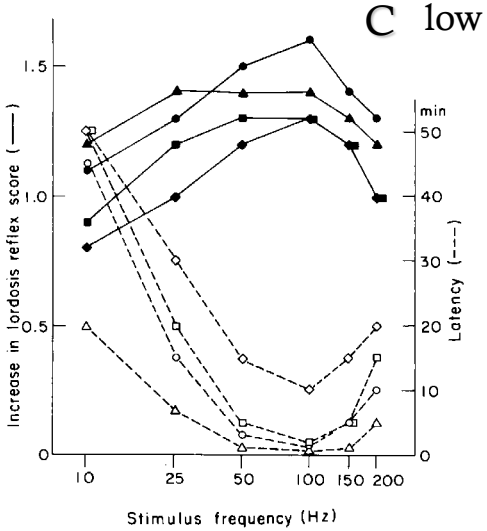
Facilitation of the lordosis reflex of female rats from mesensephalic central gray

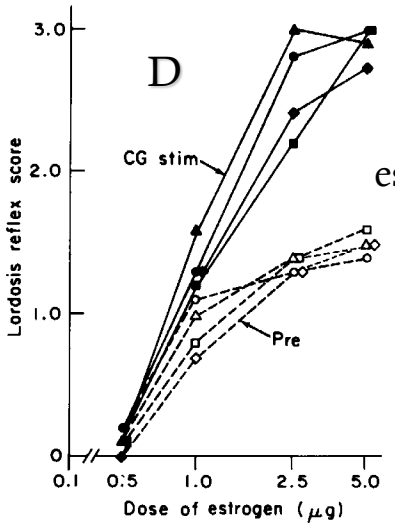


A stimulation sites

B fast onset, transient, low threshold
dose -dependent effects







estrogen dose

Am J Physiol, 1979

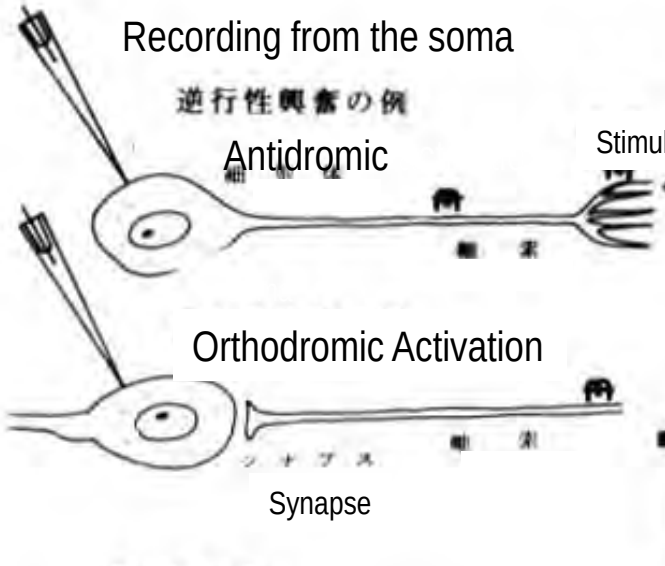
Neurophysiology of estrogen-sensitive neurons

Estrogen sensitivity as detected by:

- antidromic activation threshold
- refractory period

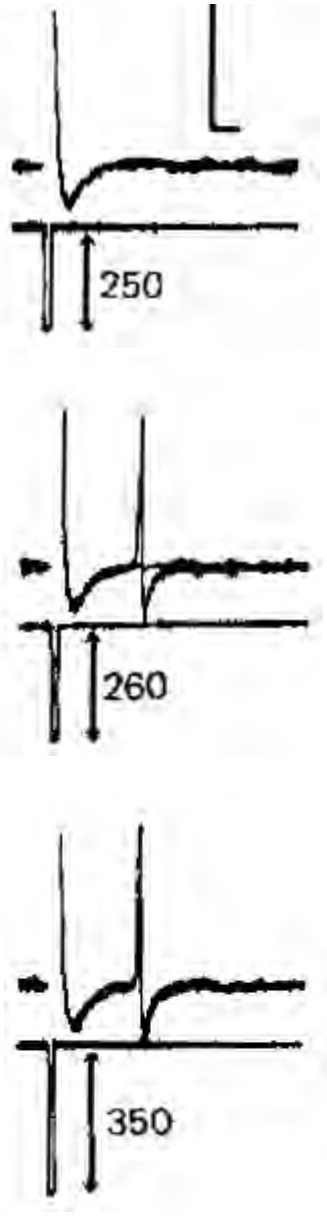
Antidromic excitation of neurons

Recording from the soma

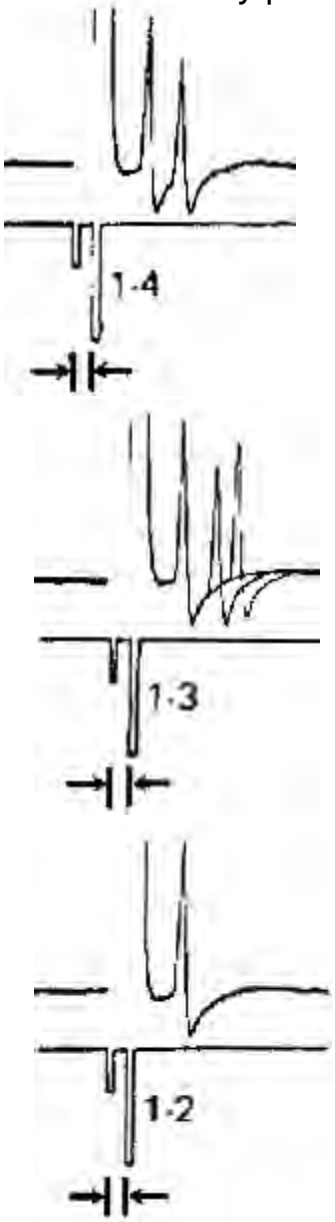


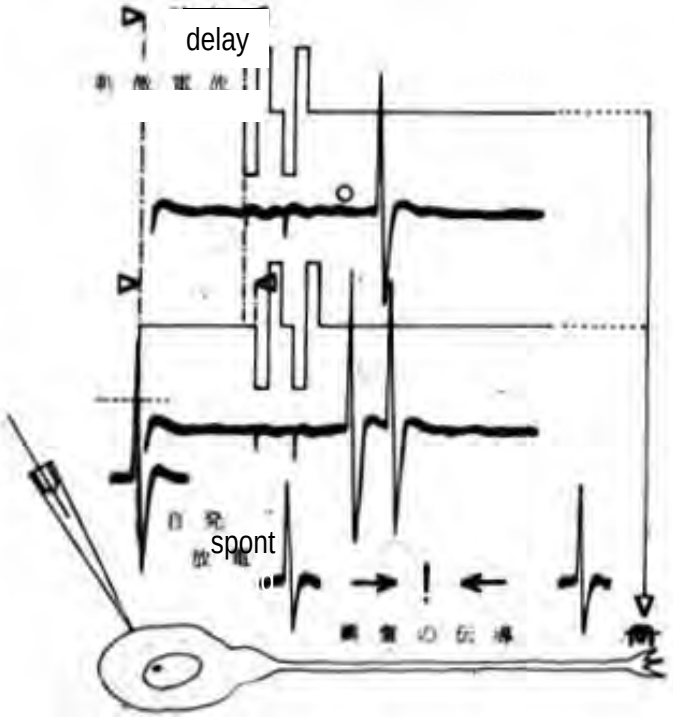
Stimulation

Antidromic activation threshold



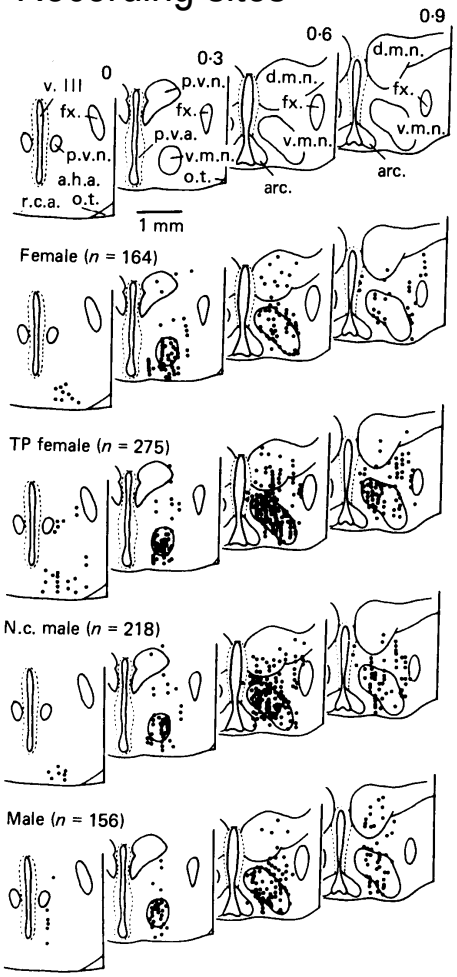
Absolute refractory period



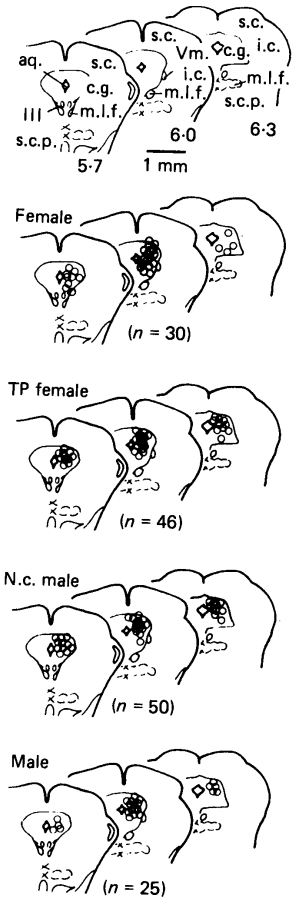


Threshold for antidromic activation of ventromedial hypothalamic neurons by stimulation of midbrain central gray: decrease by estrogen

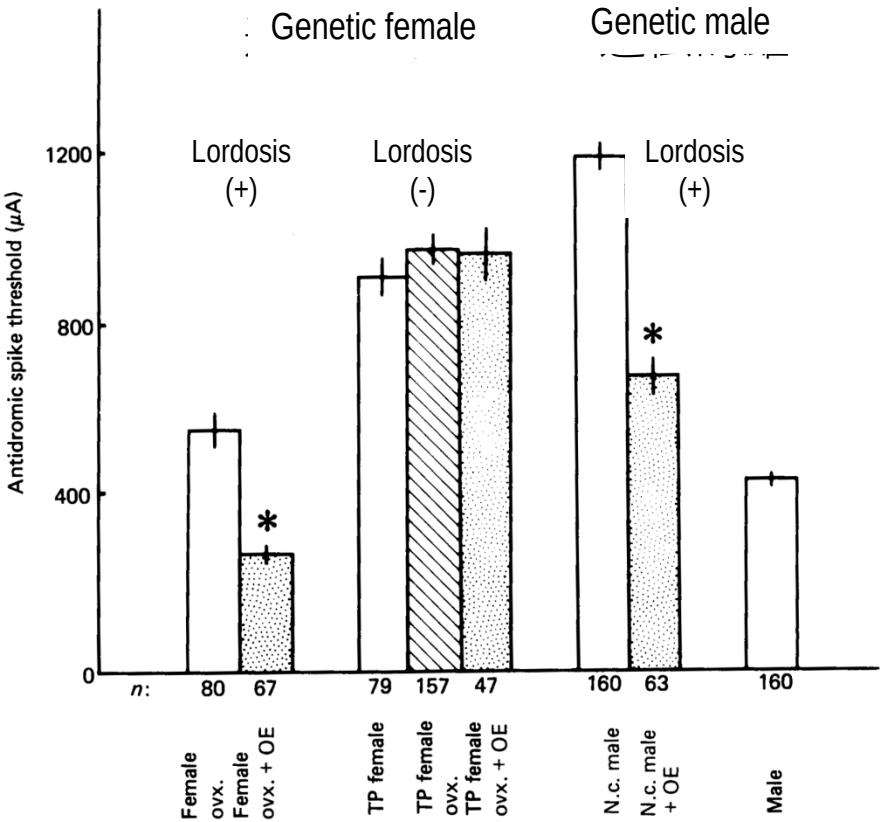
Recording sites



stimulation sites

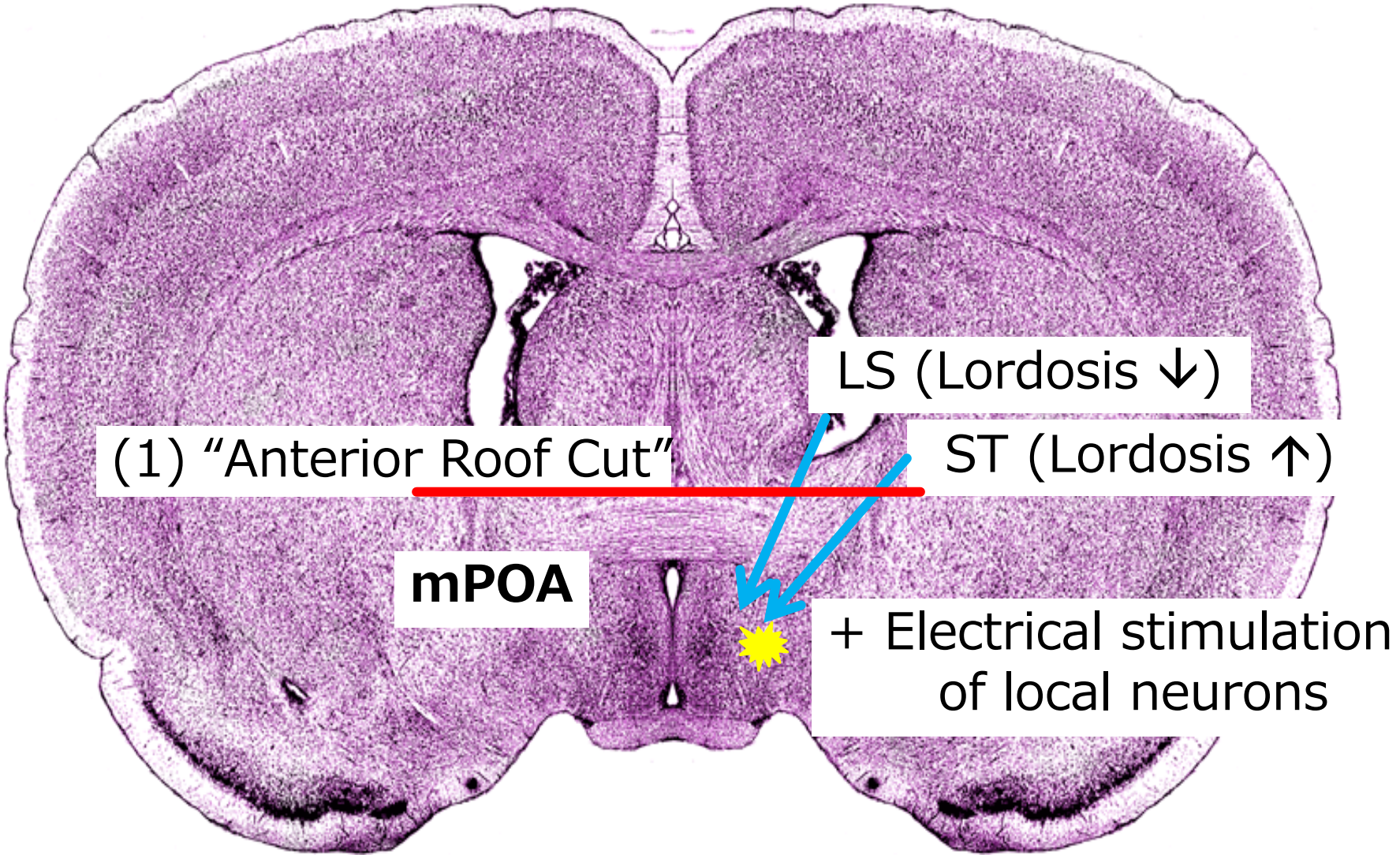


Antidromic activation thresholds

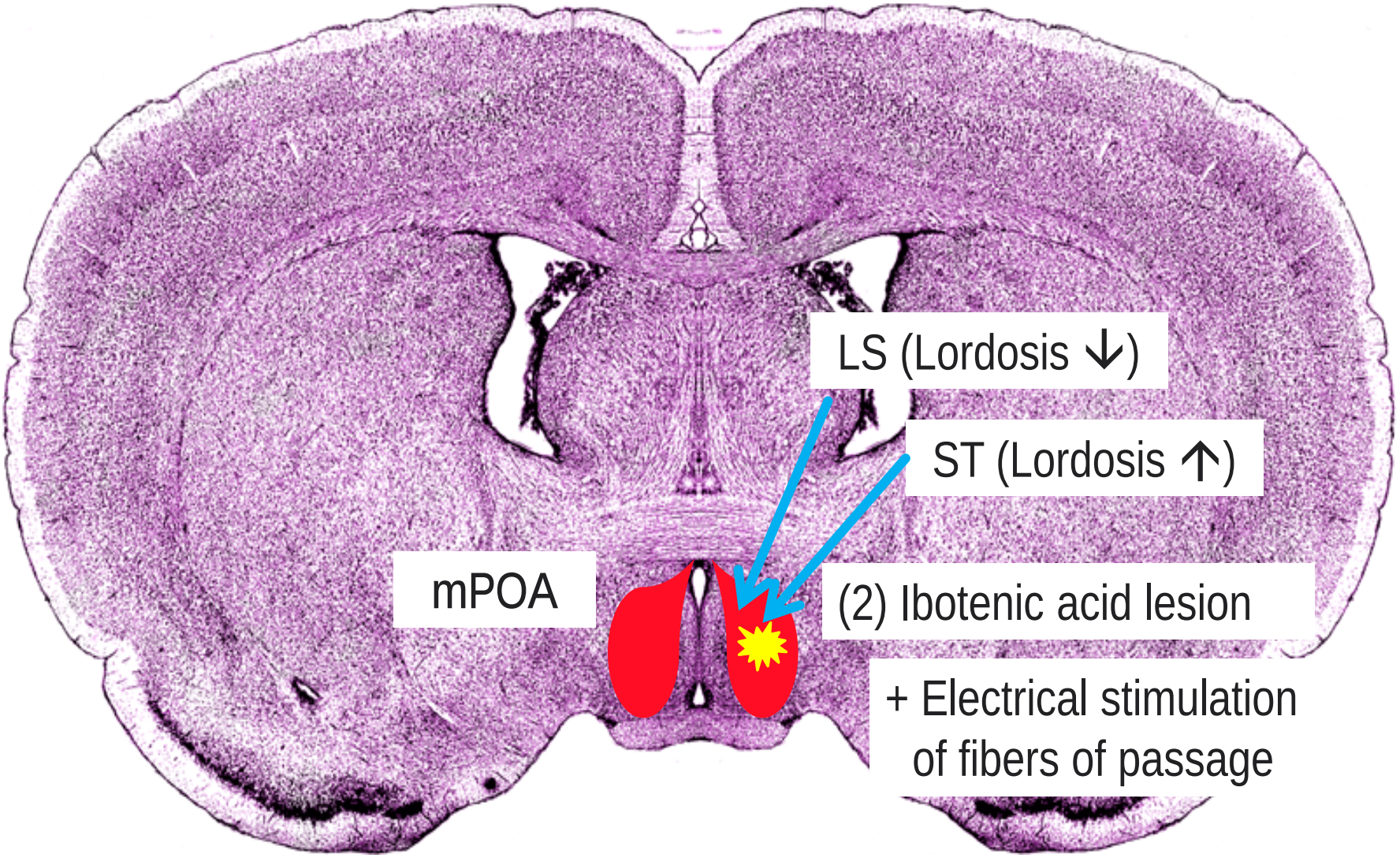


J Physiol (Lond) , 1984

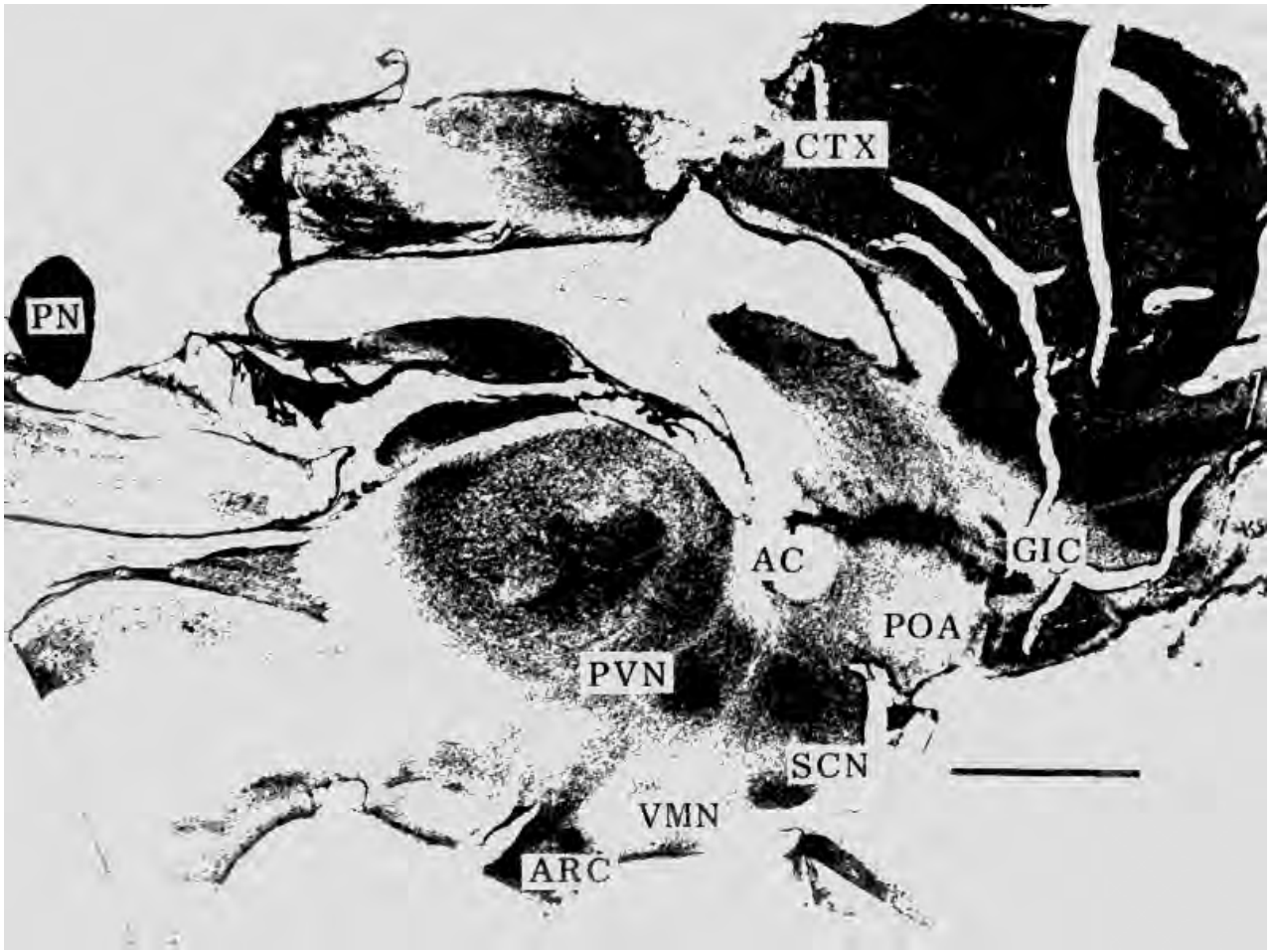
Regulation of Lordosis by Local Neurons in the Preoptic Area



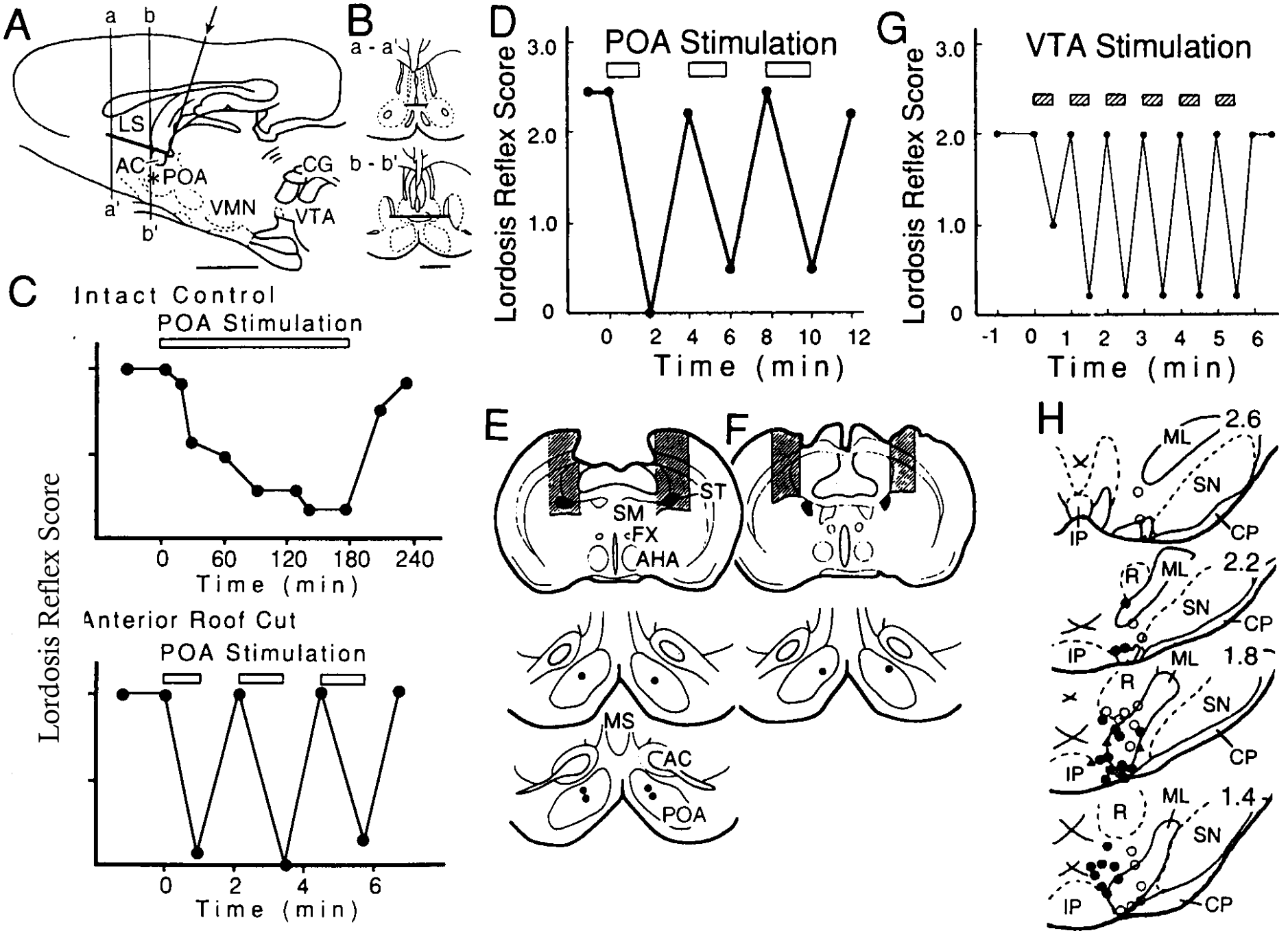
Regulation of Lordosis by Fibers of Passage in the Preoptic Area



Selective disruption of fibers-of-passage in the preoptic area

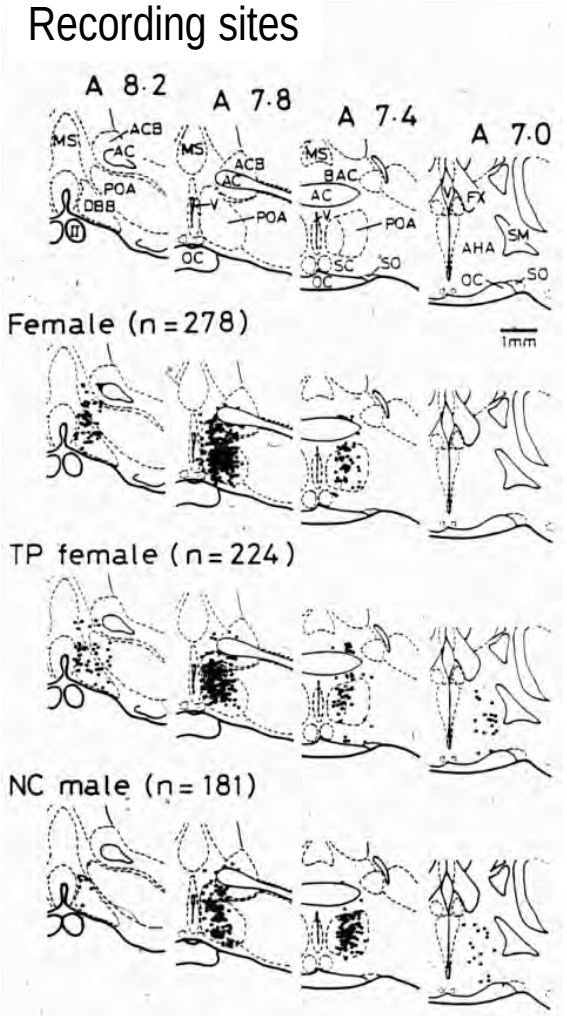


Physiol Behav, 1993

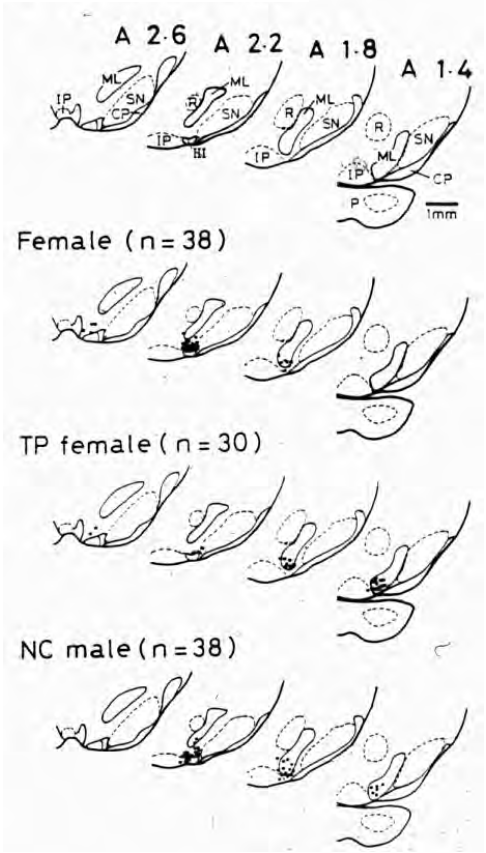

A
a
b
LS
AC
POA
VMN
CG
VTA
a'
b'
B
a - a'
b - b'
C
Intact Control
POA Stimulation
Lordosis Reflex Score
0
60
120
180
240
Time (min)
Anterior Roof Cut
POA Stimulation
0
2
4
6
Time (min)
D
POA Stimulation
Lordosis Reflex Score
3.0
2.0
1.0
0
0
2
4
6
8
10
12
Time (min)
G
VTA Stimulation
Lordosis Reflex Score
3.0
2.0
1.0
0
-1
0
1
2
3
4
5
6
Time (min)
E
F
ST
SM
FX
AHA
MS
AC
POA
H
2.6
ML
SN
IP
CP
2.2
R
ML
SN
CP
IP
1.8
ML
R
SN
CP
IP
1.4
R
ML
SN
IP
CP

Threshold for antidromic activation of preoptic neurons by stimulation of ventral tegmental area: increase by estrogen

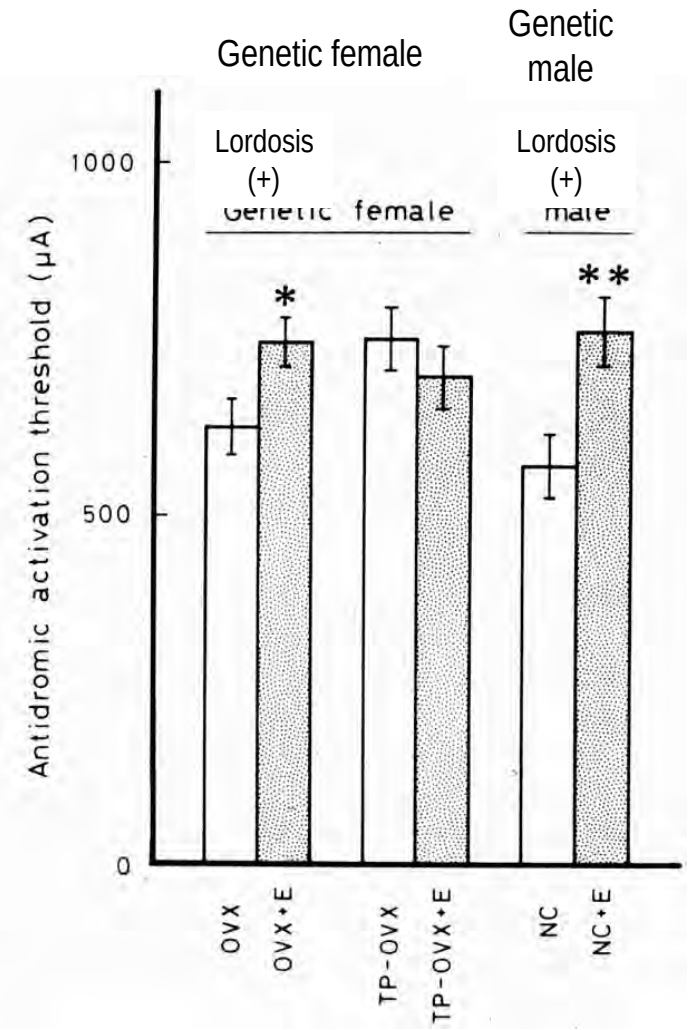
Recording sites



stimulation sites

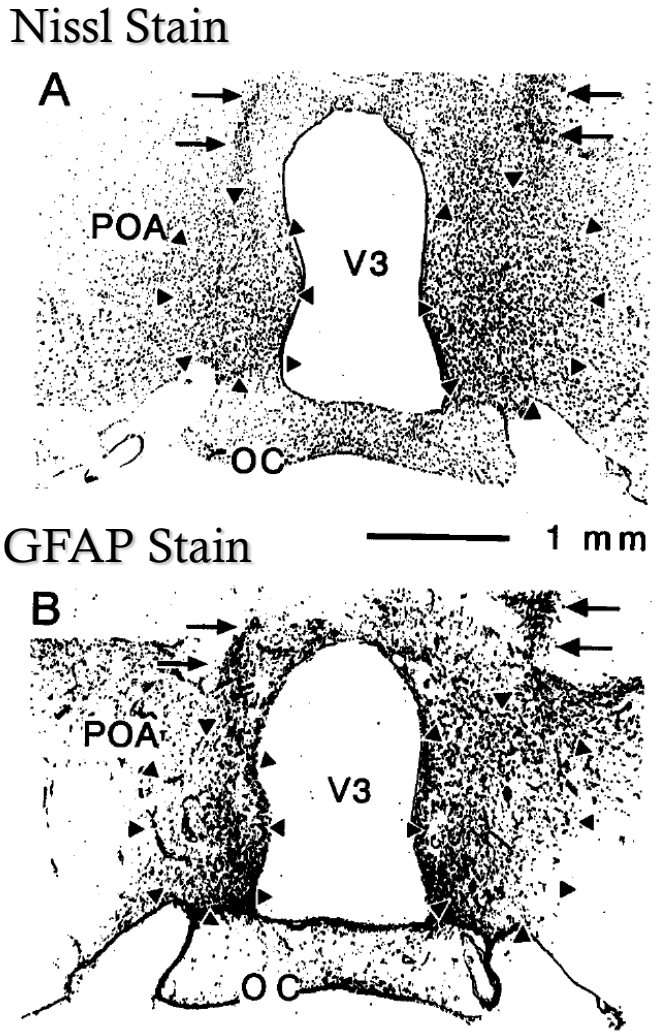


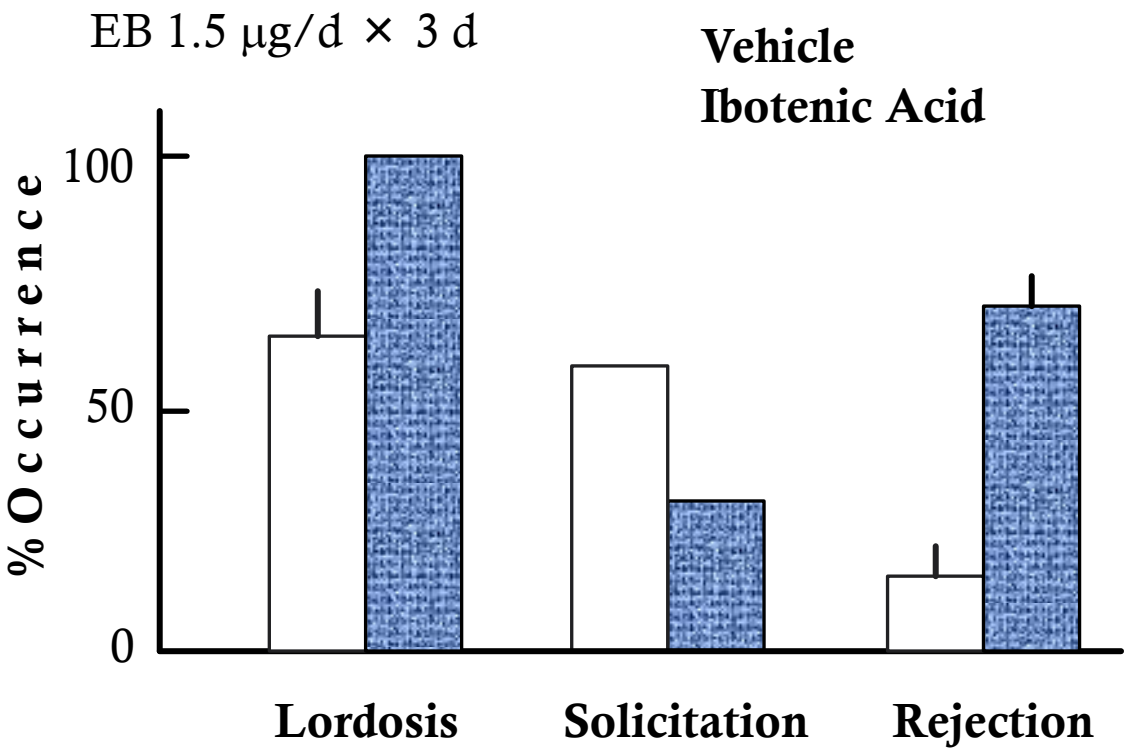
Antidromic activation thresholds



Brain Res, 1993

Excitotoxic Lesion of the POA Enhances Lordosis and Diminishes Proceptivity





Behav Brain Res, 1994

Inhibited by Estrogen:

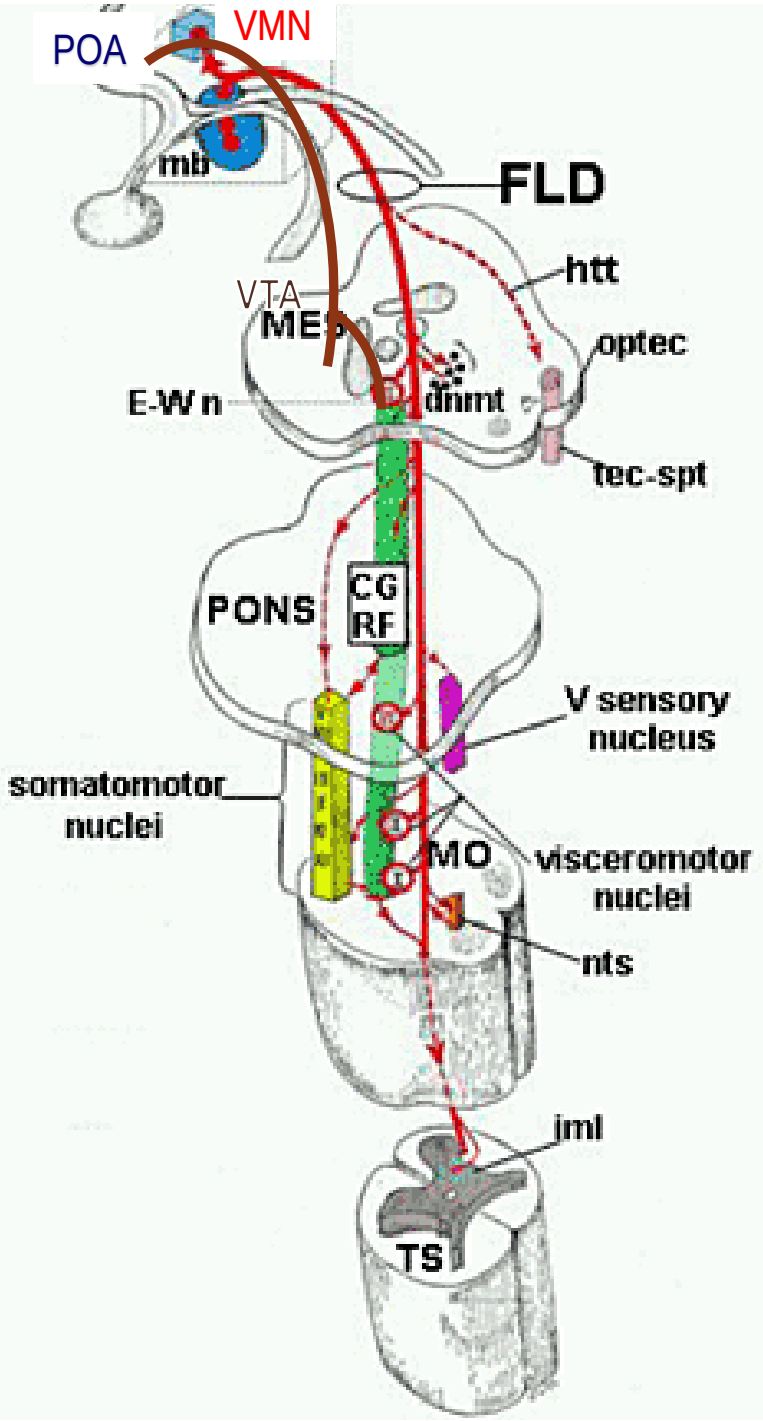
Preoptic Area (POA)

Ventral Tegmental Area (VTA)

Dorsolateral Medulla

NGc

Motoneurons



Activated by Estrogen:

Ventromedial Hypothalamic Nucleus (VMN)

Midbrain Central Gray (CG)

Medullospinal Projecrtion Neurons (NGc)

Lumbar Spinal Motoneurons

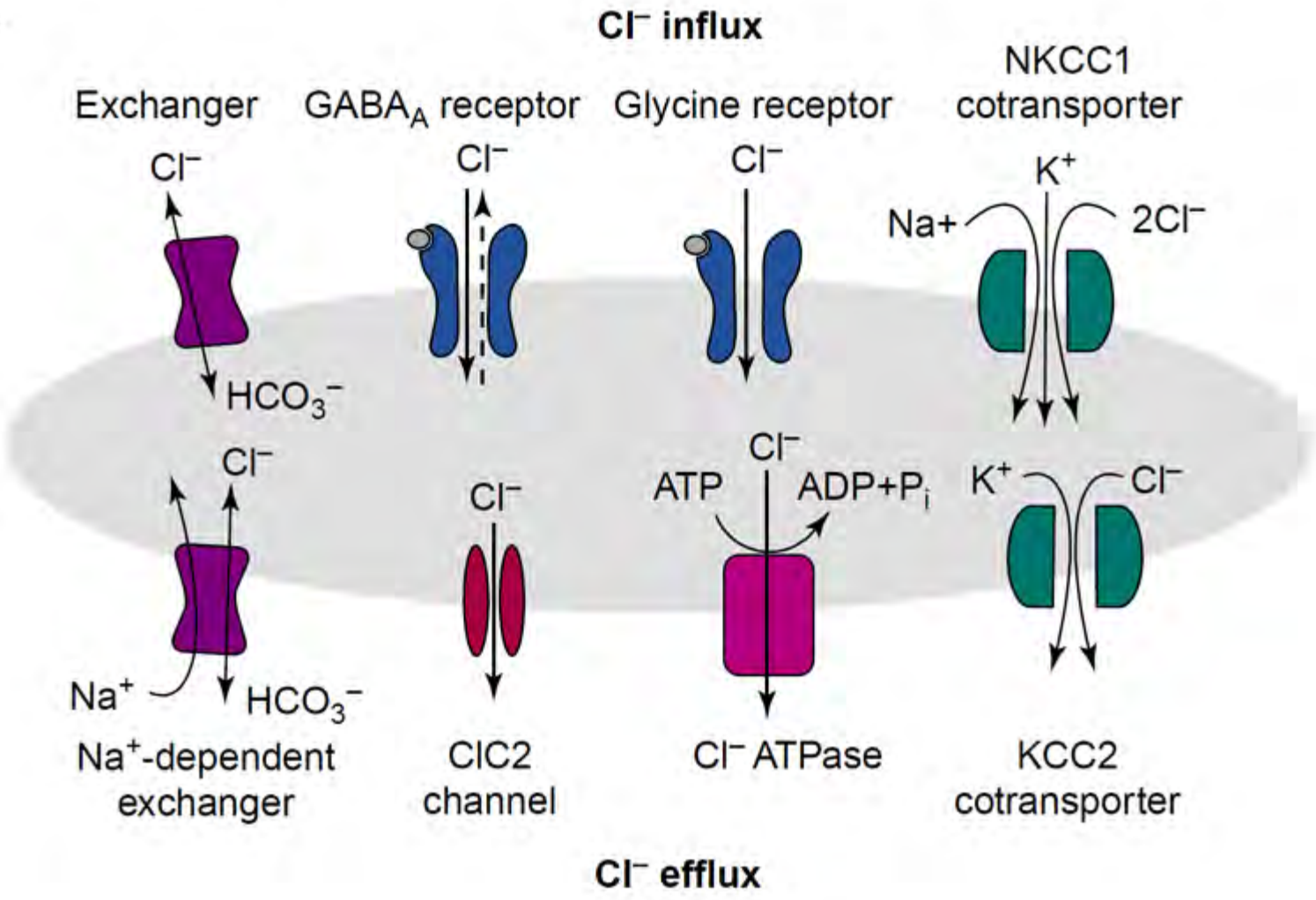
Cell physiology deploying GT1-7 cells

Patch-clamp studies

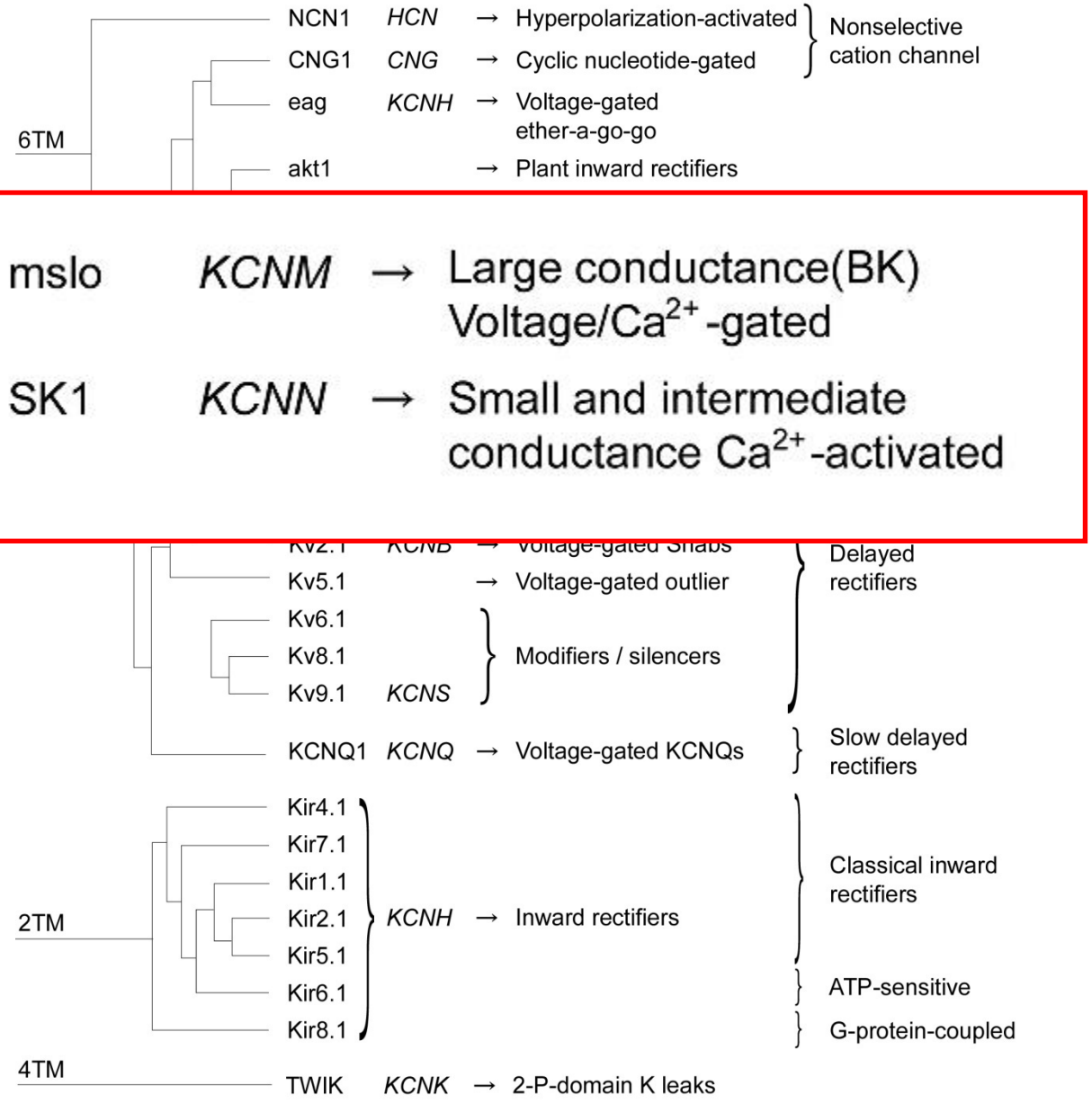
GT1-7 cells

- An immortalized GnRH neuronal cell line generated by genetically targeted tumorigenesis in transgenic mice (Mellon *et al.*, 1990; Weiner *et al.*, 1992)
- Secrete GnRH in pulsatile manner (Wetsel *et al.*, 1992)
- Generate action potentials, show oscillations of intracellular Ca^{2+} concentrations (Charles and Hales, 1995)
- Express chloride-accumulating co-transporter NKCC-1 and are excited by GABA (DeFazio *et al.*, 2002)
- Caveat: Anaplastic or dedifferentiated

NKCC1 expression is high, while KCC2 expression is low in GT1-7 cells as in adult rat GnRH neurons



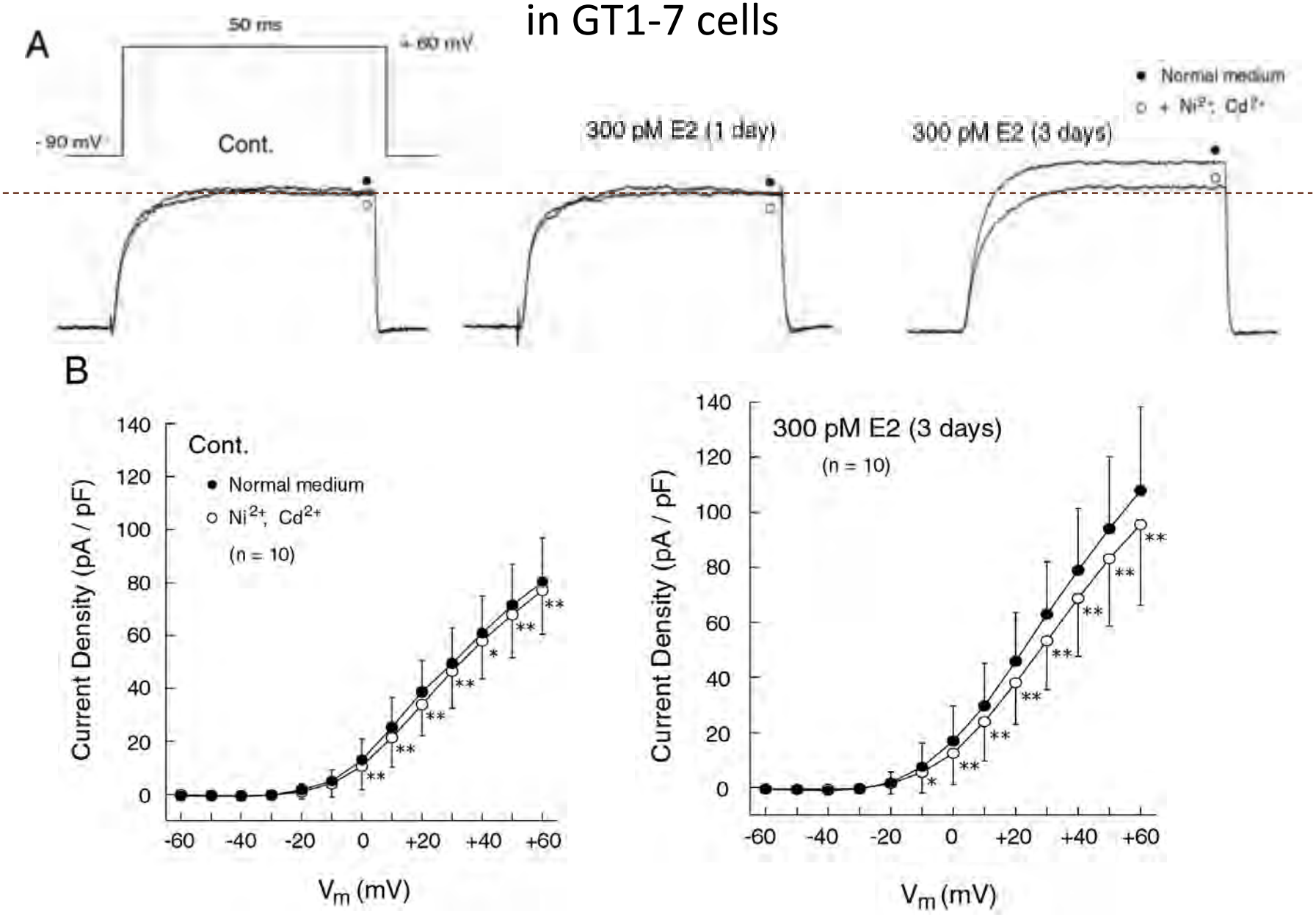
K^+ channel


NCN1 HCN → Hyperpolarization-activated
CNG1 CNG → Cyclic nucleotide-gated
Nonselective cation channel
eag KCNH → Voltage-gated ether-a-go-go
6TM
akt1 → Plant inward rectifiers
mslo KCNM → Large conductance(BK) Voltage/Ca2+ -gated
SK1 KCNN → Small and intermediate conductance Ca2+ -activated
Kv5.1 → Voltage-gated outlier
Delayed rectifiers
Kv6.1
Kv8.1
Kv9.1 KCNS
Modifiers / silencers
KCNQ1 KCNQ → Voltage-gated KCNQs
Slow delayed rectifiers
Kir4.1
Kir7.1
Kir1.1
Kir2.1
Kir5.1
Kir6.1
Kir8.1
2TM
KCNH → Inward rectifiers
Classical inward rectifiers
ATP-sensitive
G-protein-coupled
4TM
TWIK KCNK → 2-P-domain K leaks

Properties of Ca^{2+}-activated K^+ channels

Property	Channel type	
	BK channel	SK channel
Single-channel conductance (pS)	100-400	5-20
Voltage sensitivity	Yes	No
Ca^{2+} sensitivity	Low (1-10 μM)	High (100-400 nM)
Proposed role	Action-potential repolarization	After-hyperpolarization (AHP)
Blockers	TEA (<1 mM) Charibdotoxin	TEA (>20 mM) Apamin d-Tubocurarine

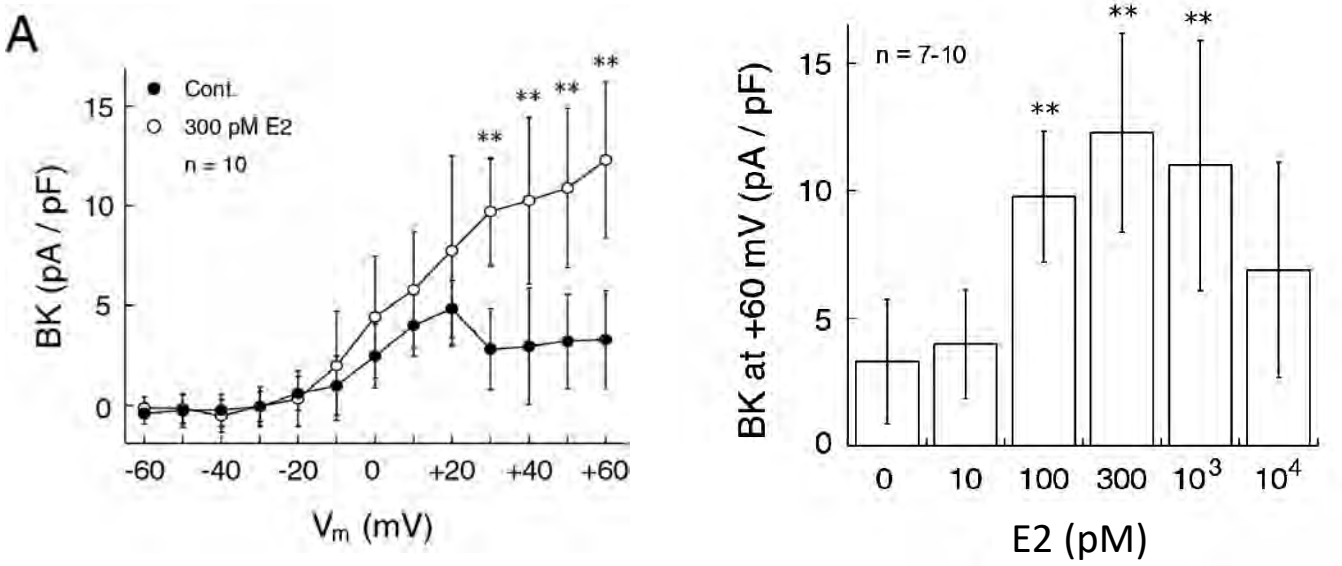
Ni^{2+}-, Cd^{2+}-sensitive BK and -resistant delayed rectifier K^+ (I_K) in GT1-7 cells



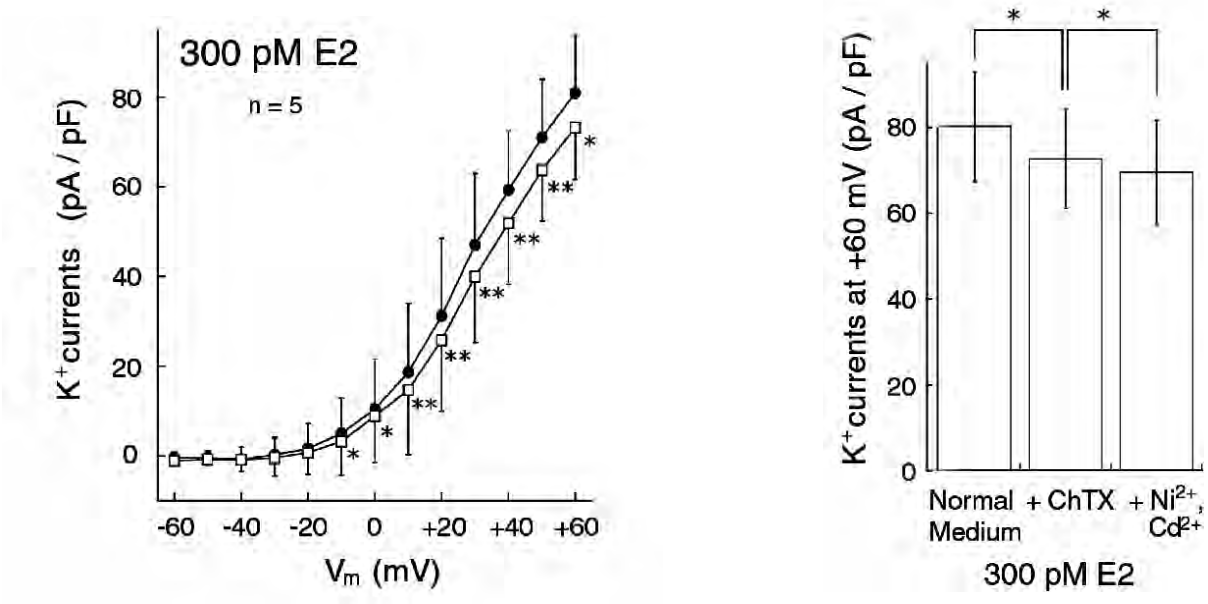
Nishimura *et al.*, ***Endocrinology*** **149**:774, 2008

E2 augments Ni^{2+}-, Cd^{2+}-sensitive BK currents

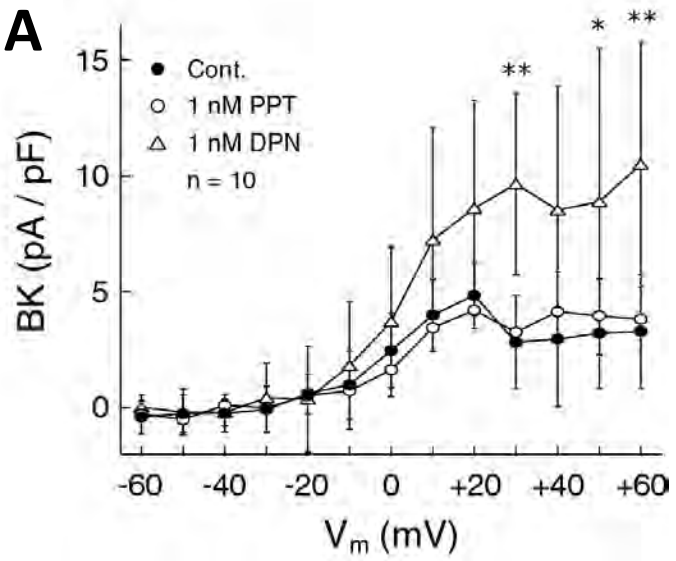
BK currents obtained by subtracting I_K from total K^+ currents

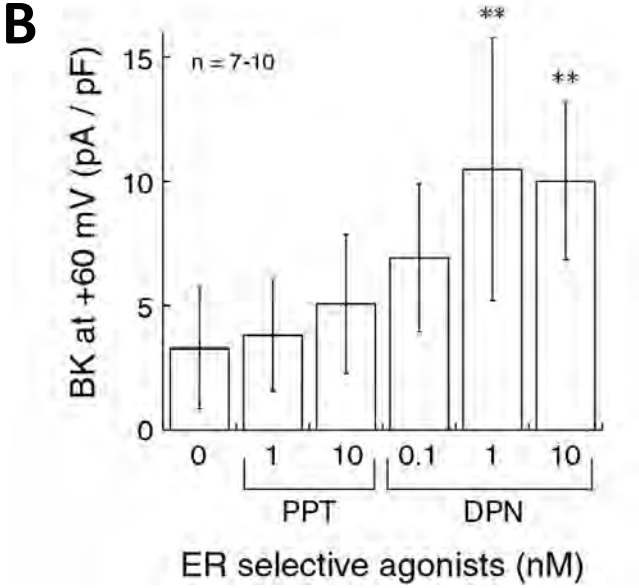


Blockade of BK by Charybdotoxin (ChTX)

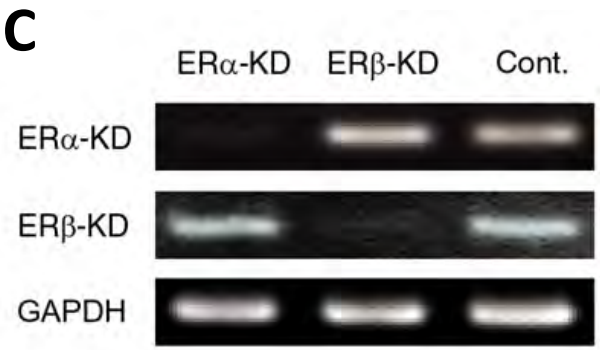


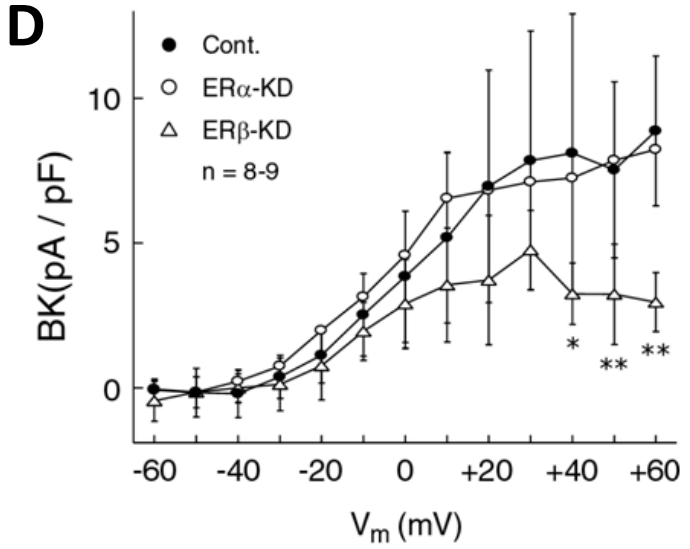
In GT1-7 cells, ERβ-, but not ERα-, selective agonist Augments BK currents





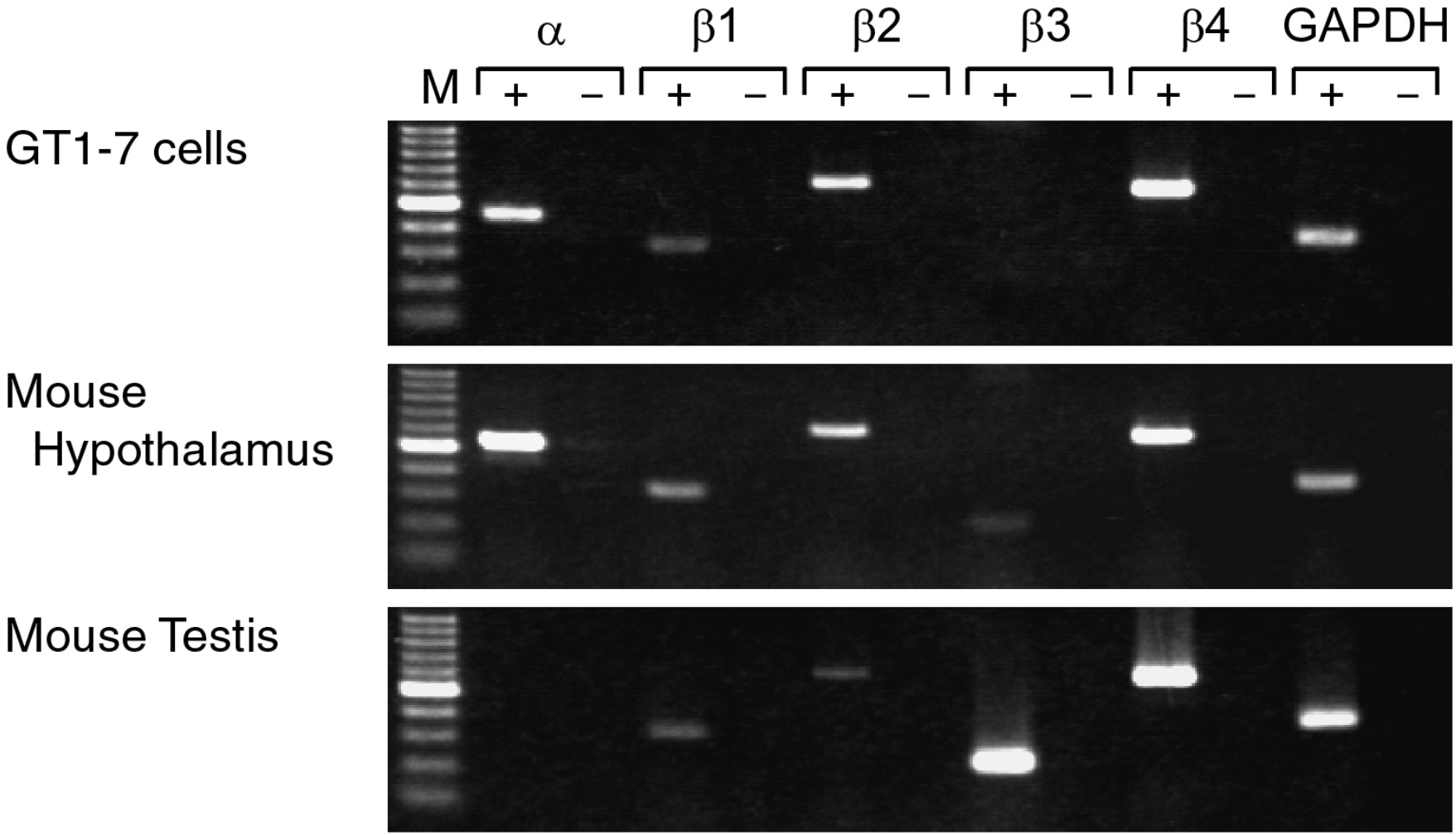
ERβ knockdown Diminishes BK currents





Nishimura *et al.*, ***Endocrinology*** **149**:774, 2008

BK channel α and β1-4 subunit mRNA in the GT1-7 cells



Nishimura *et al.*, ***Endocrinology*** **149**:774, 2008

In GT1-7 cells:

- Estradiol at physiological dosages augments BK currents
- Estrogen-receptor blocker ICI-182,780 (fulvestrant) antagonizes the effect
- Augmented BK diminishes neuronal excitability

Sex Differences in Brain Morphology

Two distinct examples:

- Sexually Dimorphic Nucleus of the Preoptic Area (SDN-POA)
  内側視索前野の性的二型核

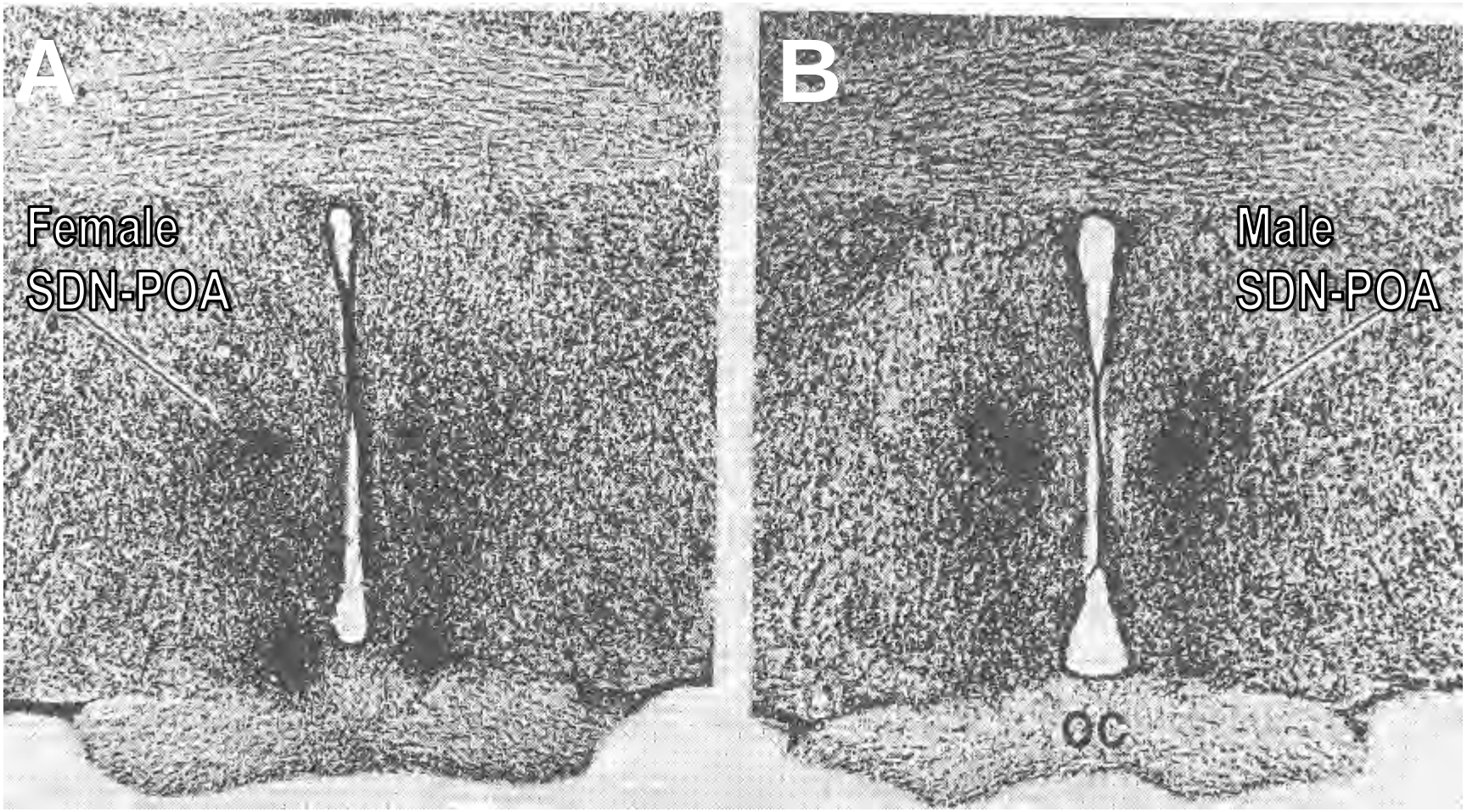
- Anteroventral Periventricular Nucleus (AVPV)
  前腹側室周囲核

Sex Difference in Brain Morphology

BRAIN REGION	SEX DIFFERENCES	COMMENTS
HYPOTHALAMUS		Strongest data on sex differences in humans come from this region
Sexually Dimorphic Nucleus (SDN-POA)	5 times larger in male rats than in female rats	Can be reversed by perinatal hormonal manipulation
Other Interstitial Nuclei (INAH)	INAH3 is larger in man	May correspond to SDN-POA
Anteroventral Periventral Nucleus (AVPV)	Larger (more compact) in female rats than in male rats. Also in mice	Can be reversed by perinatal hormonal manipulation Bax gene deletion has no effects
Bed Nucleus of the Stria Terminalis (BNST)	Larger in males in rats/ mice	Bax gene deletion enlarges female mouse BNST (Forger, 2004)
THALAMUS Massa Intermedia	More often absent in men than in women	Difficult to quantify differences
CORPUS CALLOSUM	Splenium: More bulbous in women; Isthmus: Larger in women. CC shrinks with age in men – but not in women	Conflicting data
ANTERIOR COMMISSURE	Larger in women	Little data
HIPPOCAMPUS	11% larger in polygynous male voles – no larger in monogamous male voles	Spine density increase (male) or decrease (female) in response to acute stress (Shors, 2004)
AMYGDALA	Posterodorsal nucleus of the medial amygdala in the rat (cell size, male>female)	Depend on DHT & estrogen in adults (Cooke, 2003)

Modified from theTable "Vive la Différence" in *Science* 253: 959, 1991

Sexually Dimorphic Nucleus of the Rat Preoptic Area (SDN-POA)



Gorski RA *et al.*, 1978

The SDN-POA has been identified in the *rat, hamster, ferret, guinea pig, sheep, monkey* and *human*. And now, in the *mouse*

Function: inhibition of female sexual behavior?

In defense of rams who love rams—and the scientists who are studying them

By JOHN CLOUD

ZOOLOGISTS HAVE KNOWN FOR MANY years that homosexuality isn't uncommon among animals. (My own cat has raised suspicions ever since he tried to mount a cowering male dachshund.) But I was surprised to learn recently that male sheep exhibit homosexuality at least as often as humans: roughly 8% of rams turn out to have sex exclusively with other rams.

This little piece of faunal ephemera might otherwise have gone unnoticed outside the rarely intersecting subcultures of gays and shepherds. But a few months ago, People for the Ethical Treatment of Animals launched a p.r. campaign on behalf of gay sheep. PETA claims that researchers in Oregon are killing gay sheep and cutting open their brains in order to learn how to turn gay rams straight. A few weeks ago, London's *Sunday Times* picked up the story in an unnerving article that states the research "raises the prospect that pregnant women could one day be offered a treatment to reduce or eliminate the chance that their offspring will be homosexual." The story has pinged around quite a few blogs since, and Rush Limbaugh and Martina Navratilova have taken their predicted positions. (Limbaugh: gay activists finally have a reason to oppose abortion. Navratilova: homophobes are murdering gay sheep.)

It's a pity that a story with so much potential for moral indignation and bad sheep puns (ewegenics!) turns out to be wrong. To be sure, a group of researchers led by physiologist Charles Roselli of Oregon Health & Science University has killed about 55 sheep, homosexual and heterosexual, in order to study the neurological basis of sexual attraction. They have confirmed that test sheep are gay by allowing them to pick among males and females that have been restrained in stanchions to await sexual intercourse.

But Roselli says he and his colleagues never had any intention of creating a drug that will turn people straight. And while they have examined whether sheep sexuality can be altered with various treatments, that's not the ultimate point of their work. Instead, like many other scientists over the past two decades, they are conducting basic research into the nature of sexuality by manipulating hormones in animals. (Such experiments were done on zebra finches—to see if females would pair with other females—as long ago as 1988.) A colleague of Roselli's, Fredrick Stormshak of Oregon State, says a means of identifying gay sheep would be useful to breeders who need to ensure that males will reproduce, but the team hasn't had much success. In its most recent experiments, the group used drugs to block the action of a hormone thought to play a role in making most sheep straight (in other words, this test was designed to produce more homosexual sex, not less). But the results were inconclusive.

The Oregon group's work has shown, however, that gay rams have different brain structures from heterosexual ones, news that should cheer those who see homosexuality and heterosexuality as mere biological variations. (Another small but fascinating finding: all gay rams are butch—none present themselves sexually the way ewes do.)

As Roselli acknowledges in his papers, sexuality in humans is far more complex than in sheep. The whole notion that researchers studying farm animals could develop a "cure" for human homosexuality is a fantasy of the far left and the far right, which both value a gay-sheep "scandal" more than the messy reality that is Roselli's work.

But one could have a good argument about whether adorable little sheep should be killed for sex research. As a gay man, I tend to believe the more we know about the complex interplay of biology and environment that shapes sexuality, the less time we will spend nourishing Old Testament anachronisms about sex.

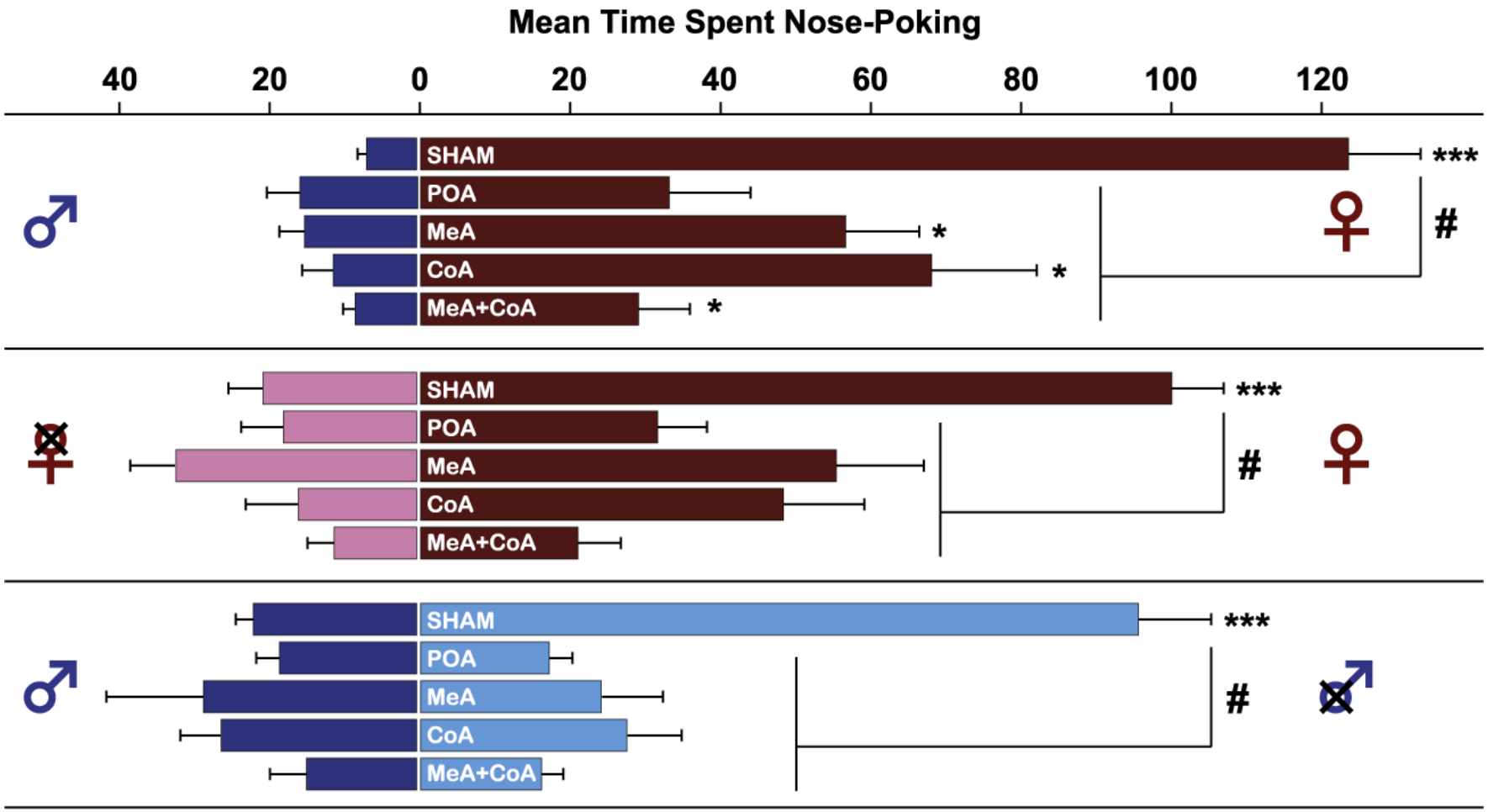
The more pressing question for me is, What would happen if research like Roselli's did lead to, as the *Sunday Times* imagined, "a 'straightening' procedure [such as] a hormone supplement for mothers-to-be, worn like a nicotine patch"? I hope scientists have better things to do, but would a Hetero Patch be so awful? It would allow bigoted women to get what they want—straight kids—and ensure that gay kids grow up with moms who, at the very least, didn't try to prevent their existence. Gay people seem to fear we would die out if such a device existed. But the elaborate combination of genes, hormones and psychology that produces same-sex attraction has persisted, against all odds, through the millenniums. Gays have survived Darwinian selection, Nazis, the dulling effects of *Will & Grace*. I don't think a little patch would ever keep some rams from wanting other rams. ■

Roselli CE, Larkin K, Schrunk JM, Stormshak F: Sexual partner preference, hypothalamic morphology and aromatase in rams. *Physiol Behav* 2004 Nov 15; **83**(2): 233-45.

The ovine SDN (oSDN) is larger in female-oriented rams than in male-oriented rams and similar in size in male-oriented rams and ewes. oSDN aromatase mRNA levels were higher in males than in females and were higher in female-oriented rams than in male-oriented rams.

Odor preference

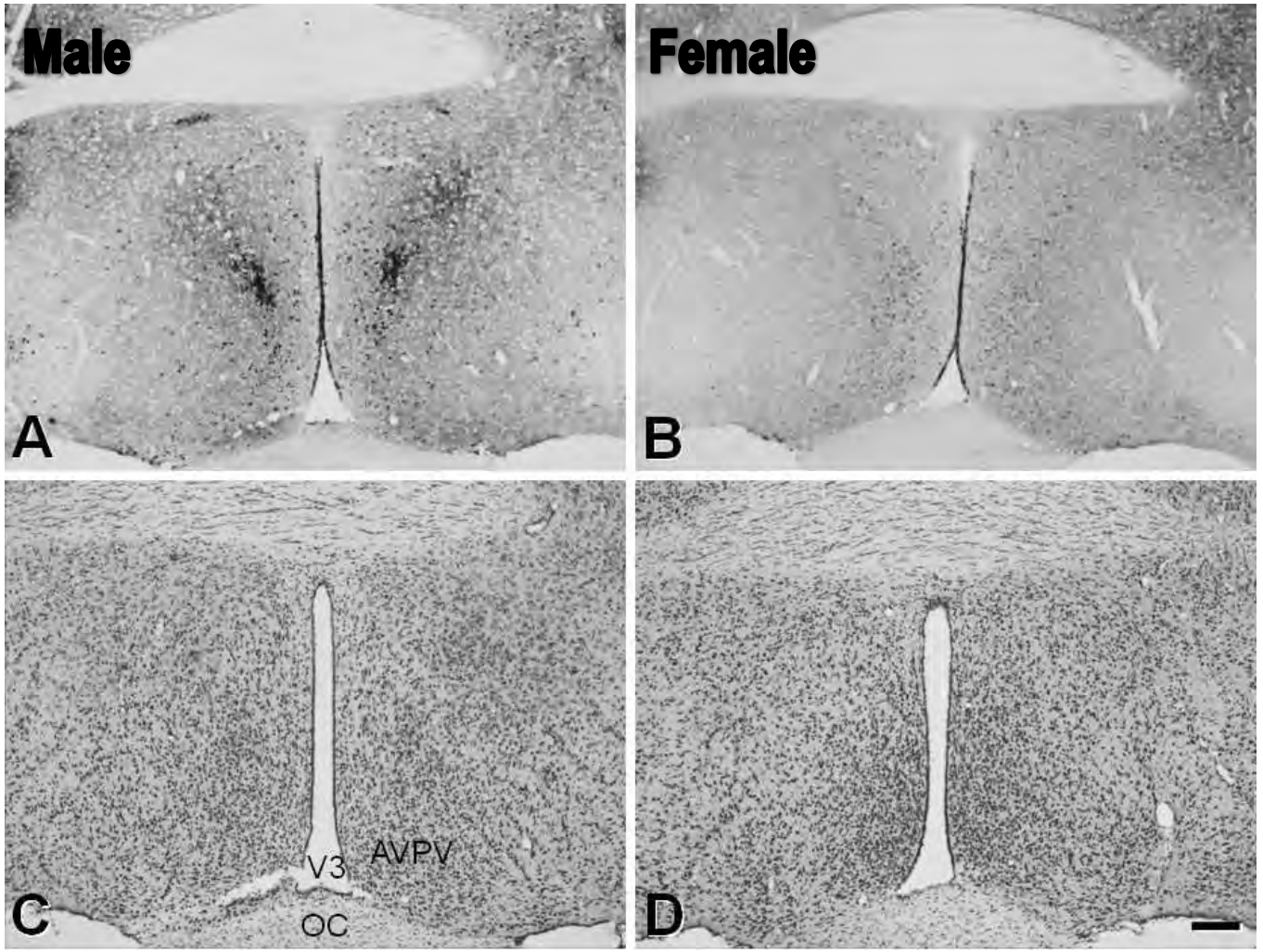
Odor-Preference in Male Rats



Mouse Homolog of Rat SDN-POA

The importance of understanding the structure and expression of the MPO in the mice is imperative, because homologous recombination is routinely undertaken in mice to produce knockout animals

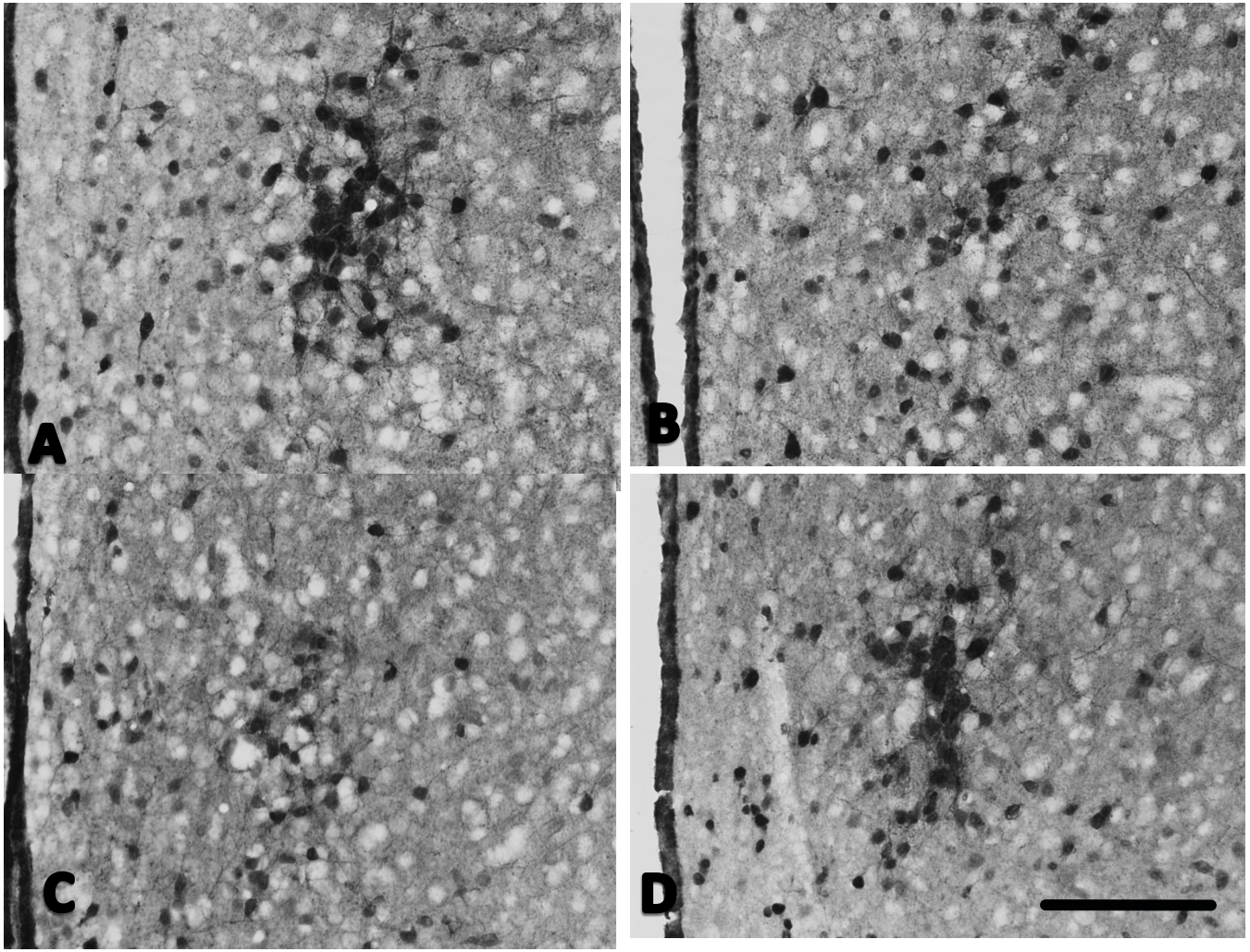
Calbindin D28k-ir visualized the SDN-POA in C57/BL6J Mice



Orikasa & Sakuma, *J Comp Neurol,* 20 May 2010, doi:10.1002/cne.22419

Mouse SDN-POA

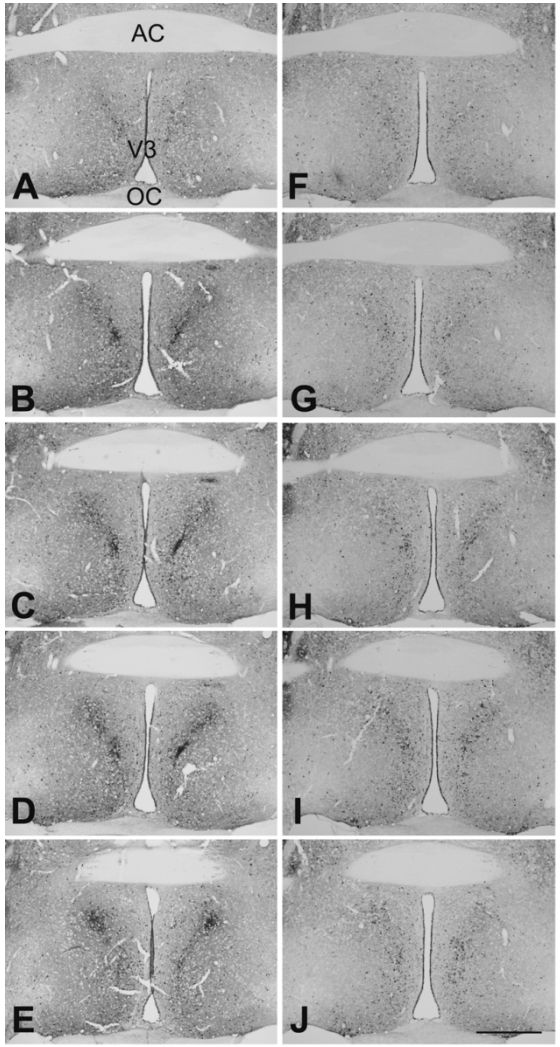
C57BL/6J



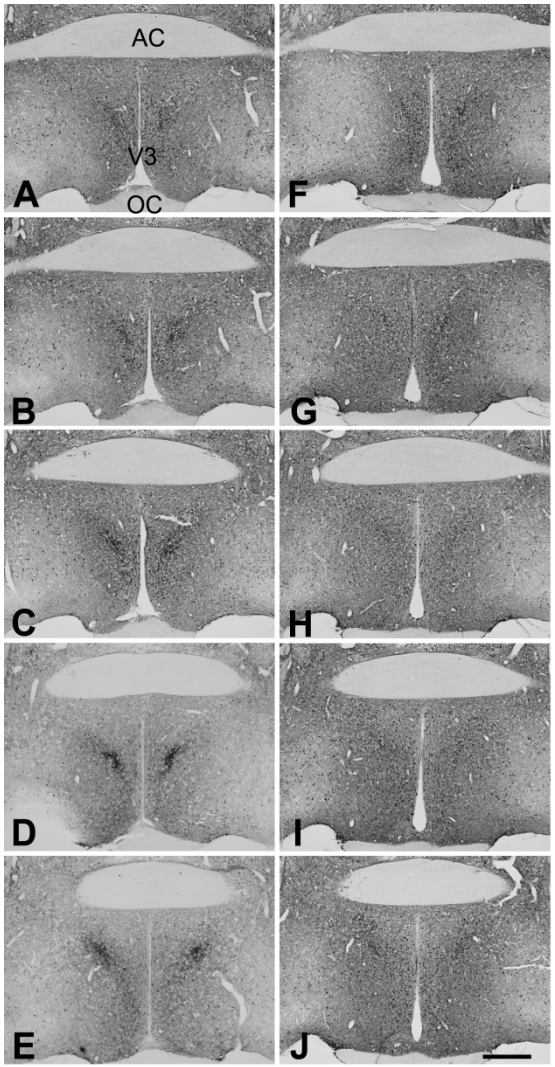
Orikasa & Sakuma, *J Comp Neurol,* 20 May 2010, doi:10.1002/cne.22419

Mouse SDN-POA

C57BL/6J



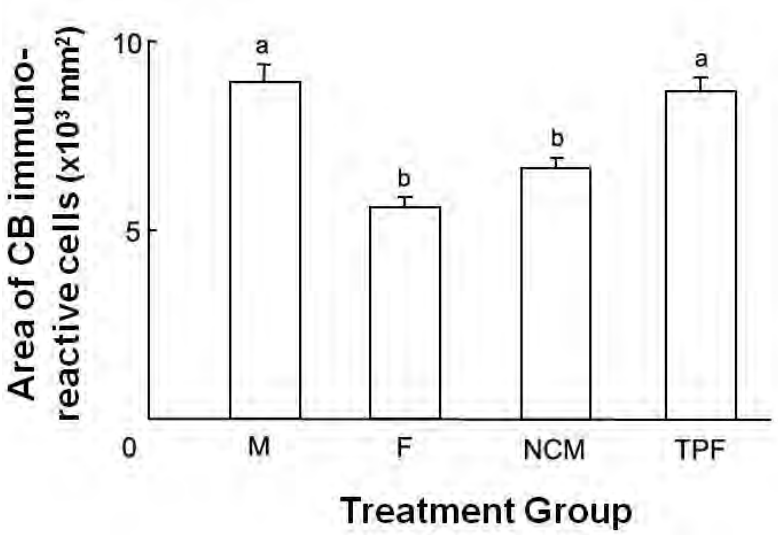
ddN



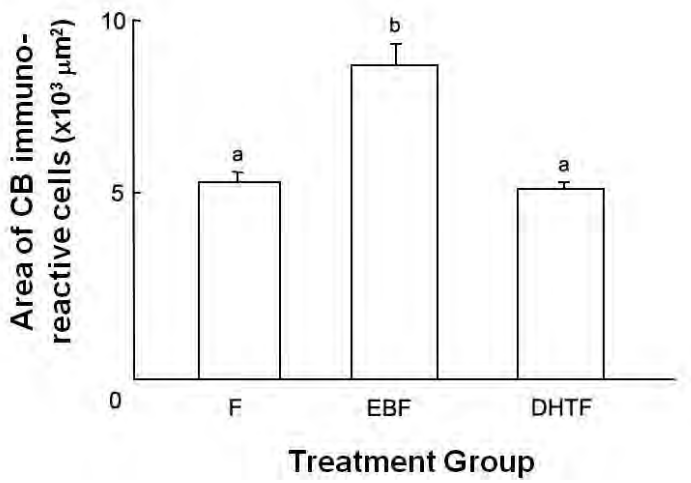
Orikasa & Sakuma, *J Comp Neurol,* 20 May 2010, doi:10.1002/cne.22419

The SDN-POA in C57/BL6J mice

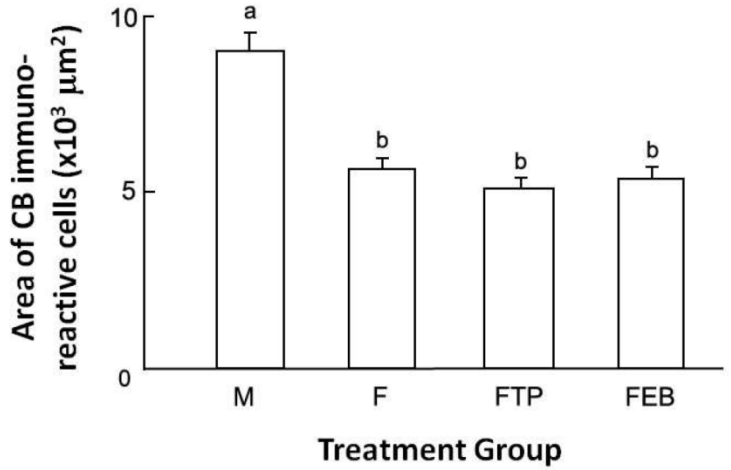
A. Neonatal testosterone masculinizes the SDN-POA



B. Estradiol, but not DHT masculinizes the SDN-POA



C. Endocrine manipulations as adults are ineffective



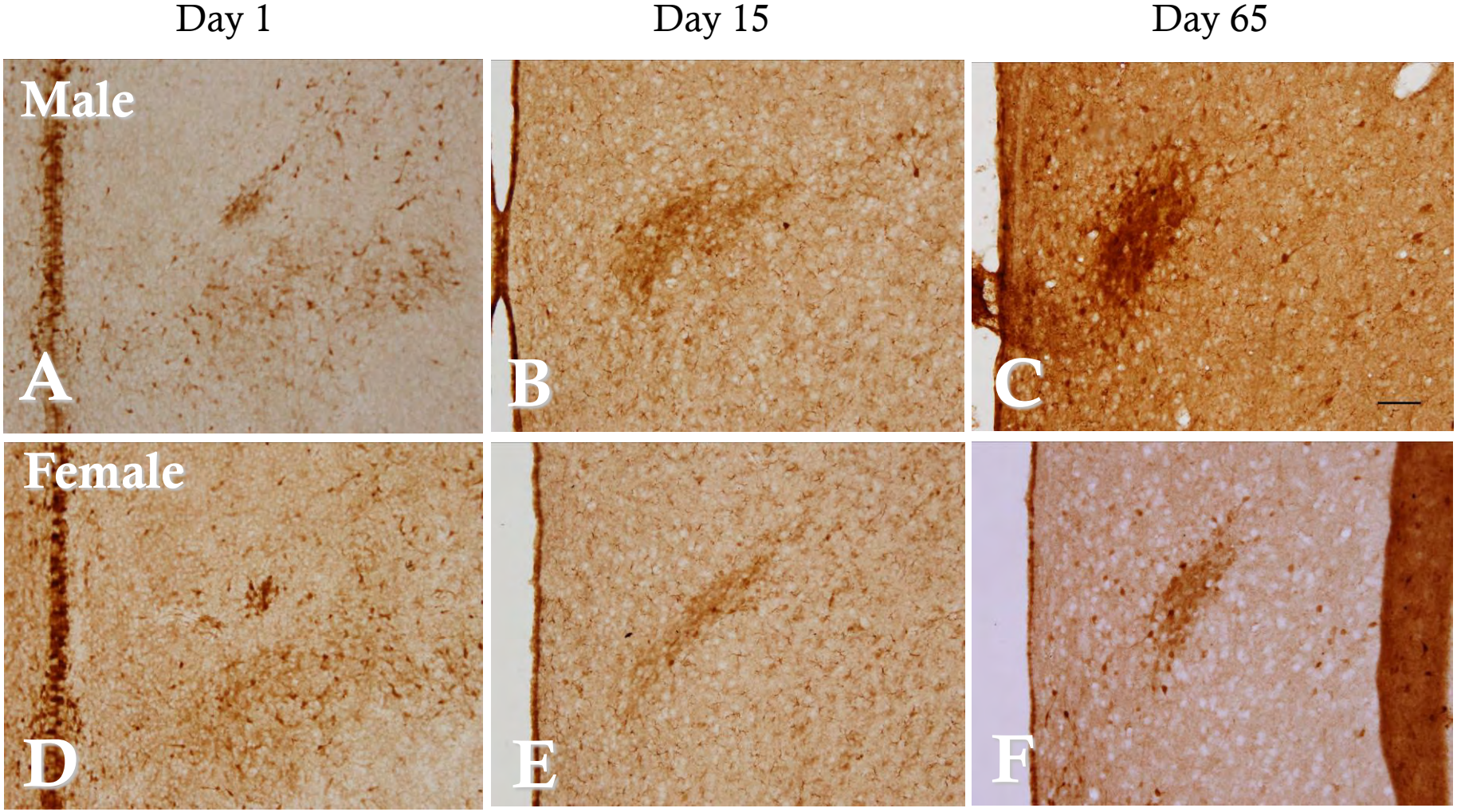
As in the rat, estrogen or aromatizable androgen masculinizes the mouse SDN-POA

Orikasa & Sakuma, *J Comp Neurol,* 20 May 2010, doi:10.1002/cne.22419

Morphological sex difference

- Apoptosis?
- Migration?
- Neurogenesis?

Calbindin D28k as a marker protein of the Rat SDN-POA



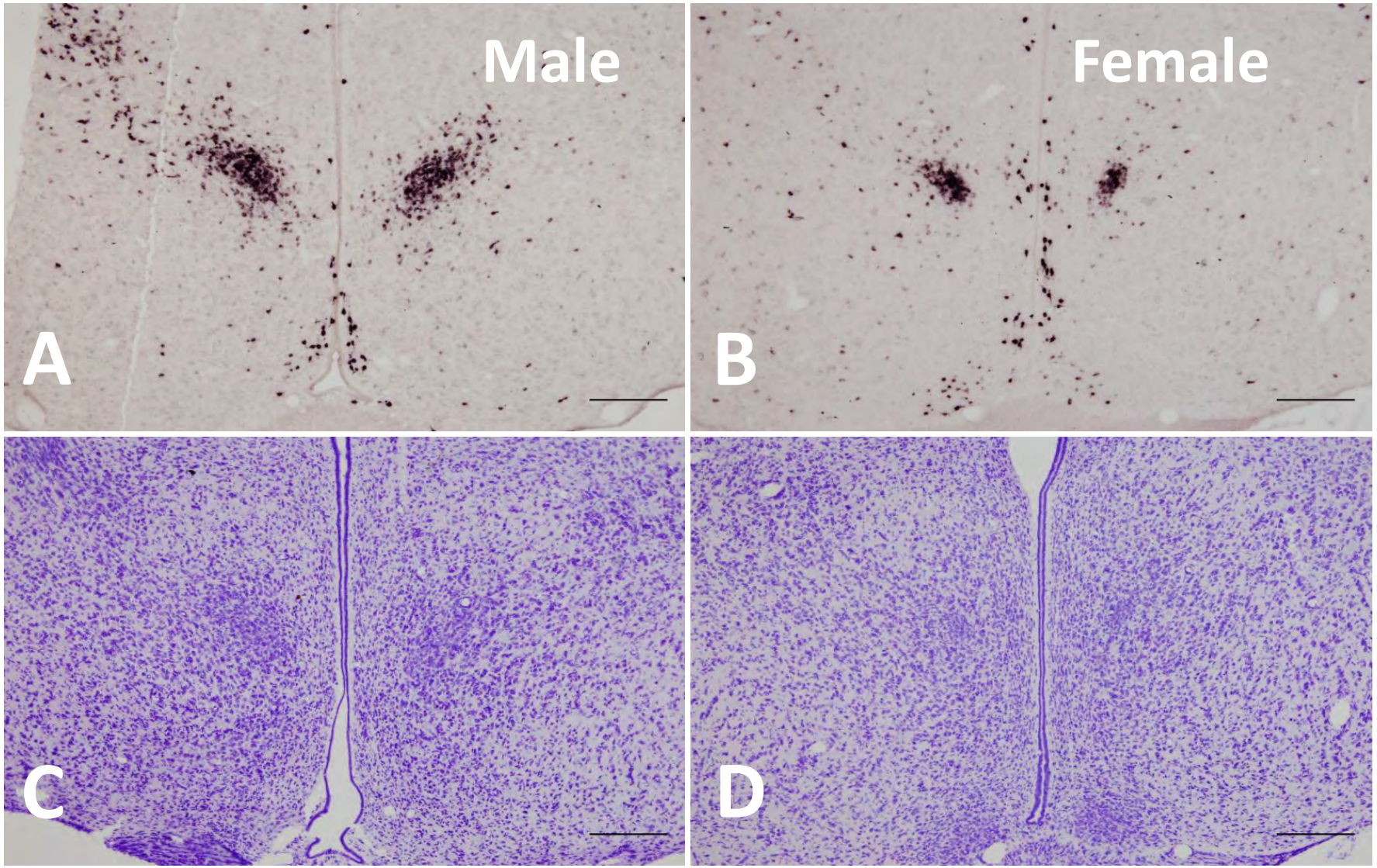
Orikasa et al, ***Endocrinology*** **148**: 1144, 2007

Morphological sex difference

- Apoptosis is unlikely

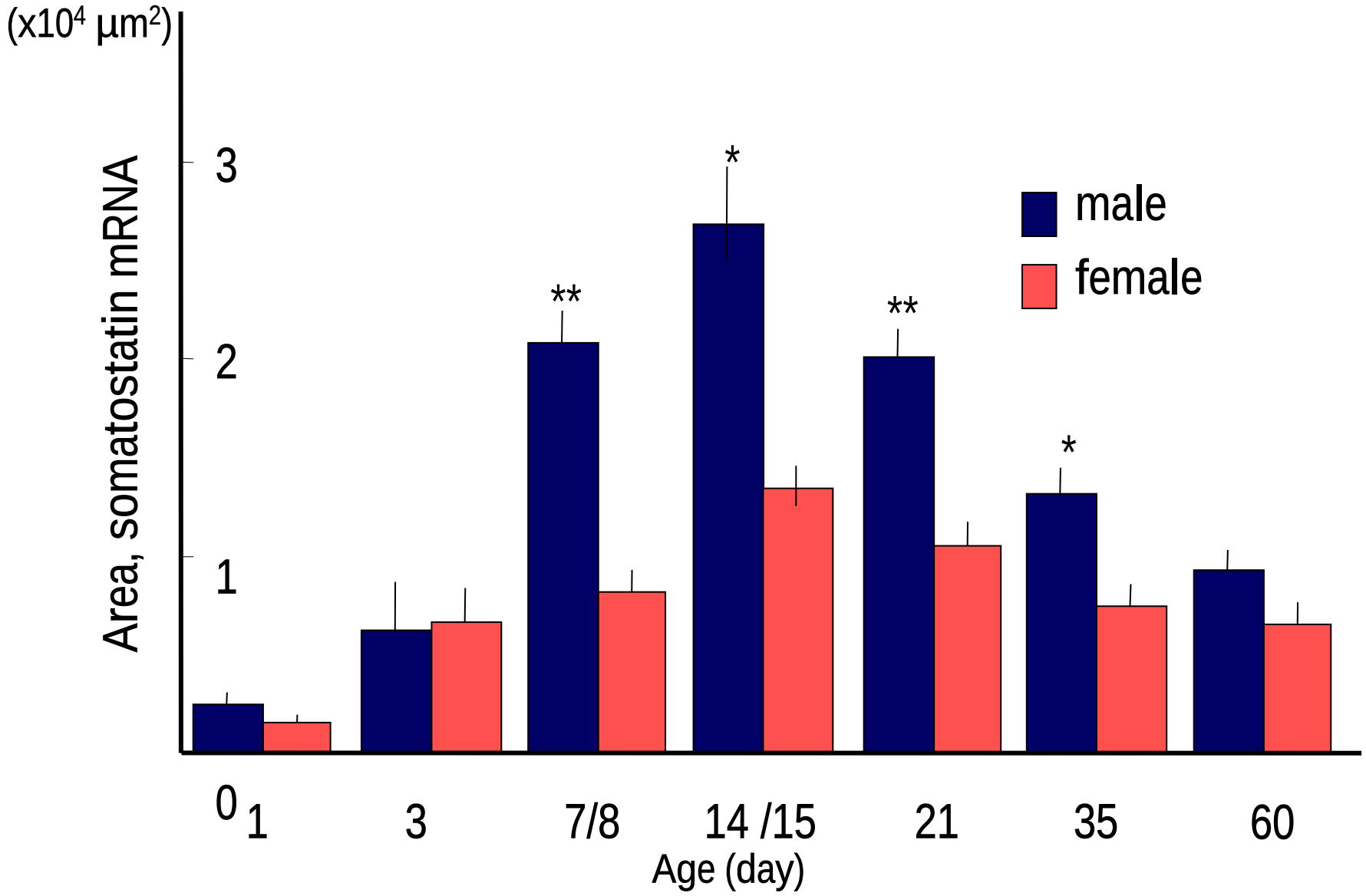
Somatostatin mRNA Expression in the SDN-POA

(14d old)



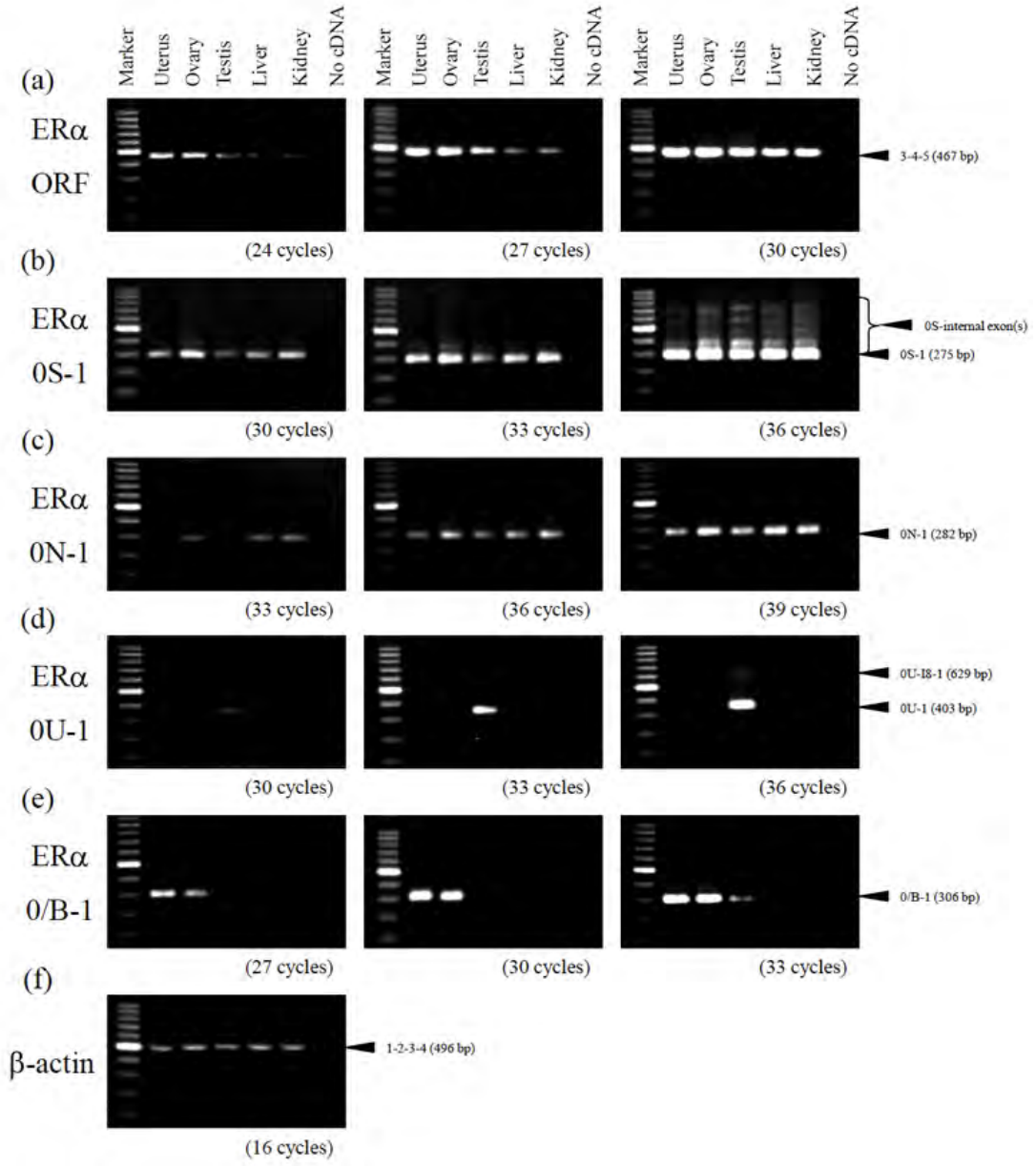
Orikasa et al, ***Endocrinology*** **148**: 1144, 2007

Developmental Changes of Male and Female Somatostatin mRNA Expression in the SDN-POA



Orikasa et al, ***Endocrinology*** **148**: 1144, 2007

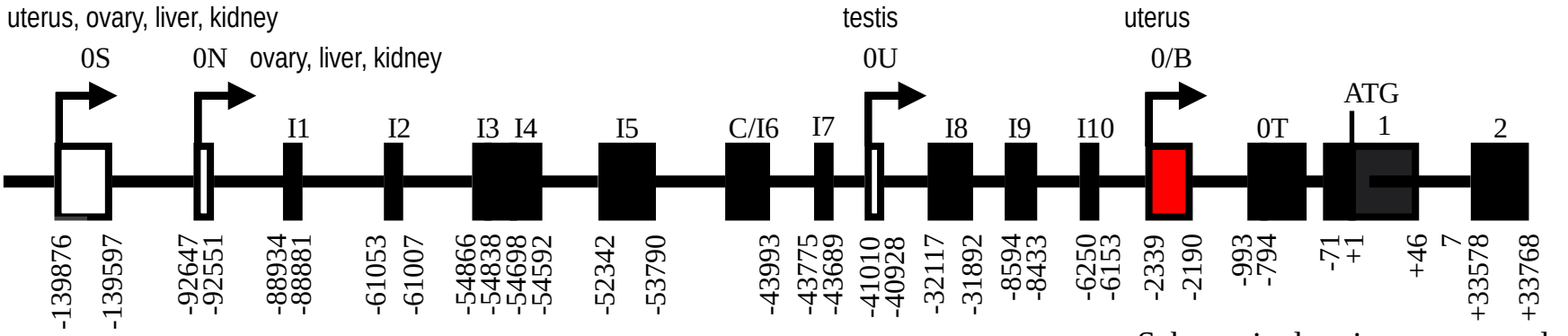
Tissue-specific promoter usage



Ishii *et al., Steroid Biochem Mol Biol* **118**: 59-69, 2010

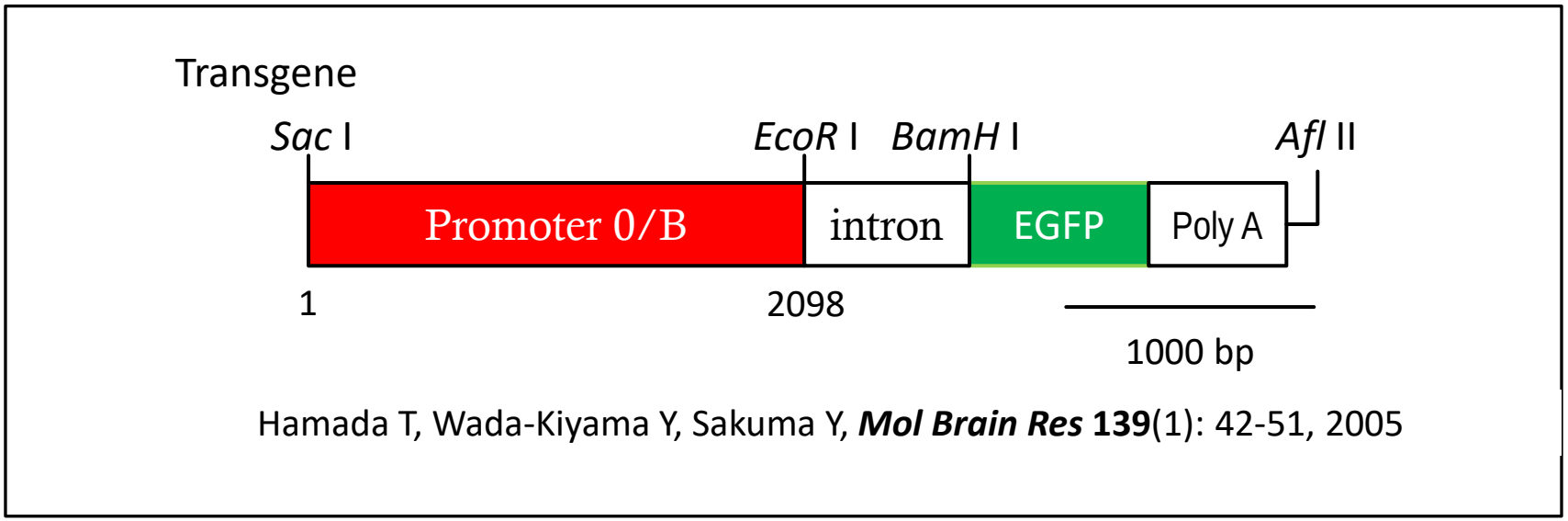
Visualization of the SDN-POA in ERα Promoter Transgenic Rat

Location: Rat chromosome 1, 1p11



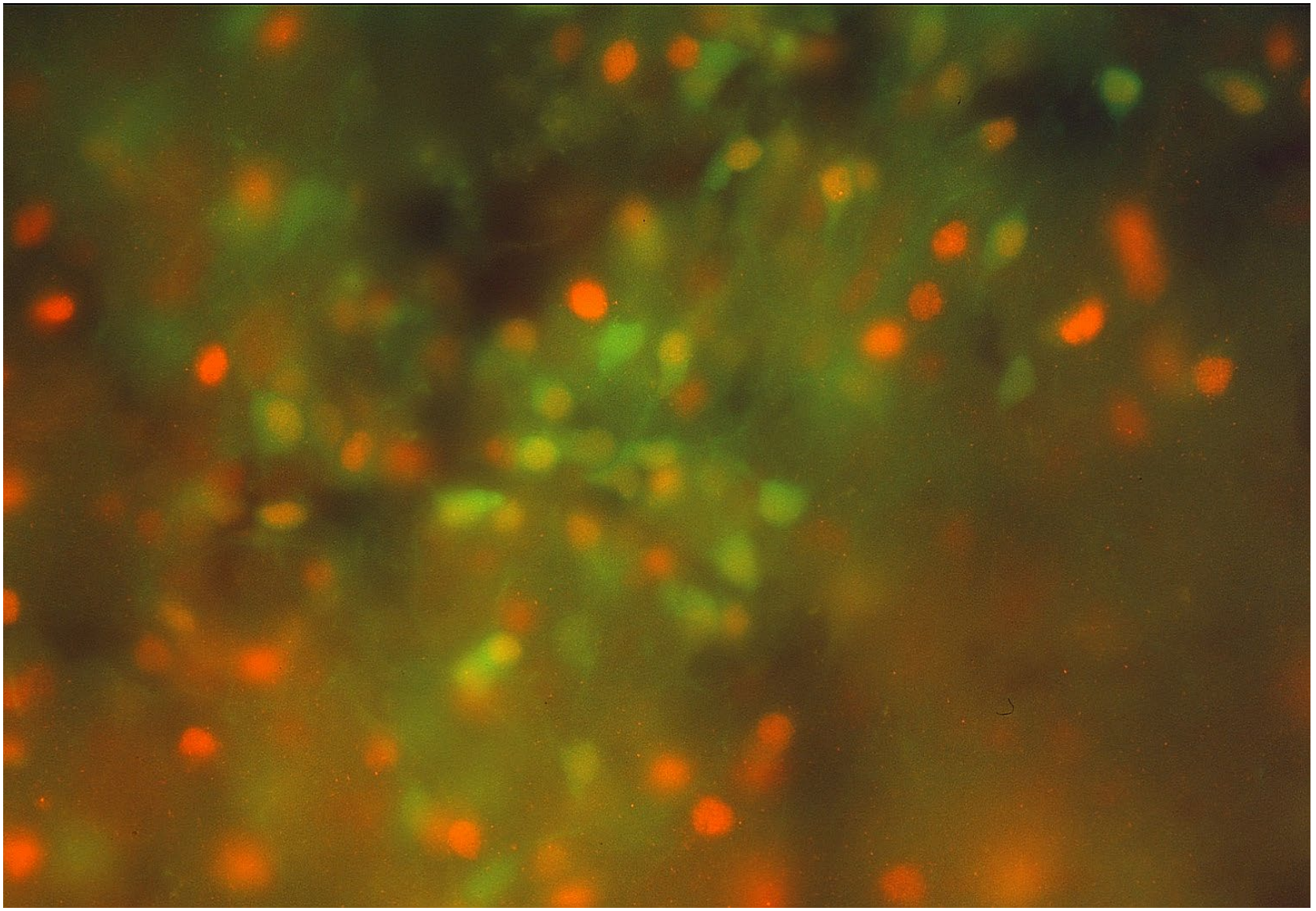
Schematic drawing, not to scale

Ishii H, Kobayashi M, Sakuma Y, ***J Steroid Biochem Mol Biol*** **118**(1/2): 59-69, January 2010



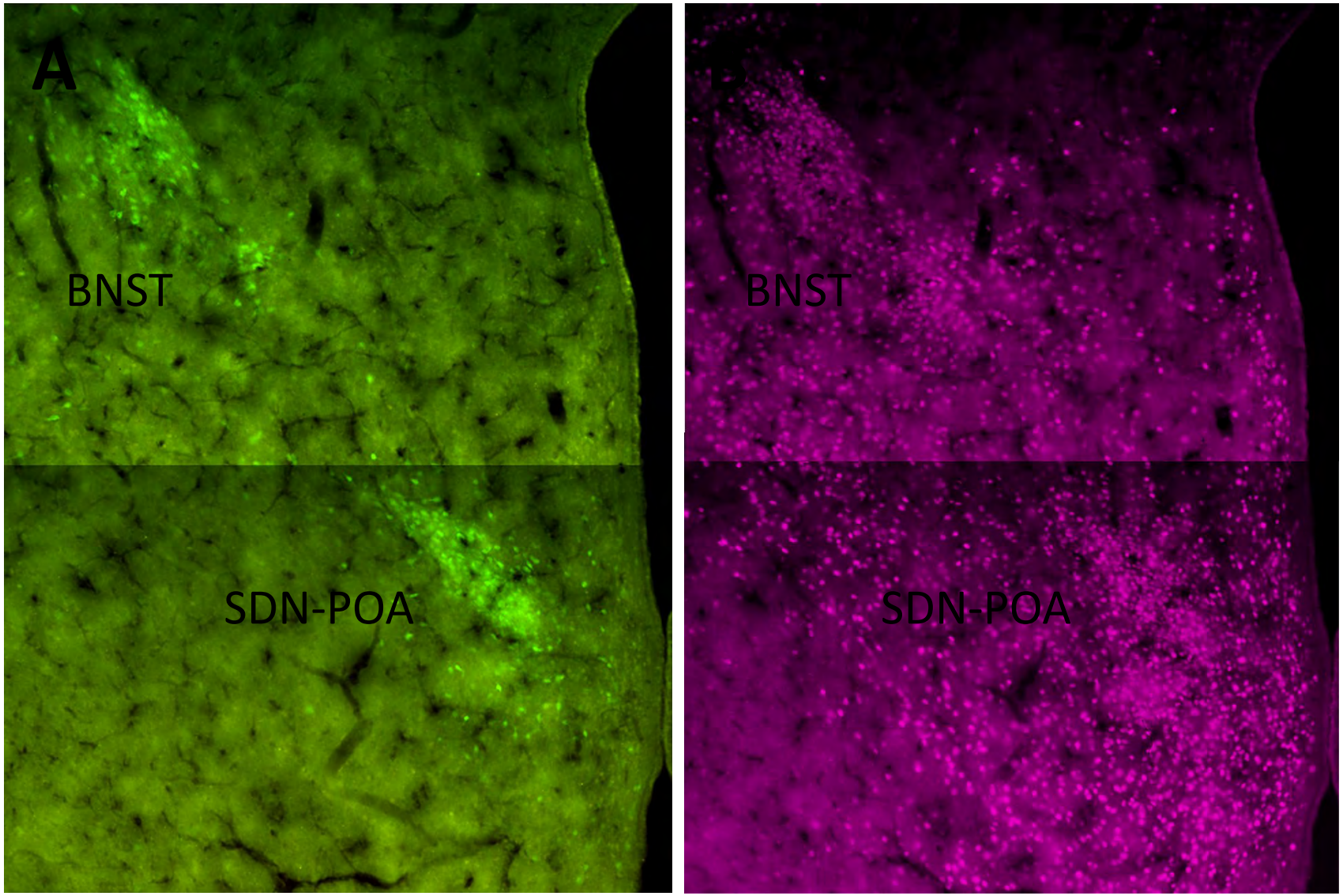
Hamada T, Wada-Kiyama Y, Sakuma Y, ***Mol Brain Res*** **139**(1): 42-51, 2005

Double Labels: irERα & EGFP



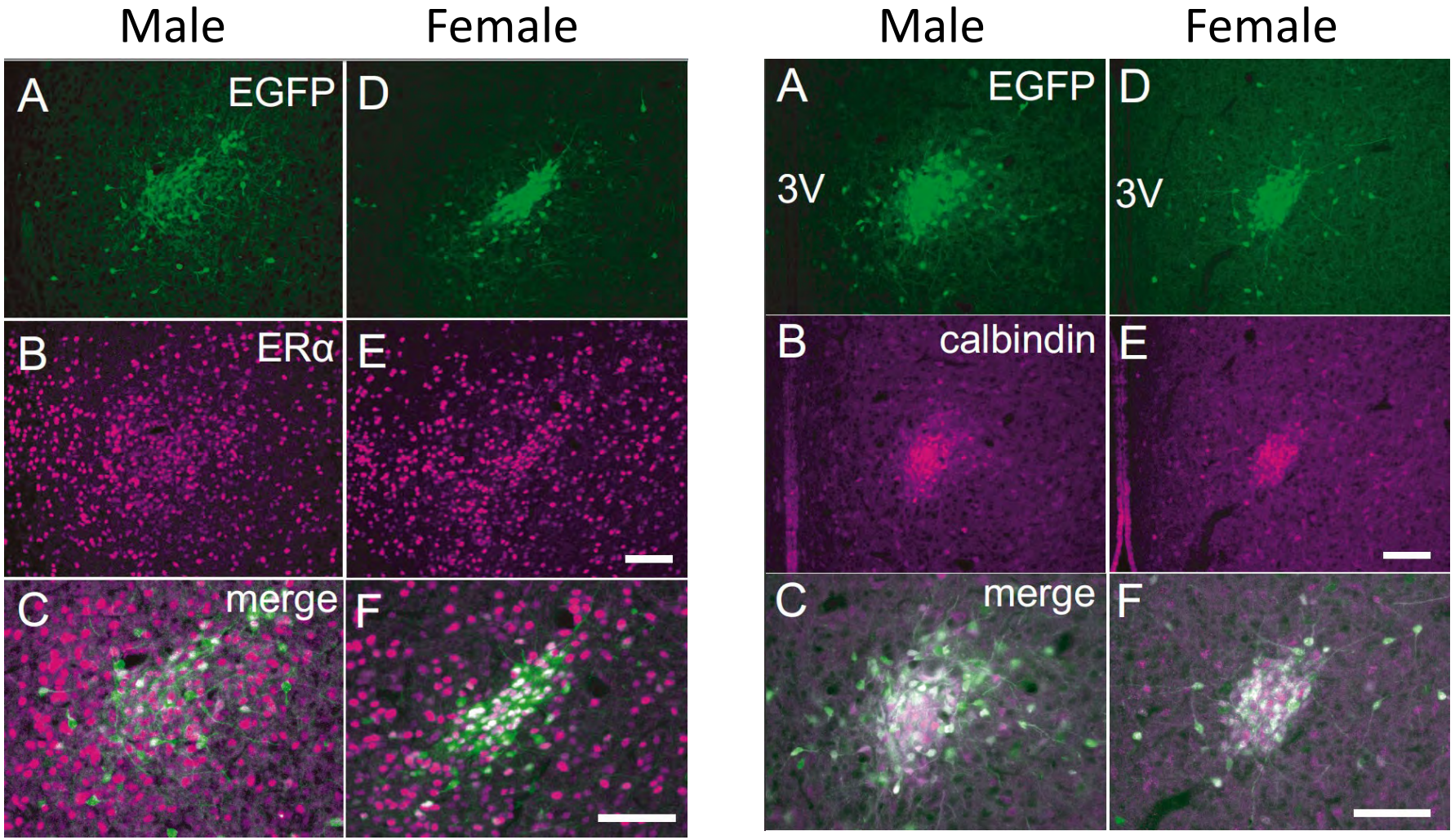
Hamada *et al., Mol Brain Res*, 2005

EGFP fluorescence (A) and ERα immunoreactivity (B) in the SDN-POA of the ERα-gene promoter 0/B transgenic rat (day 21, male)



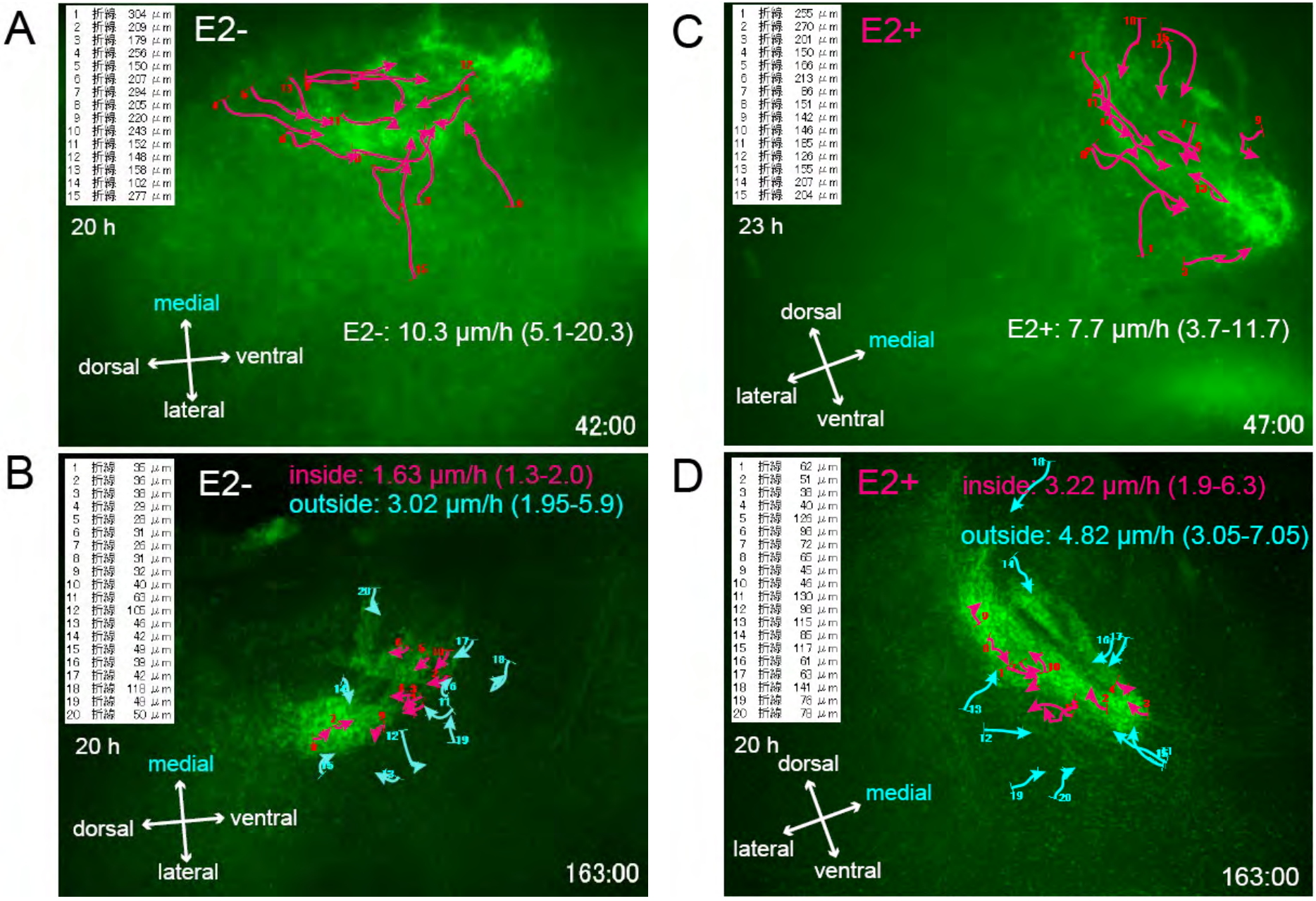
Hamada & Sakuma, ***Endocrinology*** 151(4): 1923-1928, April 2010

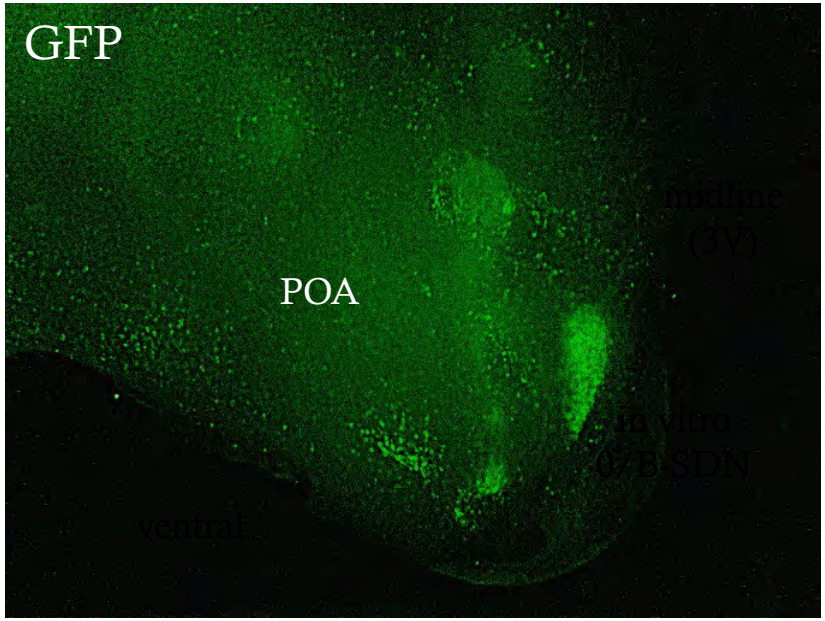
Sexually Dimorphic Nucleus of the Rat Preoptic Area (SDN-POA)

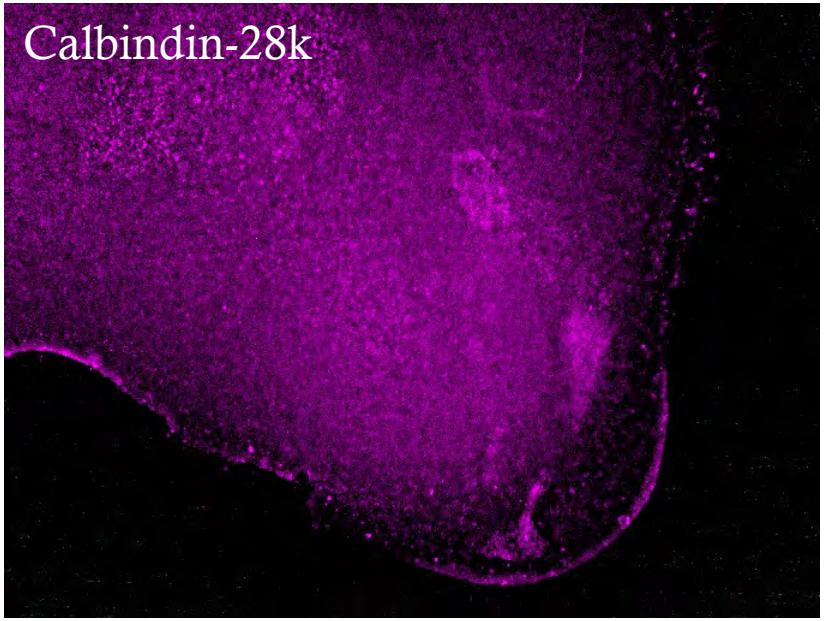


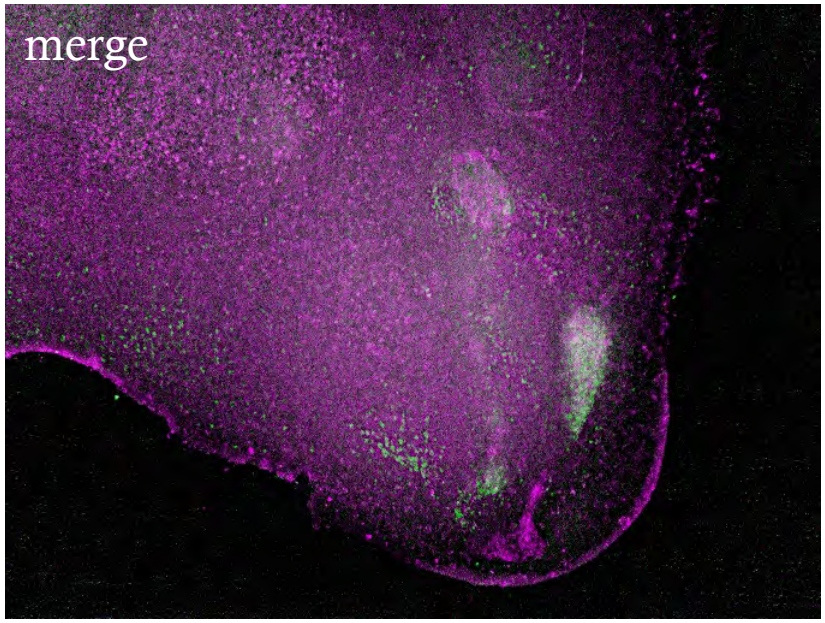
Hamada & Sakuma, ***Endocrinology*** 151(4): 1923-1928, April 2010

Migration of 0/B-SDN cells in slice culture





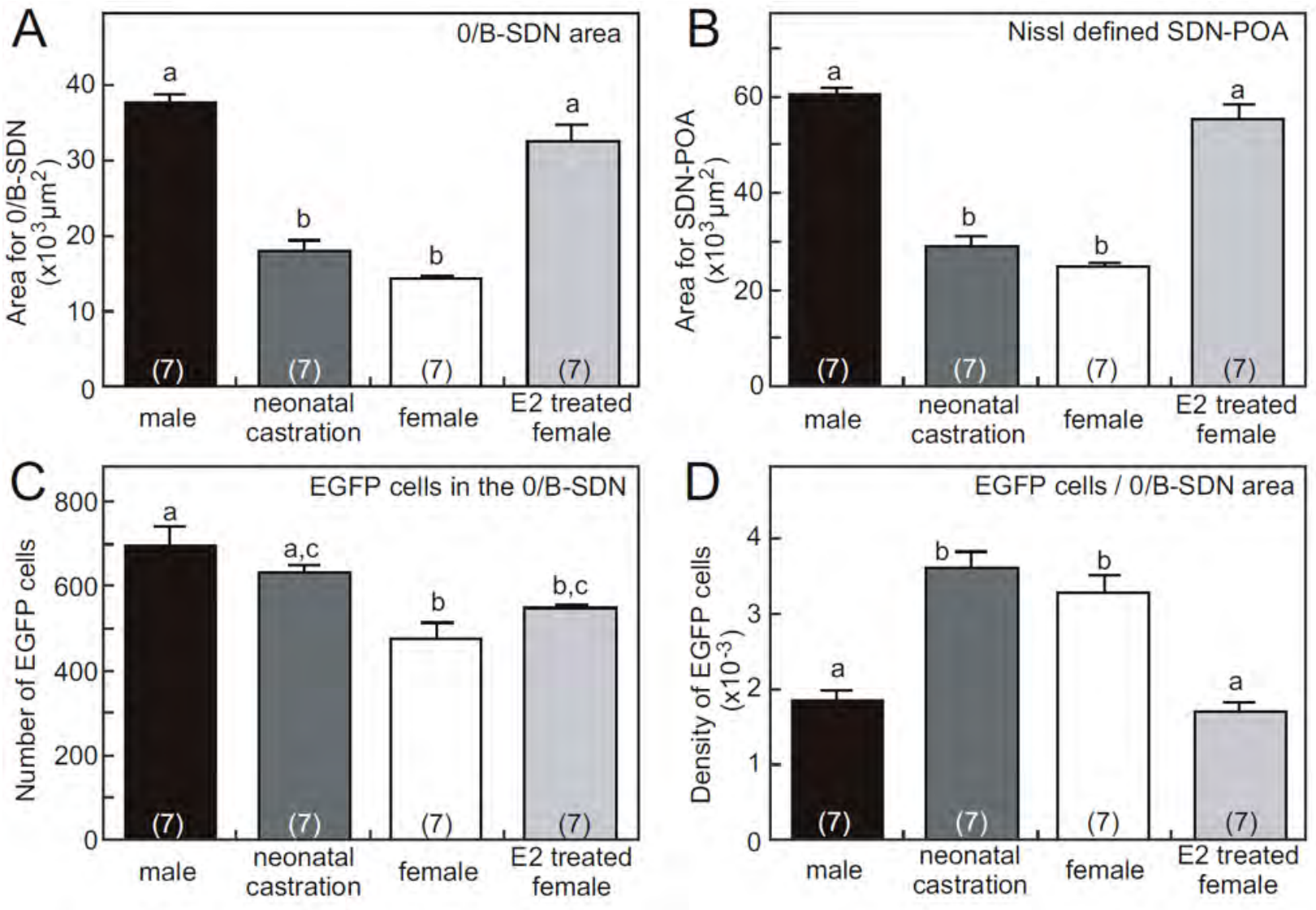




Slice culture: E18 (DIV 1)
Fixation: DIV 20

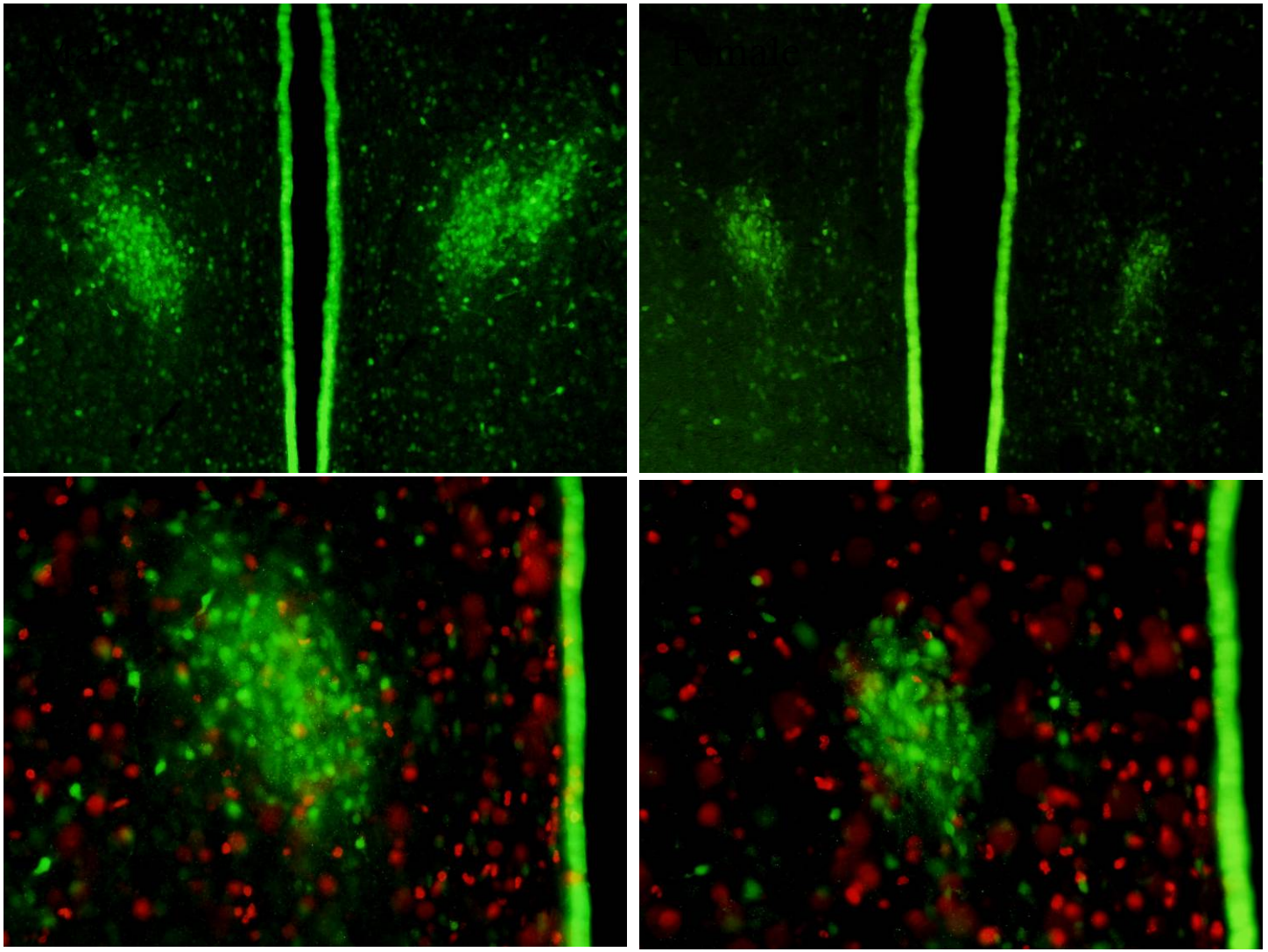
0206F3

Effects of estradiol treatment on the 0/B SDN-POA



Hamada & Sakuma, ***Endocrinology*** 151(4): 1923-1928, April 2010

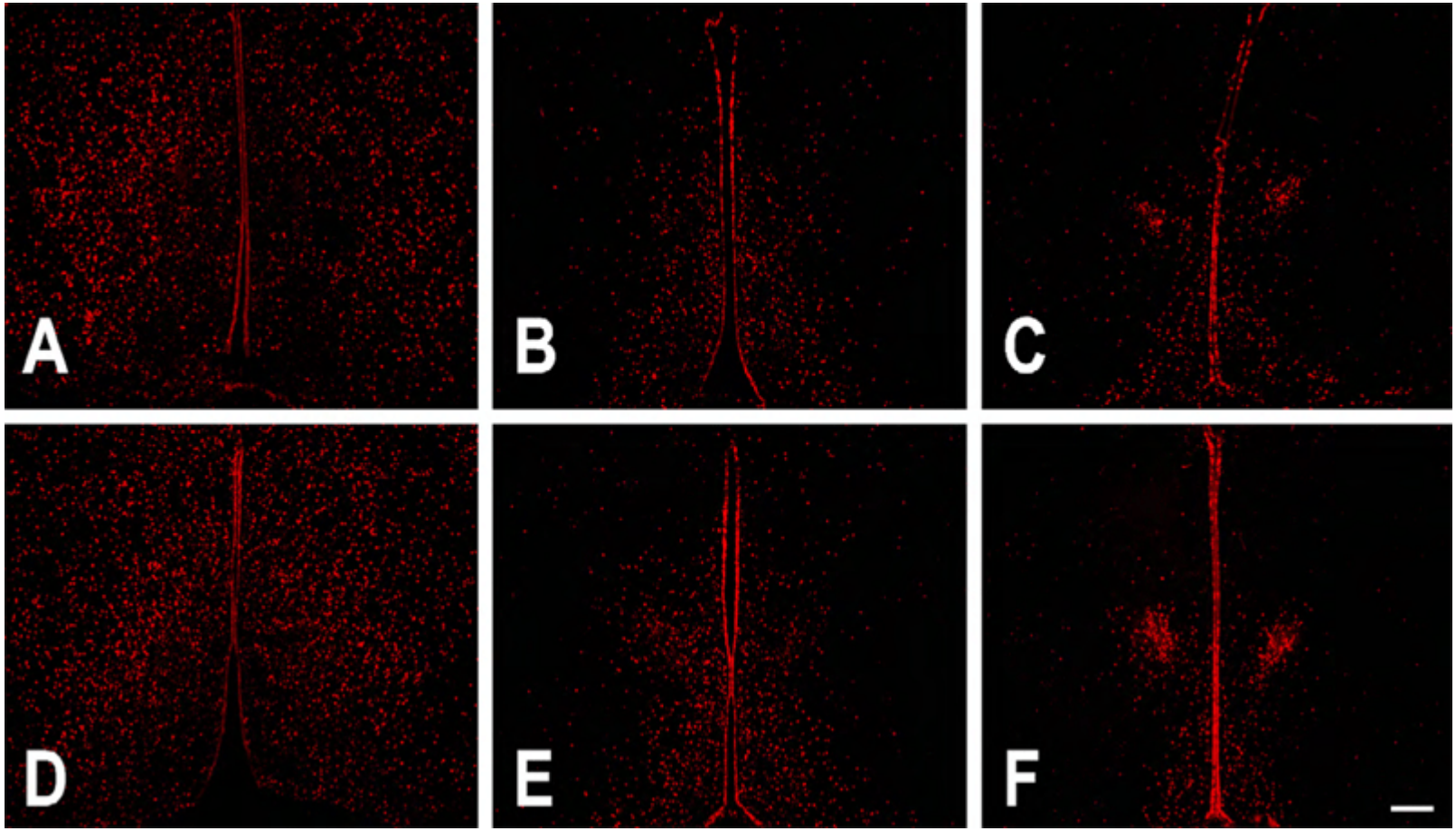
BrdU on P1-10 do not label calbindin expressing cells in the SDN-POA in 14/15-day old rats



Green, calbindin; Red, Brdu

BrdU-immunoreactive cells in the rat POA

BrdU on ED 14 ED 16 ED 18 PD15



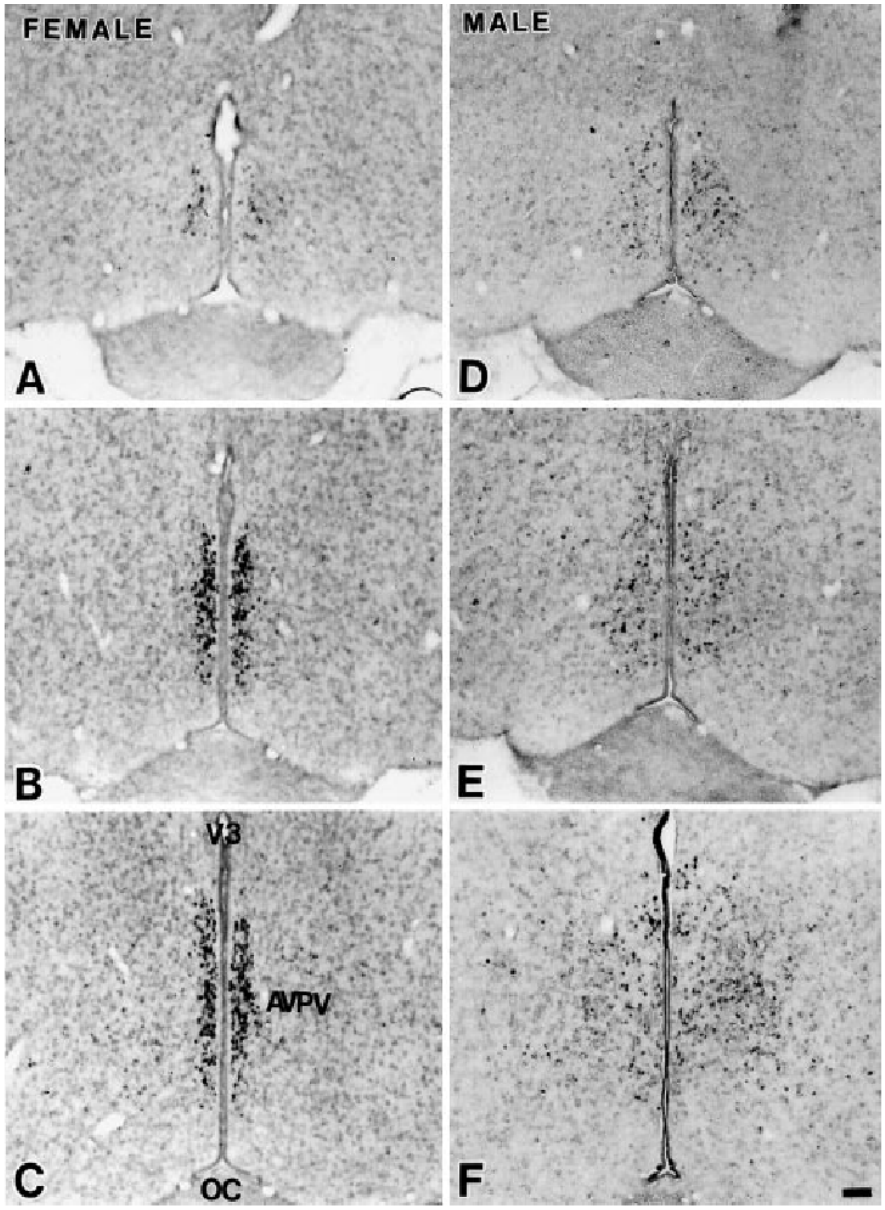
Orikasa C et al, Neurosci Res (2010), doi:10.1016/j.neures.2010.05.008

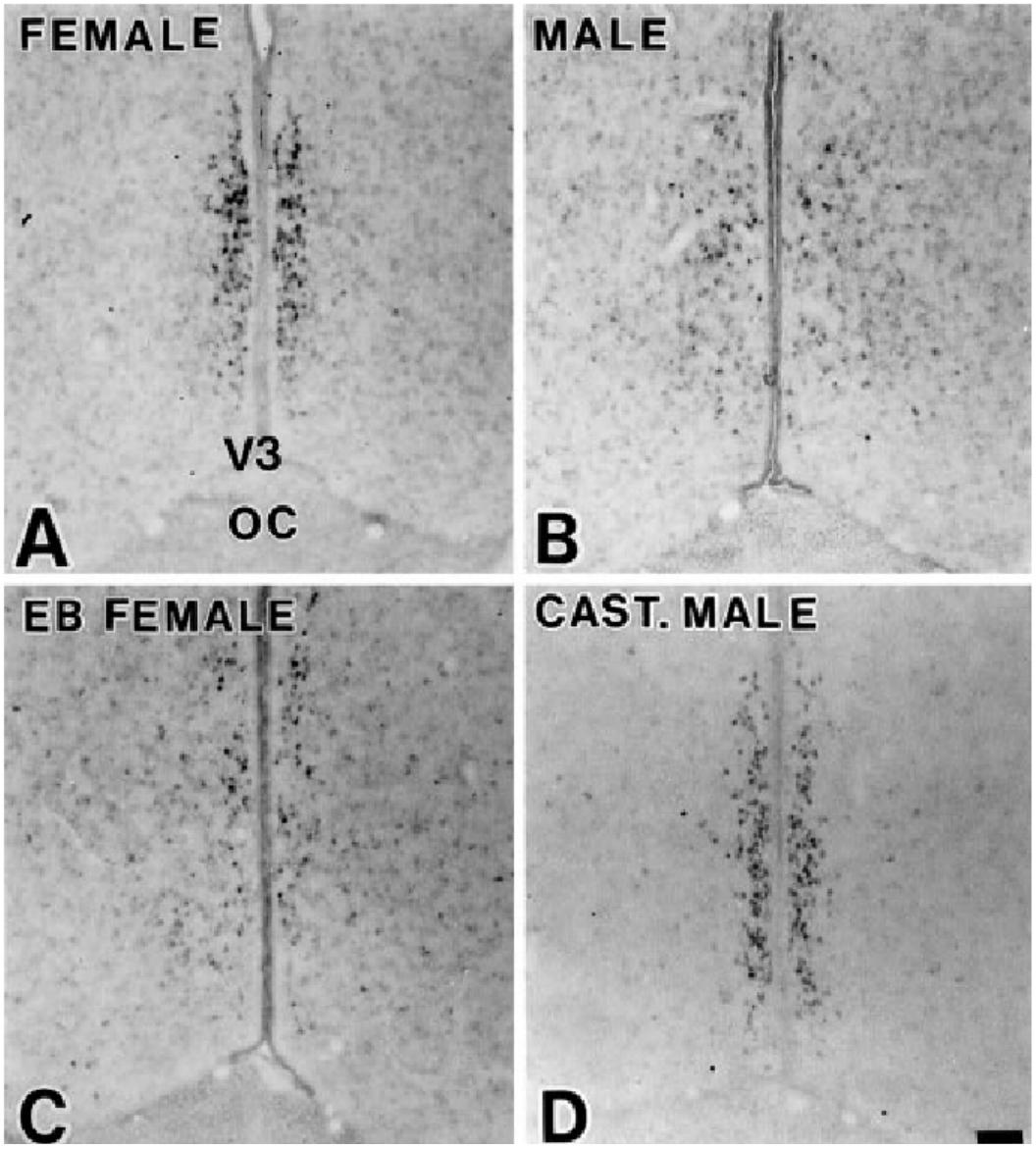
Morphological sex difference

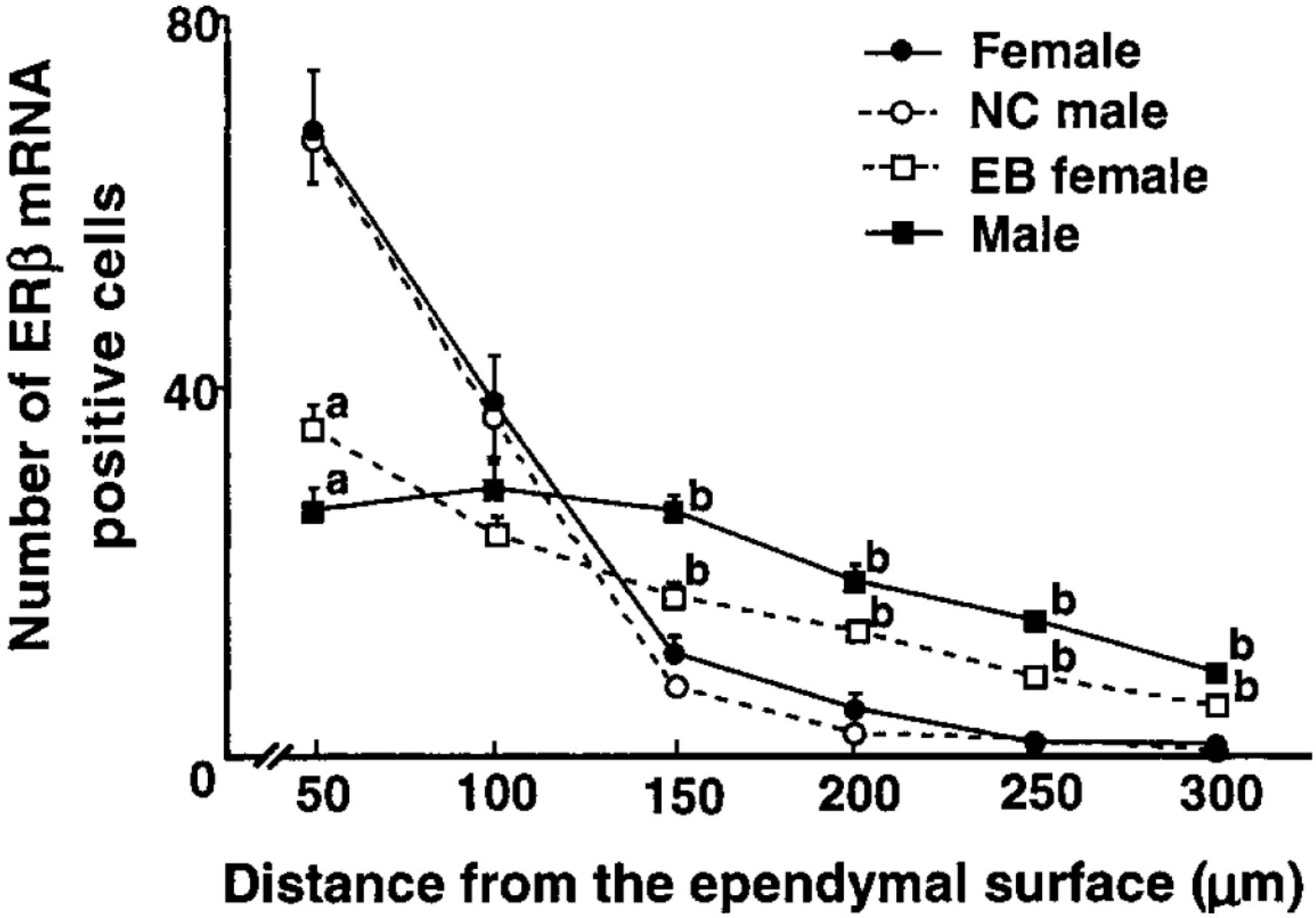
- No neurogenesis at the time of the establishment of Rat SDN-POA

Estrogen-induced neuronal migration establishes the SDN-POA

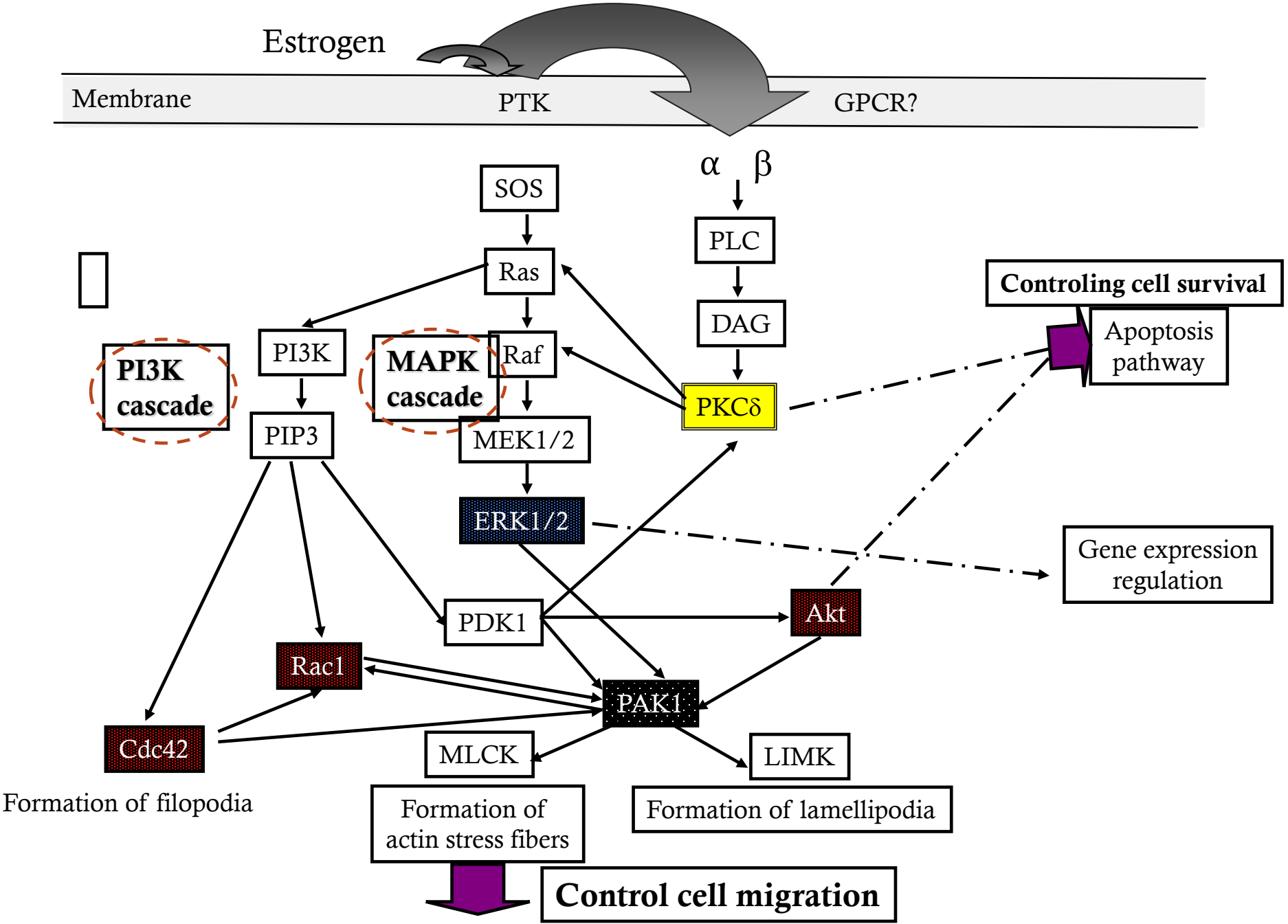
Another evidence for migration: The anteroventral periventricular nucleus (室周囲核, AVPV)







A Model of the Estrogen Signaling Involving PKCδ in POA of Newborn Rats



- 内側視索前野の性的二型核
- 前室周囲核

性差は主に細胞移動の結果

GnRH neurons

Gonadotropin-releasing hormone

Rat gonadotropin-releasing hormone neurons tagged with EGFP

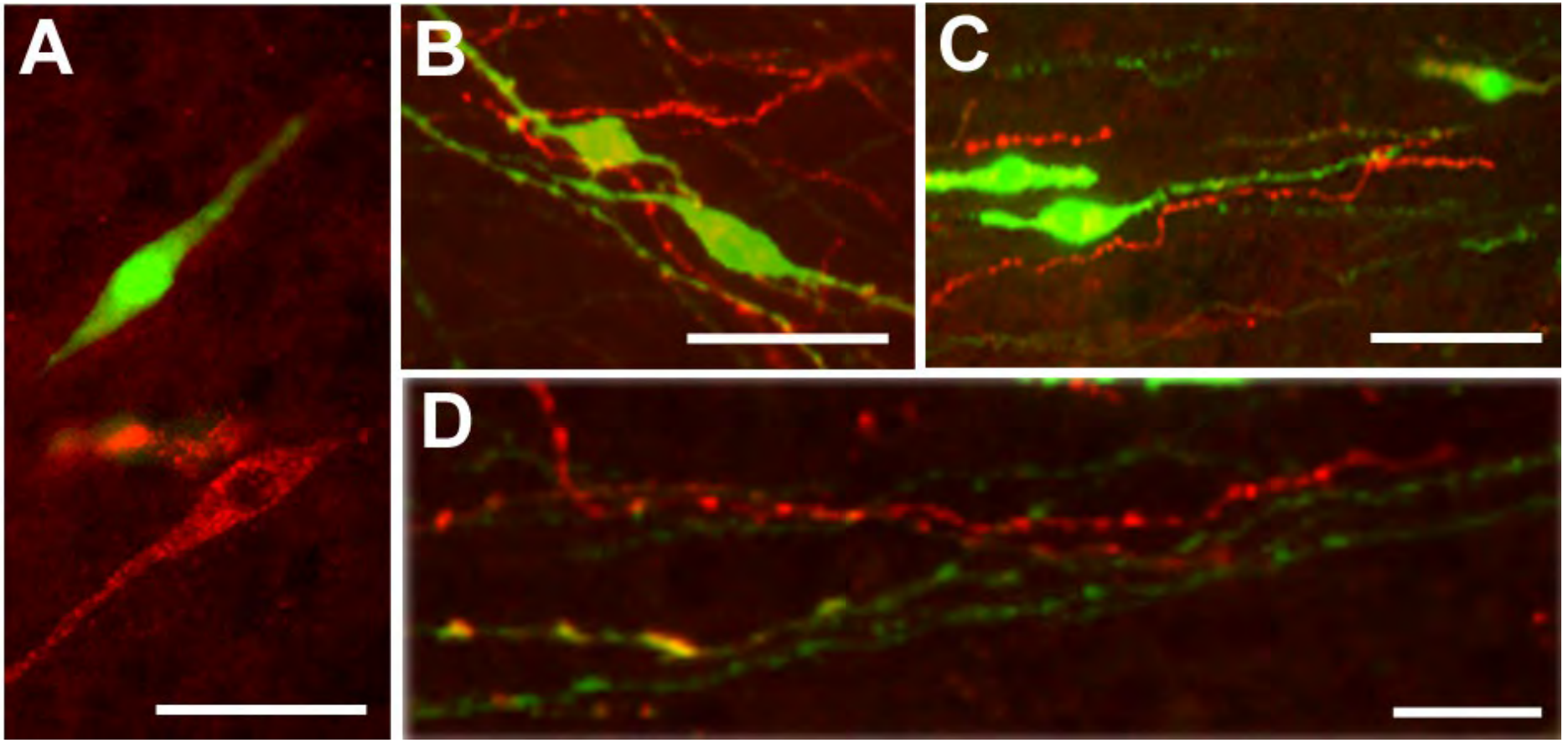
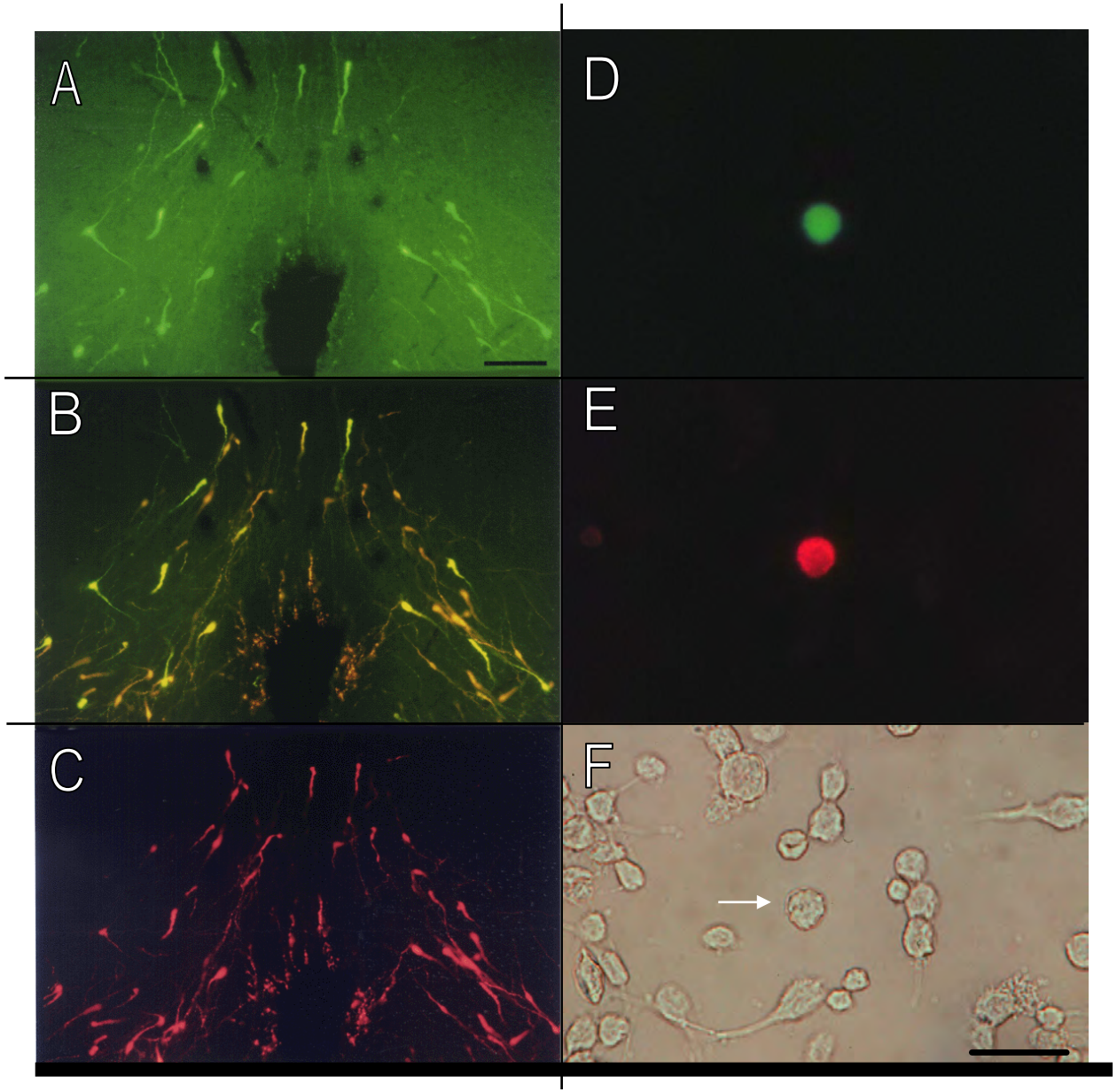


Fig. 7. Cy3-labeled GnRH molecular variants in perikarya and fibers (red) in the septopreoptic continuum in GnRH1-EGFP rat. ***A***, Cy3-labeled GnRH2 cell (red) next to a GnRH1-EGFP positive cell (green). Cy3-labeled GnRH3 (***B***) and Cy3-labeled GnRH2 (***C***) fibers (red) in close apposition to GnRH1-EGFP cells. ***D***, Cy3-labeled lamprey-III GnRH fibers in close contact with GnRH1-EGFP positive fibers. Scale bars, 50 μm

Rat gonadotropin-releasing hormone neurons tagged with EGFP



Kato *et al.*, ***Endocrinology* 144**: 5118, 2003

Na^+, K^+, Ca^{2+} channels in GnRH neurons

- Voltage-gated Ca^{2+} channels

  L, N, P/Q, R, T- channels

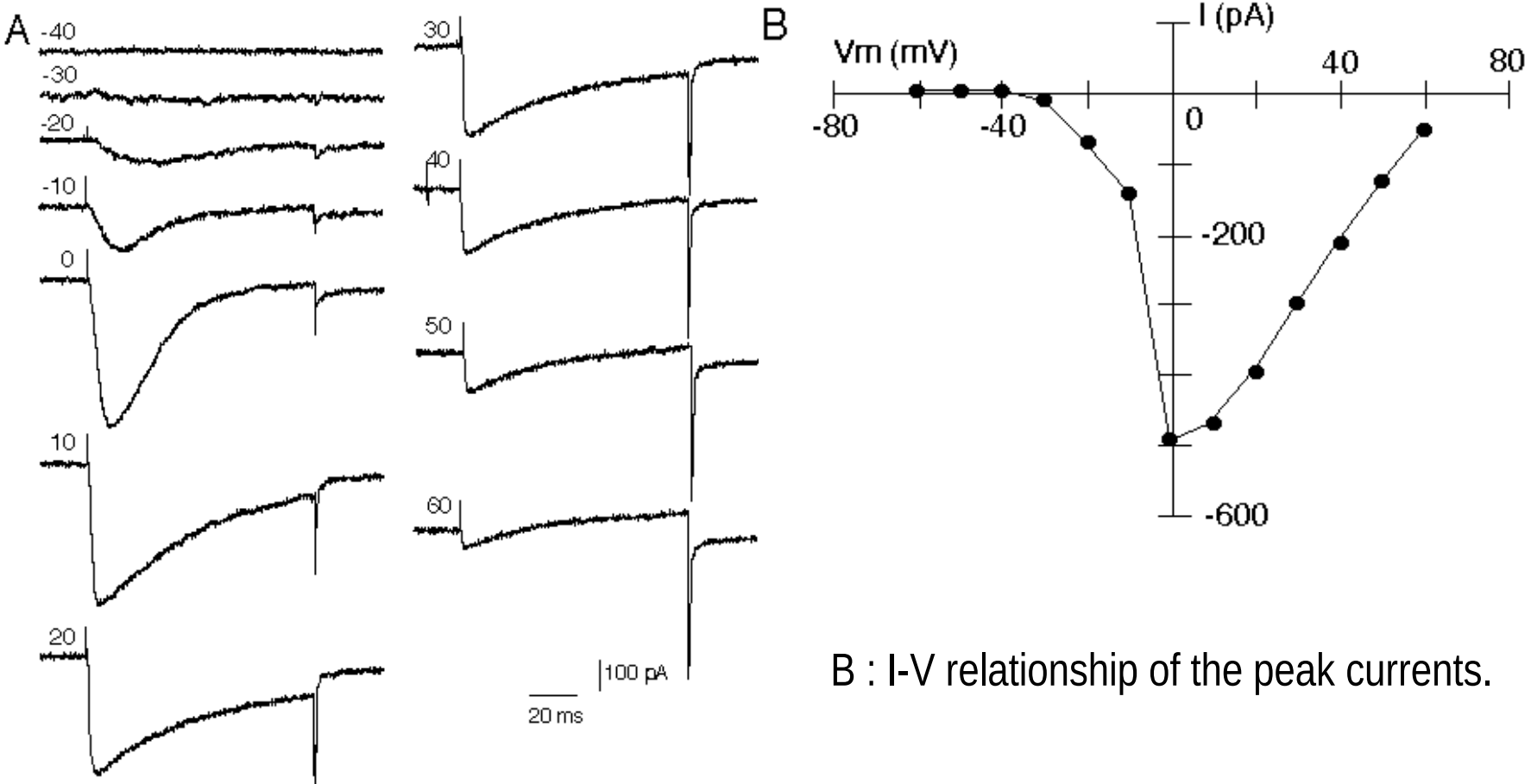
- Ca^{2+}/Voltage-dependent K^+ channels

  KCMM, BK currents determine neuronal excitability

- Ca^{2+}-activated K^+ channels

  KCMN, SK currents sustain neuronal bursts

In neonate GnRH neurons, high voltage activated Ca^{2+} currents were observed, while low voltage activated currents were negligible.



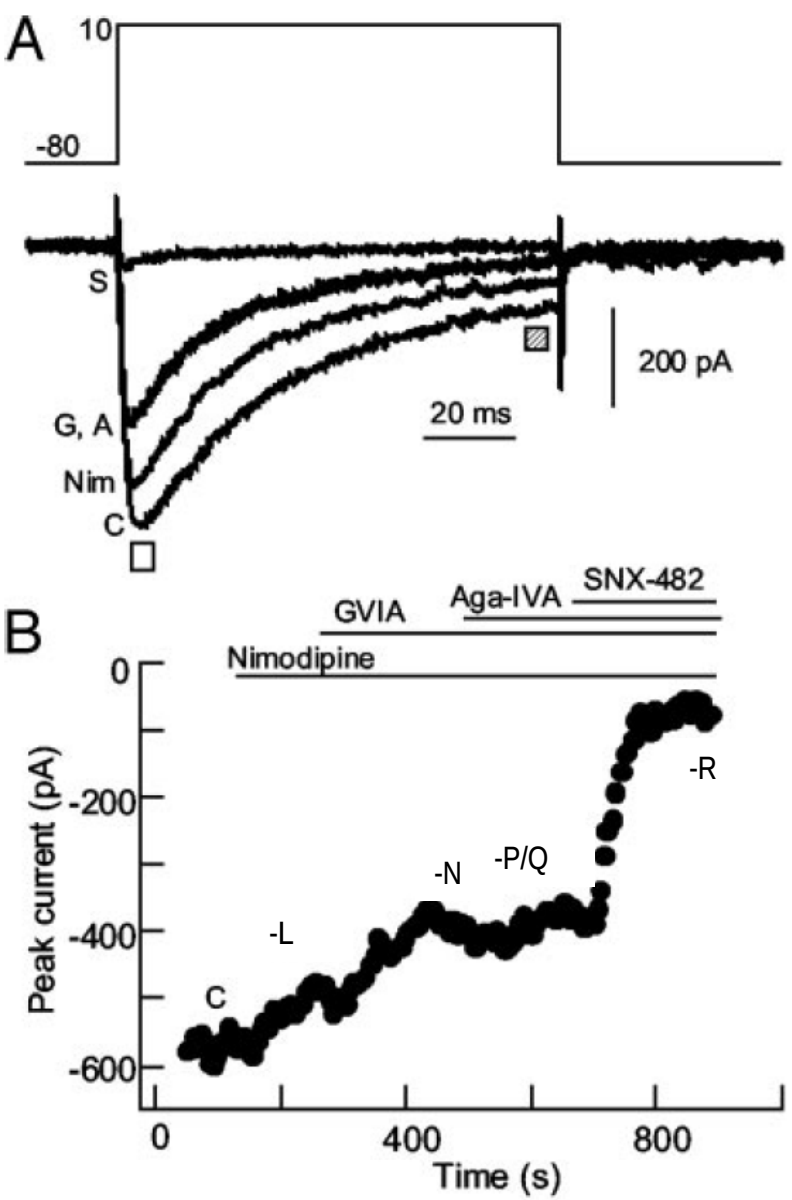
B : I-V relationship of the peak currents.

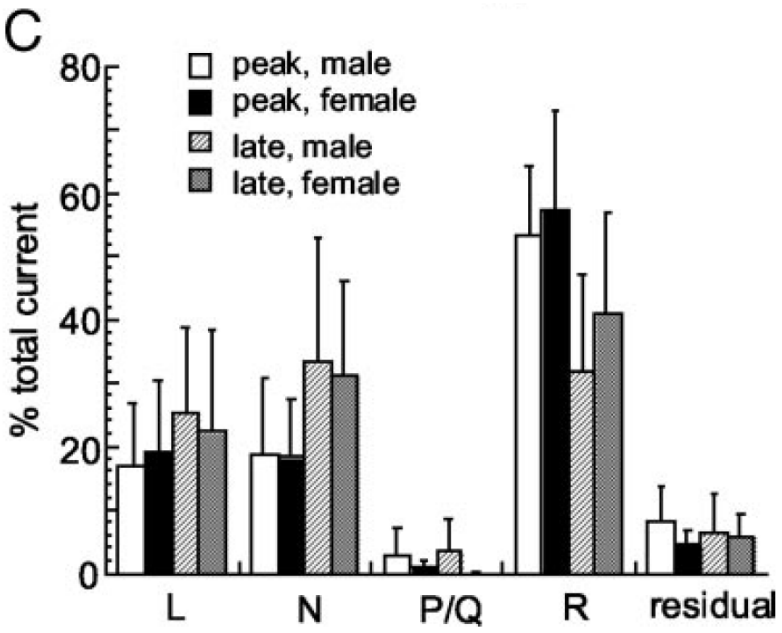
A: Cells were clamped at -80 mV in the presence of 0.3 mM TTX in the extracellular fluid, and given 100-ms voltage pulses from -40 mV to 60 mV at 10-mV steps

Kato, M. et al. Endocrinology 2003;144:5118-5125

Calcium currents in rat GnRH neurons tagged with EGFP

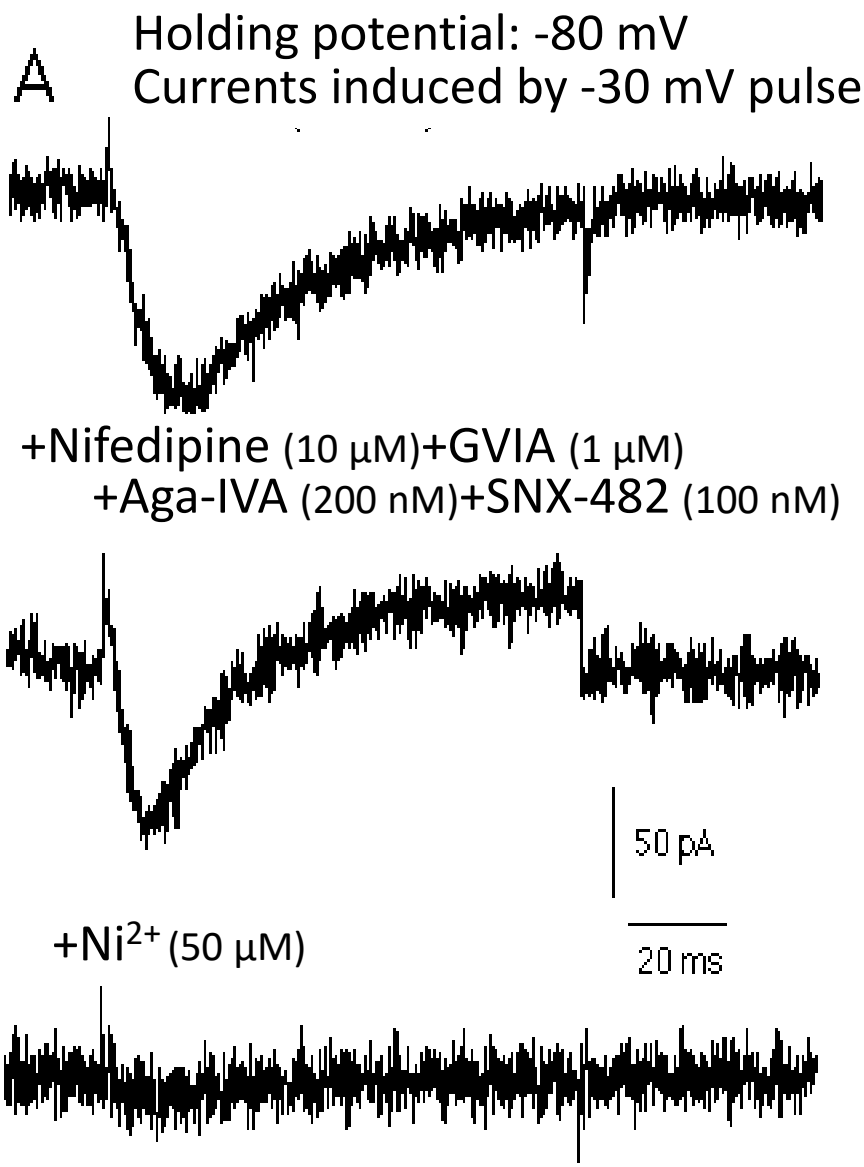
Neonate

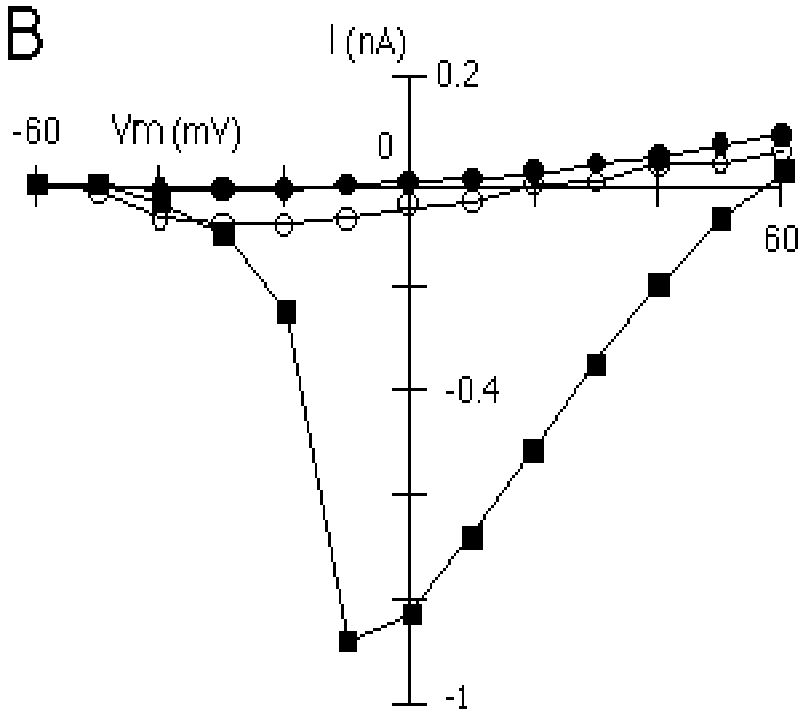




Kato, M. et al. Endocrinology 2003;144:5118-5125

In pubertal GnRH neurons, both high and low voltage activated Ca^{2+} currents were observed.



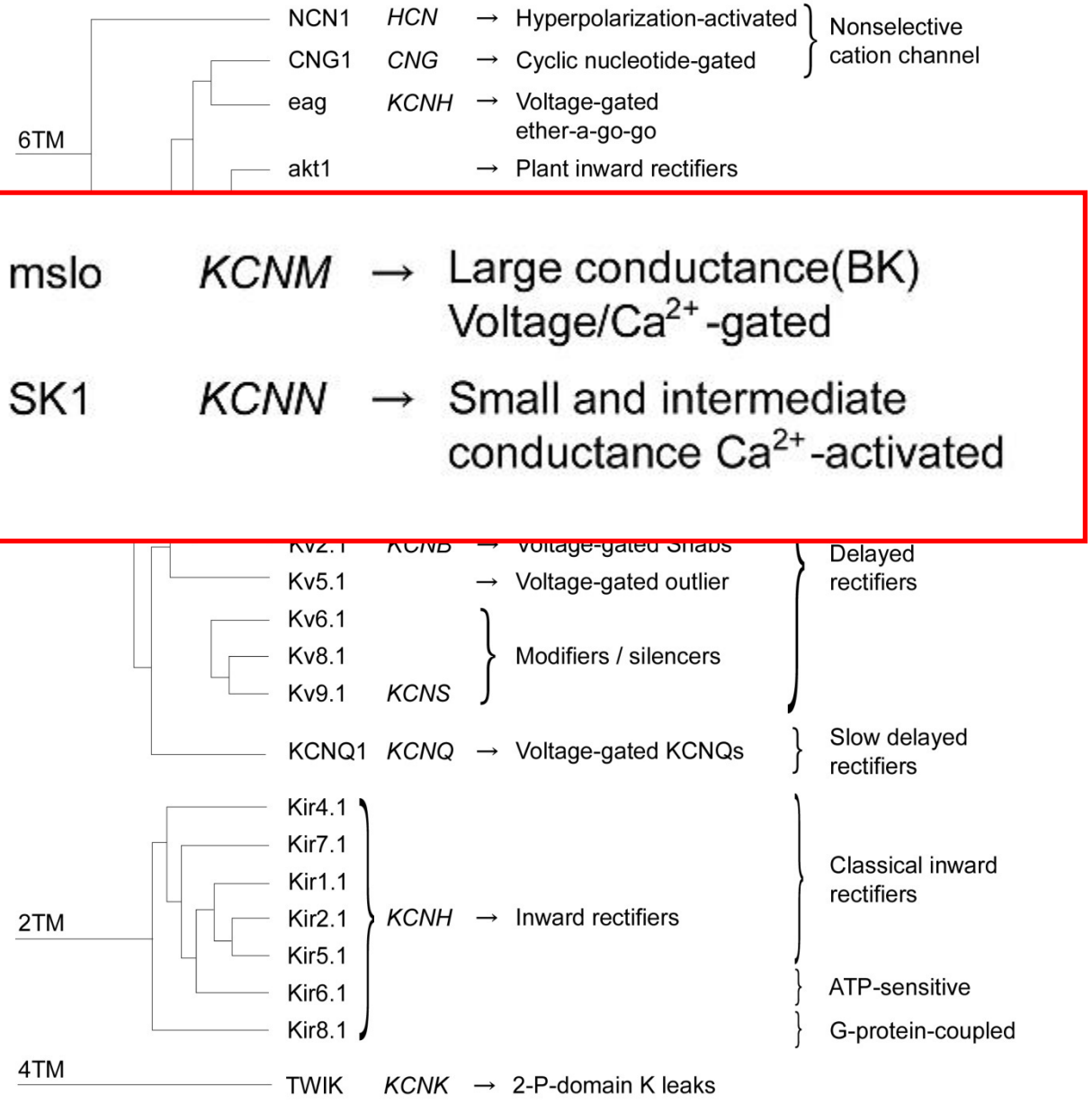


I-V relationship of the peak current in the control (■), with nifedipine, GVIA, Aga-IVA, SNX-482 (○) and with addition of Ni^{2+} (●).

Kato, M. et al. Endocrinology 2003;144:5118-5125

- GnRH neurons express functional L-, N-, P/Q-, R- and T-type channels.
- Expressions of P/Q- and T-type channels were developmentally regulated.

K^+ channel

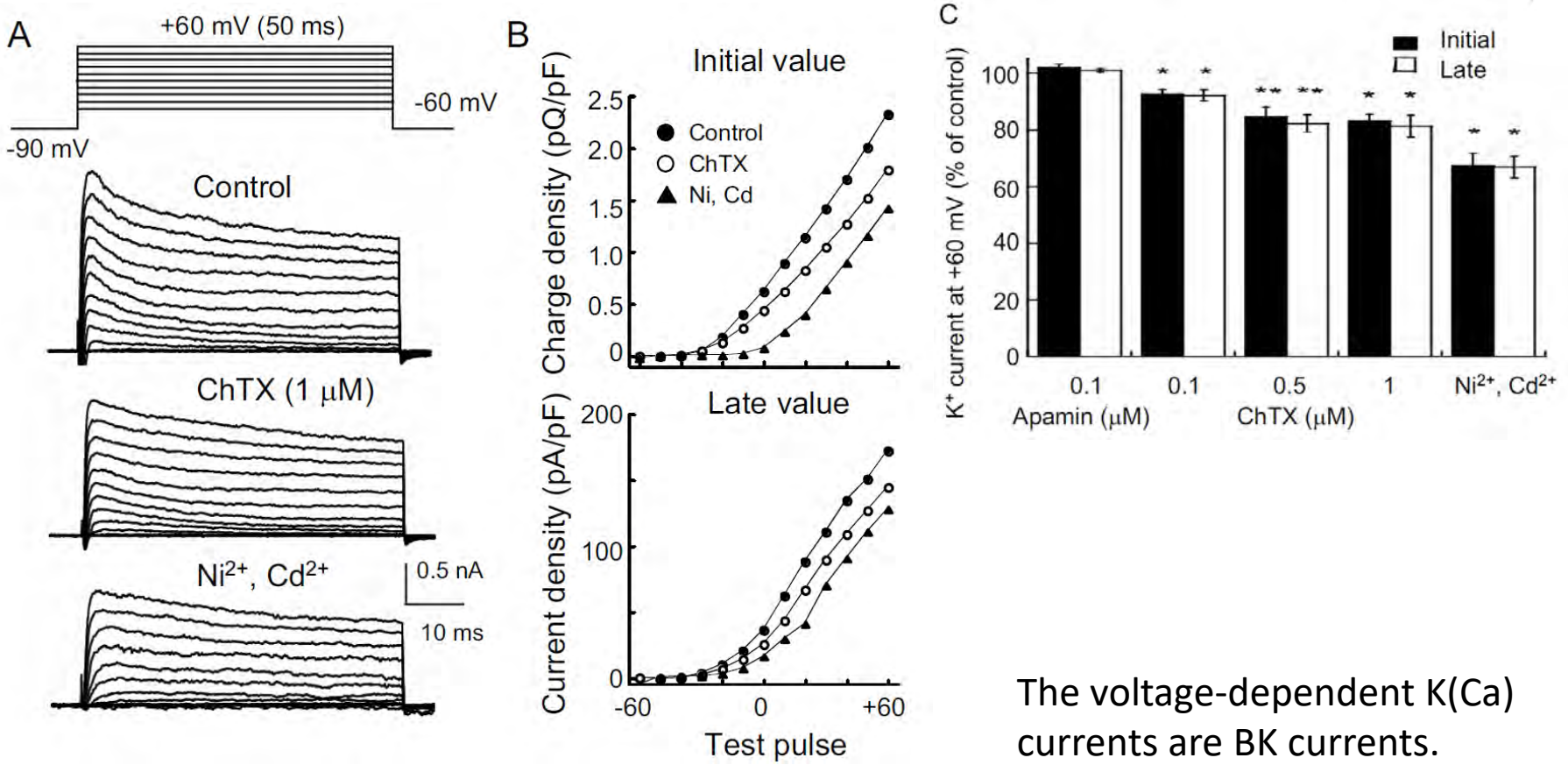

NCN1 HCN → Hyperpolarization-activated
CNG1 CNG → Cyclic nucleotide-gated
Nonselective cation channel
eag KCNH → Voltage-gated ether-a-go-go
6TM
akt1 → Plant inward rectifiers
mslo KCNM → Large conductance(BK) Voltage/Ca2+ -gated
SK1 KCNN → Small and intermediate conductance Ca2+ -activated
Kv5.1 → Voltage-gated outlier
Delayed rectifiers
Kv6.1
Kv8.1
Kv9.1 KCNS
Modifiers / silencers
KCNQ1 KCNQ → Voltage-gated KCNQs
Slow delayed rectifiers
Kir4.1
Kir7.1
Kir1.1
Kir2.1
Kir5.1
Kir6.1
Kir8.1
2TM
KCNH → Inward rectifiers
Classical inward rectifiers
ATP-sensitive
G-protein-coupled
4TM
TWIK KCNK → 2-P-domain K leaks

Properties of Ca^{2+}-activated K^+ channels

Property	Channel type	
	BK channel	SK channel
Single-channel conductance (pS)	100-400	5-20
Voltage sensitivity	Yes	No
Ca^{2+} sensitivity	Low (1-10 μM)	High (100-400 nM)
Proposed role	Action-potential repolarization	After-hyperpolarization (AHP)
Blockers	TEA (<1 mM) Charibdotoxin	TEA (>20 mM) Apamin d-Tubocurarine

BK currents:

isolated by subtracting the DRK current in the presence of Ni^{2+} and Cd^{2+} from the control



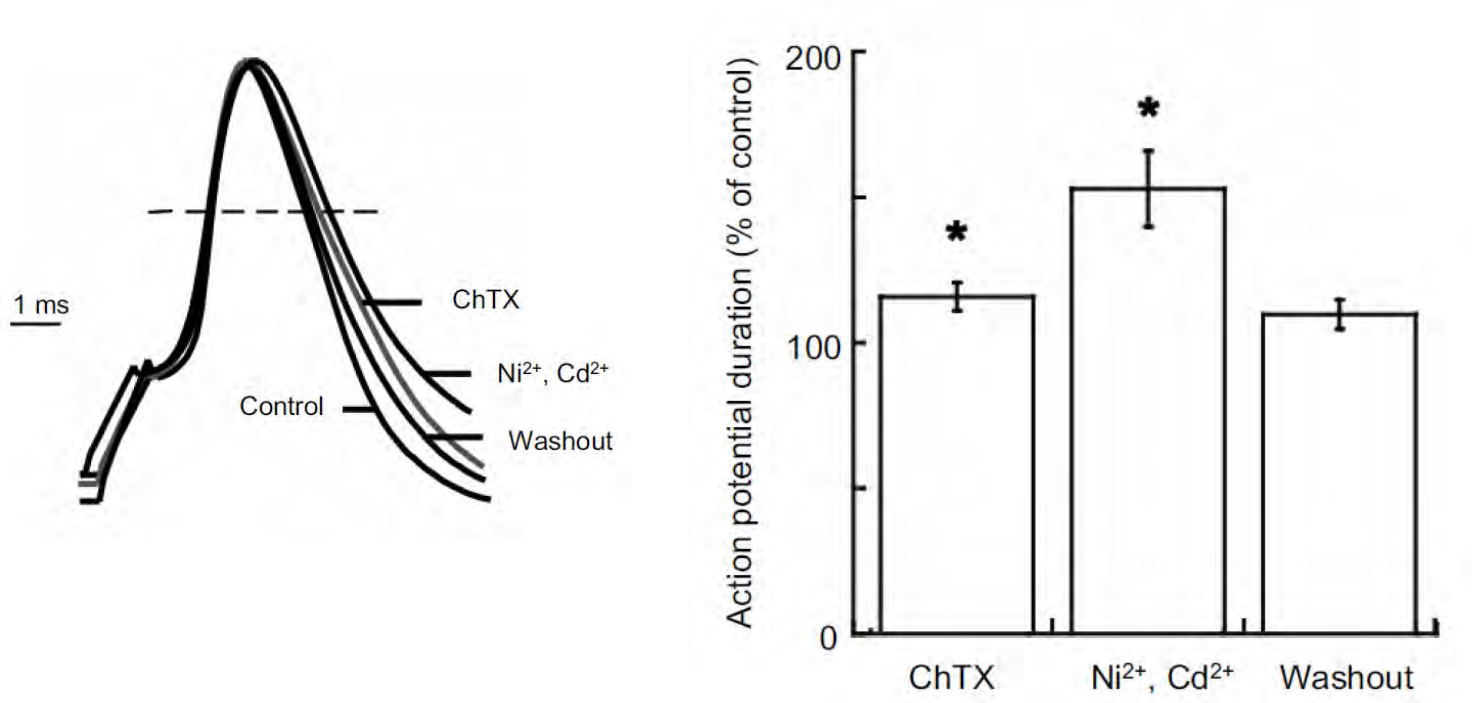
The voltage-dependent K(Ca) currents are BK currents.

The BK currents in GnRH neurons showed low sensitivity to charybdotoxin (ChTX)

Hiraizumi, Y. et al. J Physiol Sci 2008;144:21-29

BK current affects action-potential repolarization

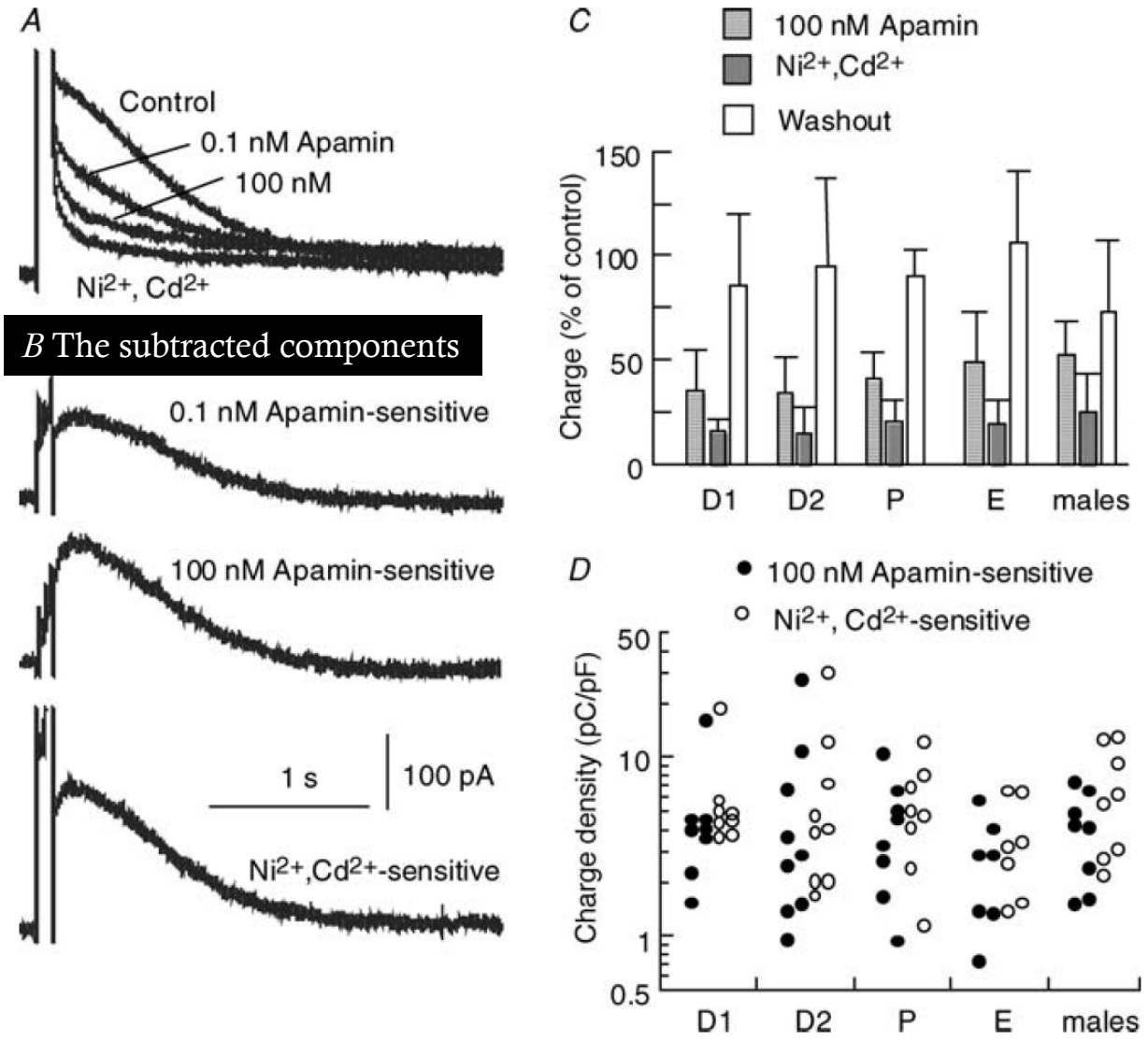
Effects of ChTX and Ni^{2+} and Cd^{2+} on the duration of action potentials



ChTX (1 µM) lengthened the duration of action potentials elicited by a 1 ms current pulse in the current-clamp mode. Ni2+ (200µM) and Cd2+ (500 µM) further lengthened the duration.

Hiraizumi, Y. et al. J Physiol Sci 2008; 144:21-29

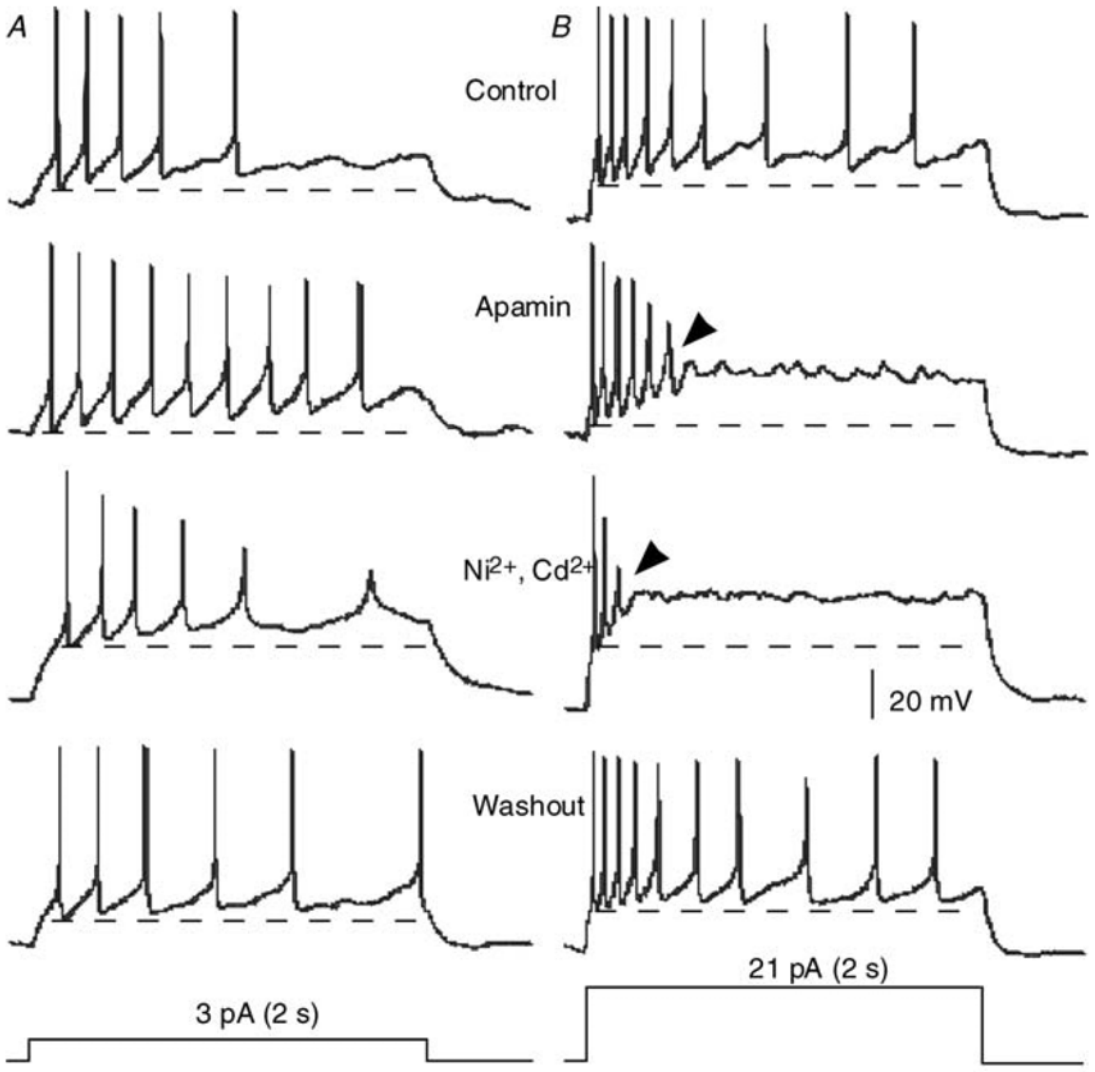
SK: Apamin-sensitive Ca^{2+}-activated K^+ currents



Kato *et al.*, *J Physiol (Lond)* **574**:431, 2006

Apamin-sensitive Ca^{2+}-activated K^+ currents

SK currents: Apamin-sensitive slow I_{AHP}

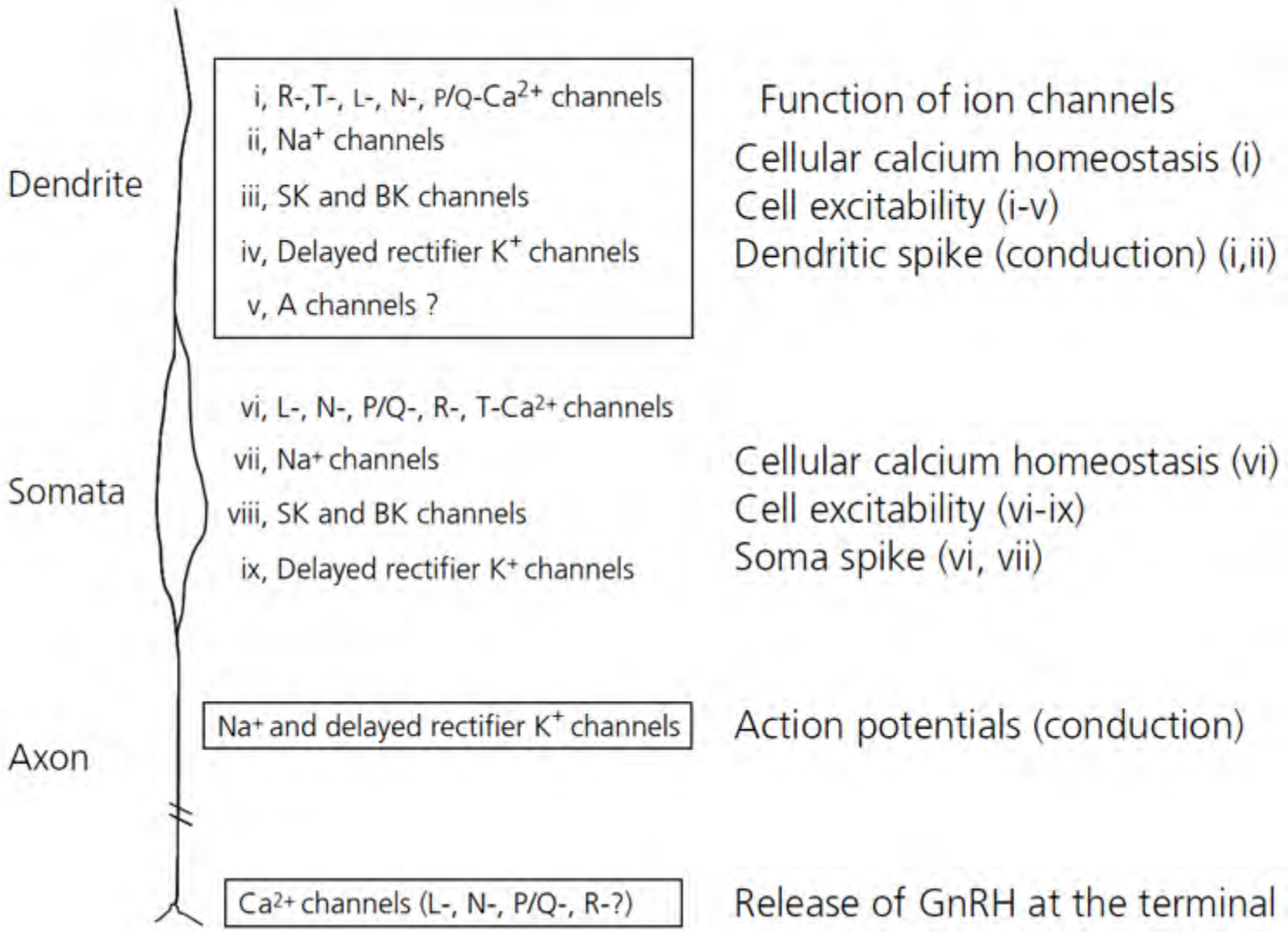


Kato *et al.*, *J Physiol (Lond)* **574**:431, 2006

- Rat GnRH neurons exhibit voltage- and Ca^{2+}-activated K^{+} currents (BK currents).

- The BK channels define cell excitability by modulating the duration of action potentials and the fast afterhyperpolarization.

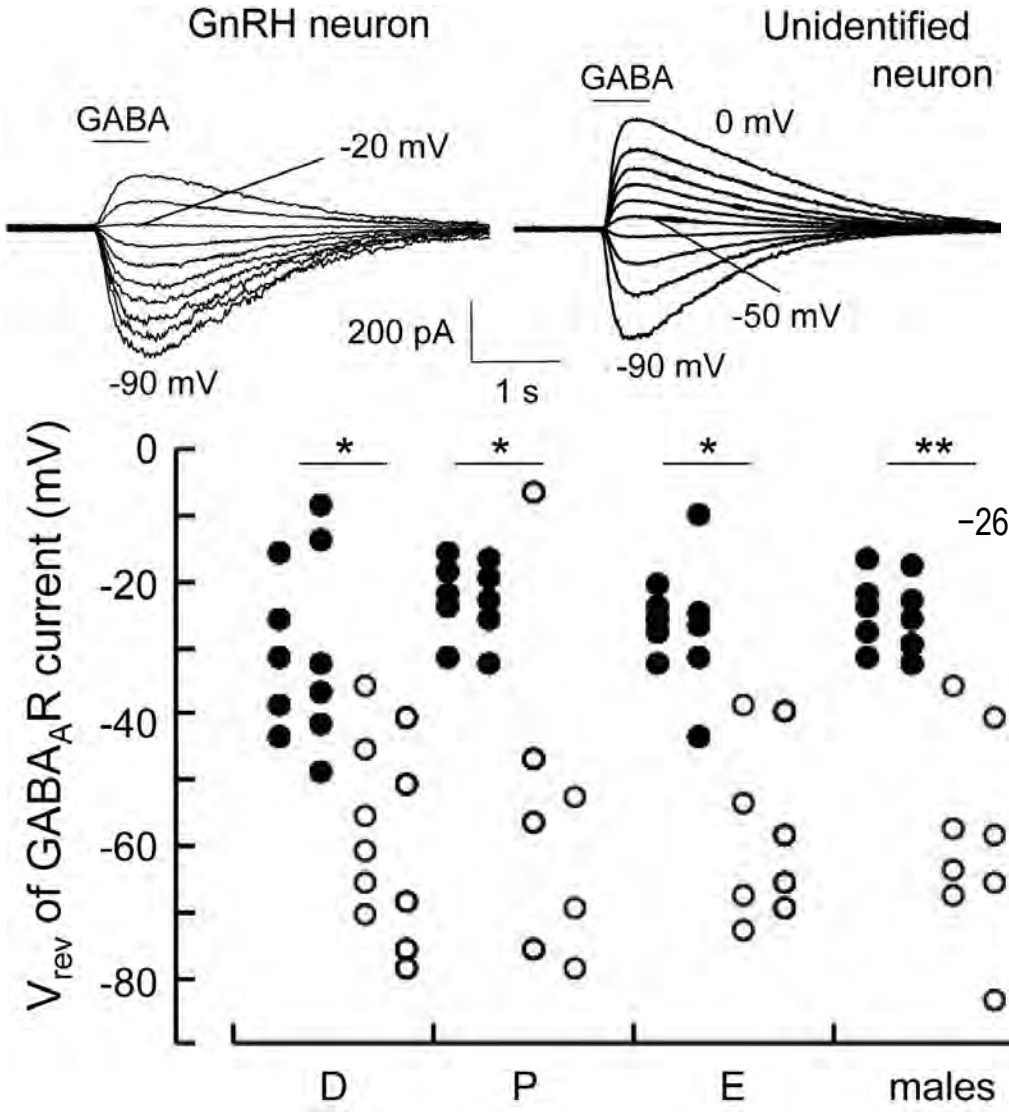
- Afterhyperpolarization in rat GnRH neurons depends on apamin-sensitive slow current (SK currents) which may allow continuous firing in response to depolarizing inputs.



Kato, *J Neuroendocrinol* 2009

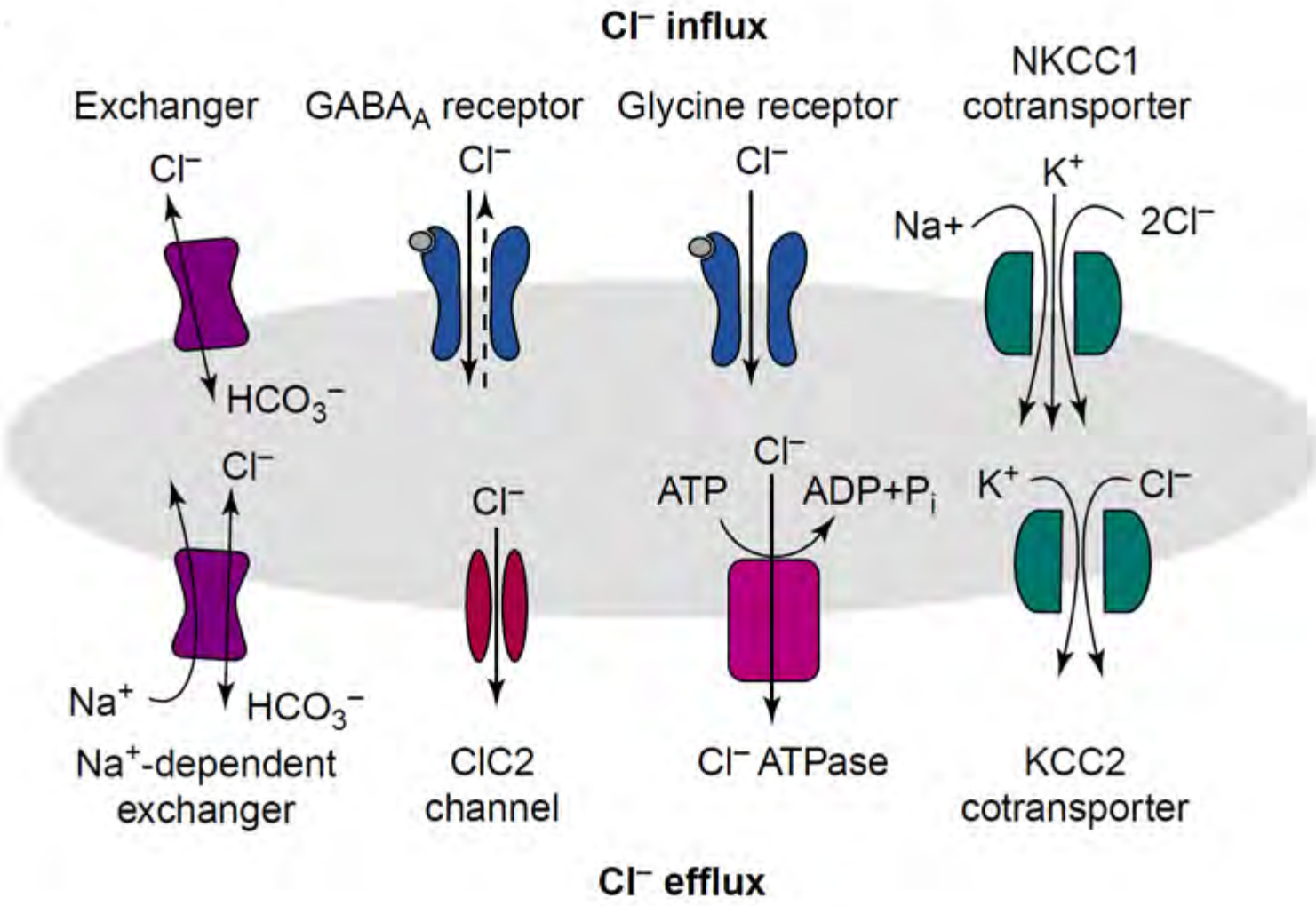
$GABA_AR$ in GnRH neurons

Reversal Potentials of $GABA_AR$ Currents



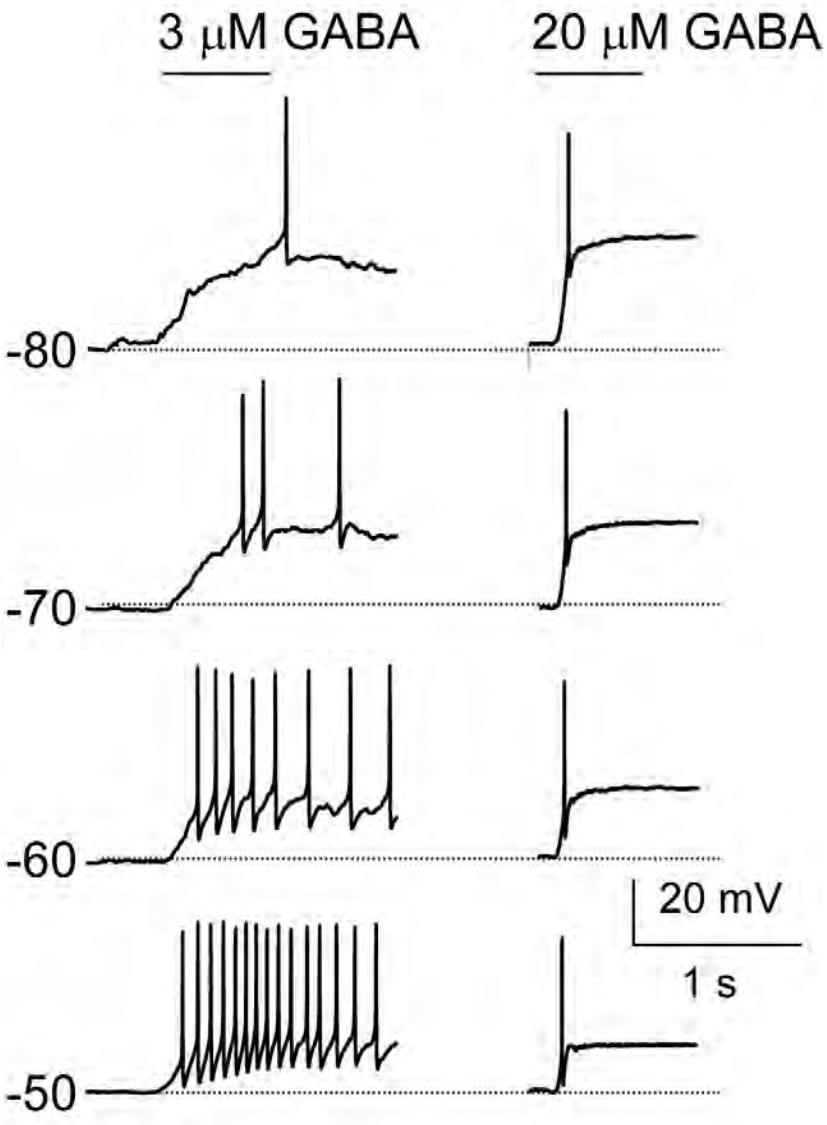
Yin *et al.*, ***J Neuroendocrinol*** **20**:566, 2008

NKCC1 expression is high, while KCC2 expression is low in adult rat GnRH neurons



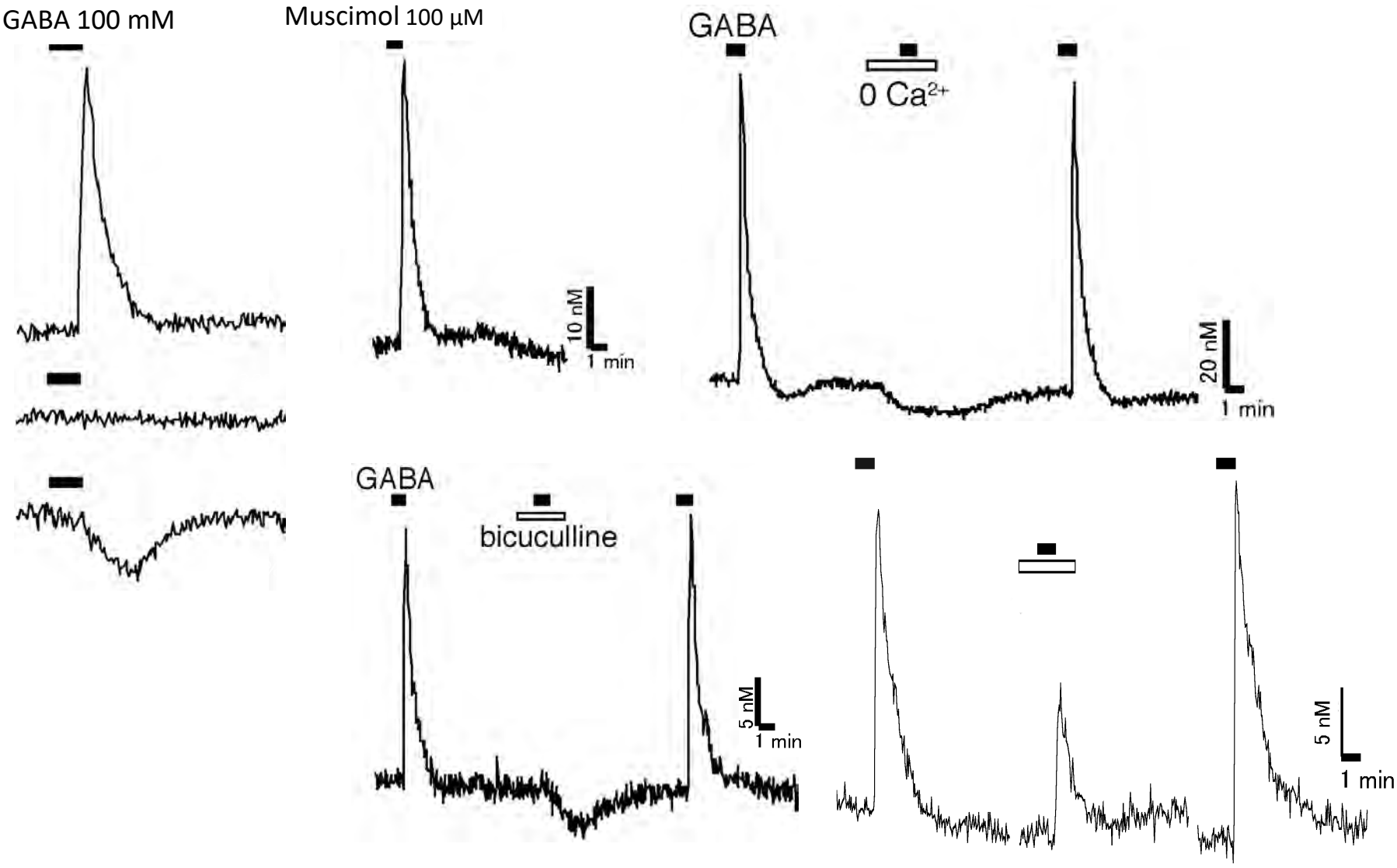
GABA Depolarizes Adult GnRH1 Neurons

B. Current Cramp



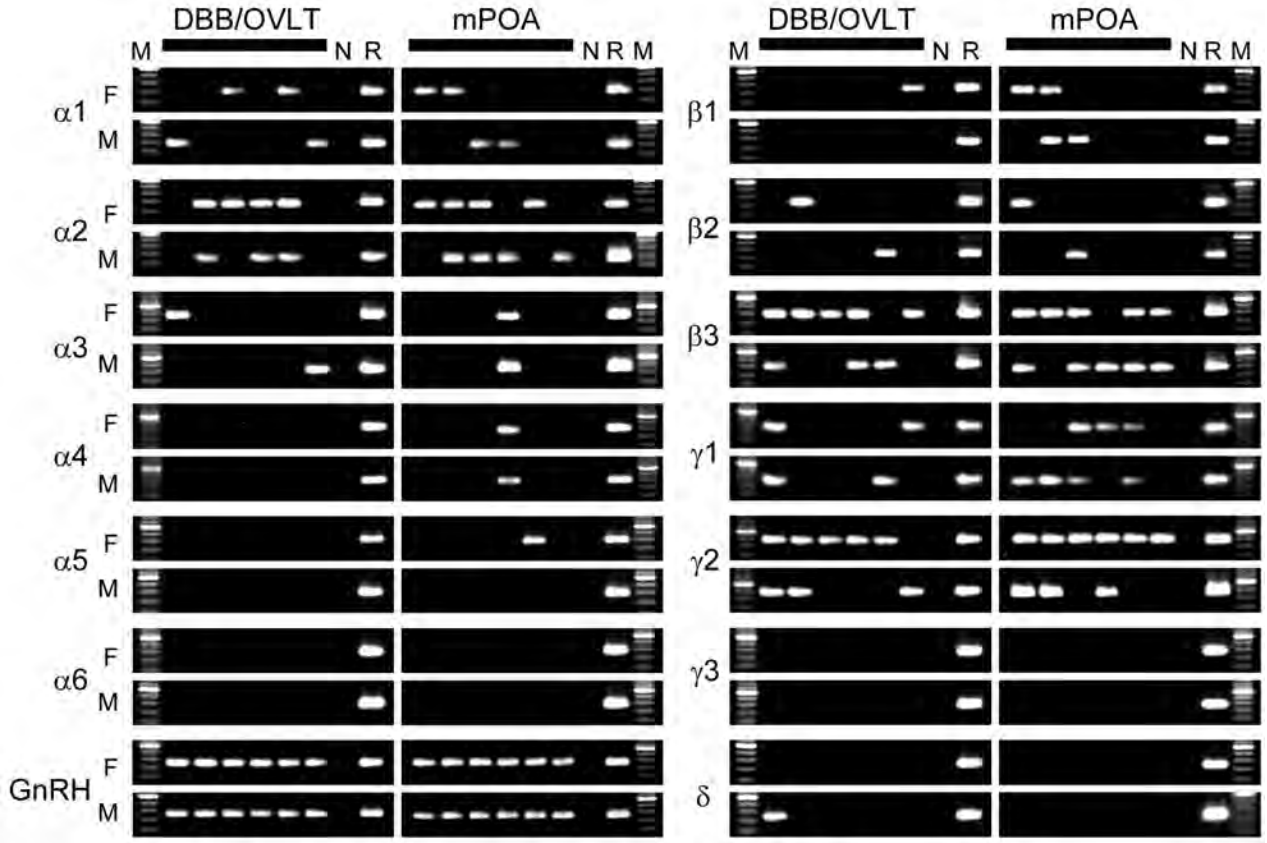
Yin *et al.*, ***J Neuroendocrinol*** **20**:566, 2008

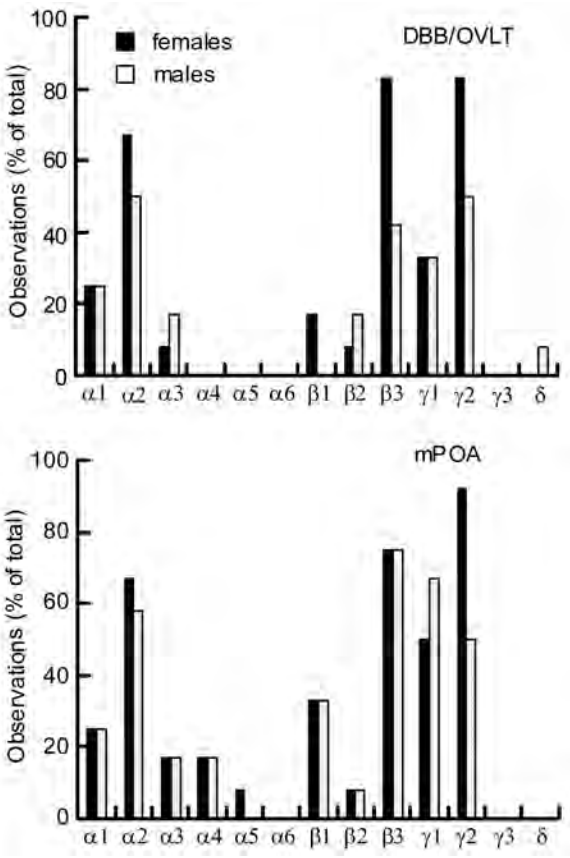
Effects of GABA on $[Ca^{2+}]_i$ in Rat GnRH Neurons



Watanabe M *et al.*, ***Biol Reprod*** **81**: 327, 2009

$GABA_AR$ subunits in Rat GnRH neurons





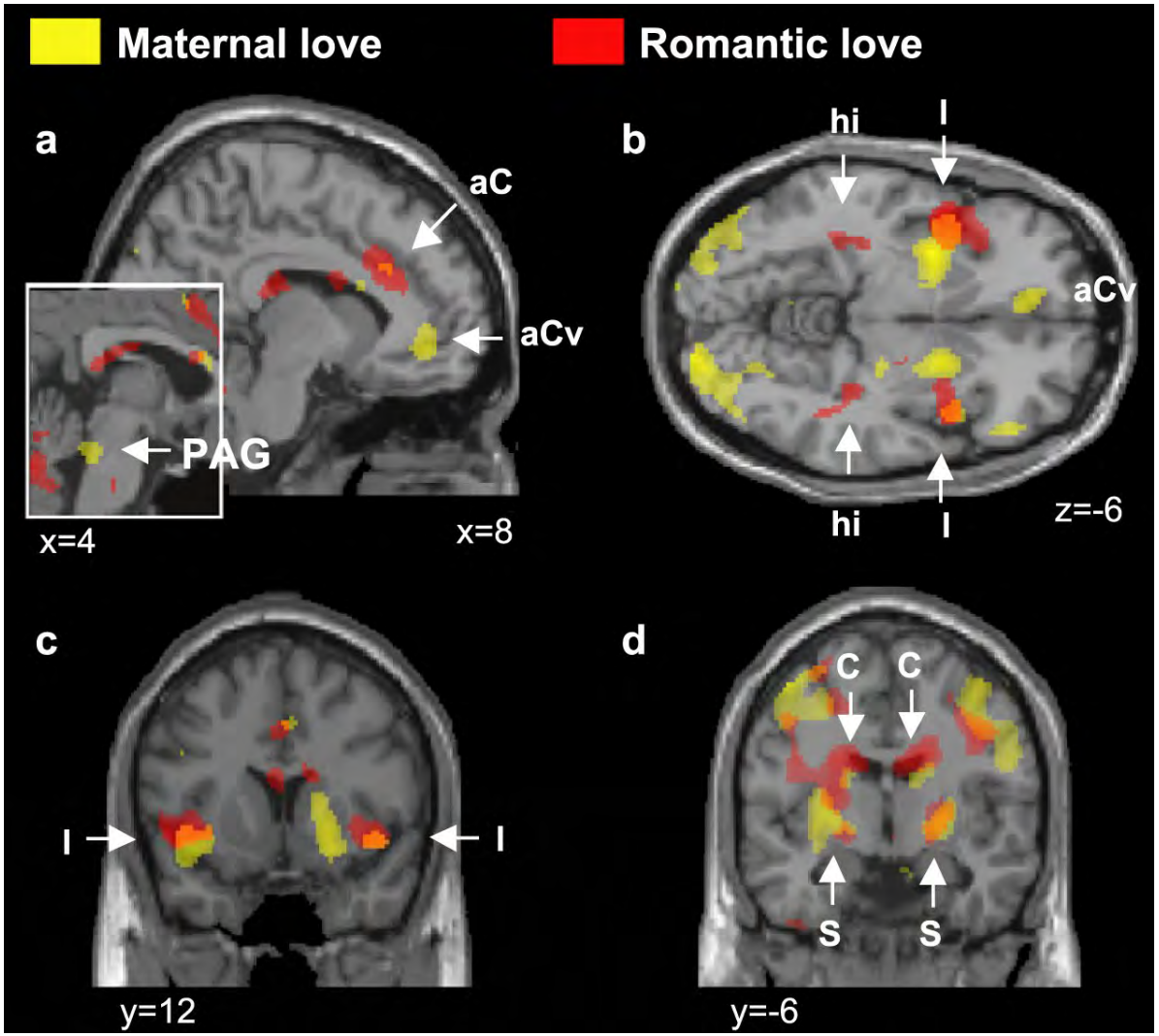
Yin C, Ishii H, Tanaka N, Sakuma Y, Kato M. ***J Neuroendocrinol* 20**: 566-575, 2008

Hormones and Social Behavior

Mother-infant bonding

Oxytocin promotes social interactions: trust

Overlap between activity of maternal love and romantic love

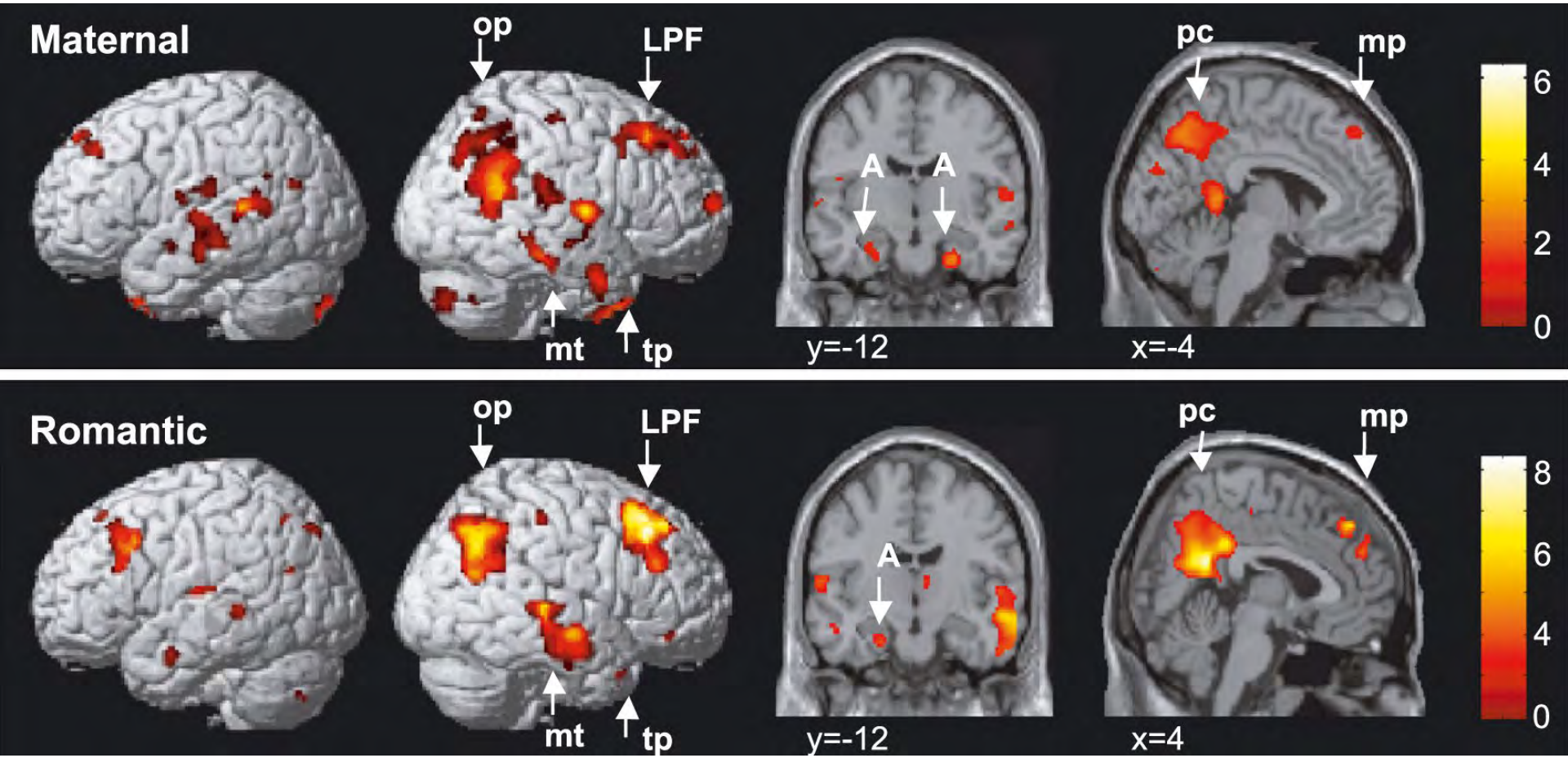


Regions displayed for romantic love (red) also reached significance when only female or only male subjects were included. Ventral anterior cingulate cortex (aCv) activation with maternal love overlapped only in females.

Bartels & Zeki, 2004

Deactivated regions with maternal and romantic love

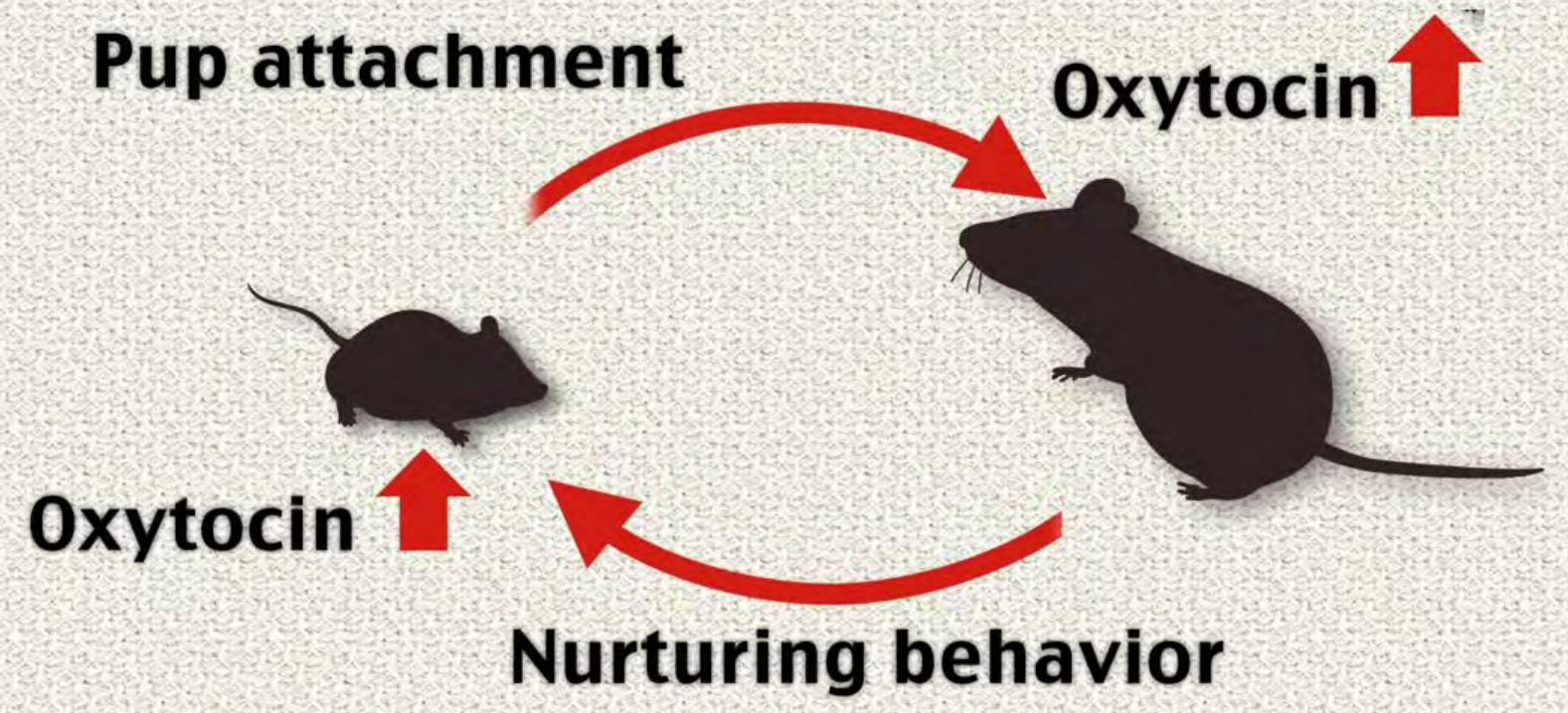
"deactivating networks used for critical social assessment and negative emotions"

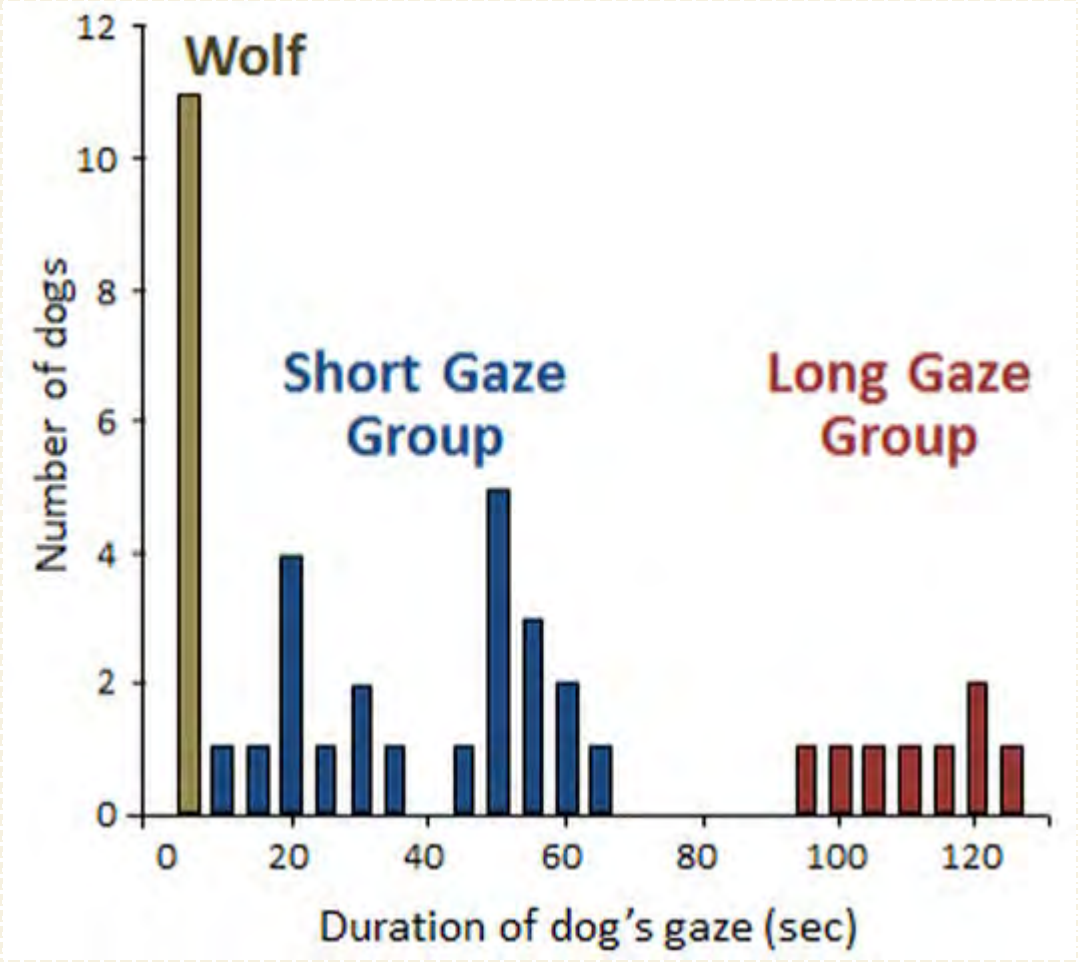


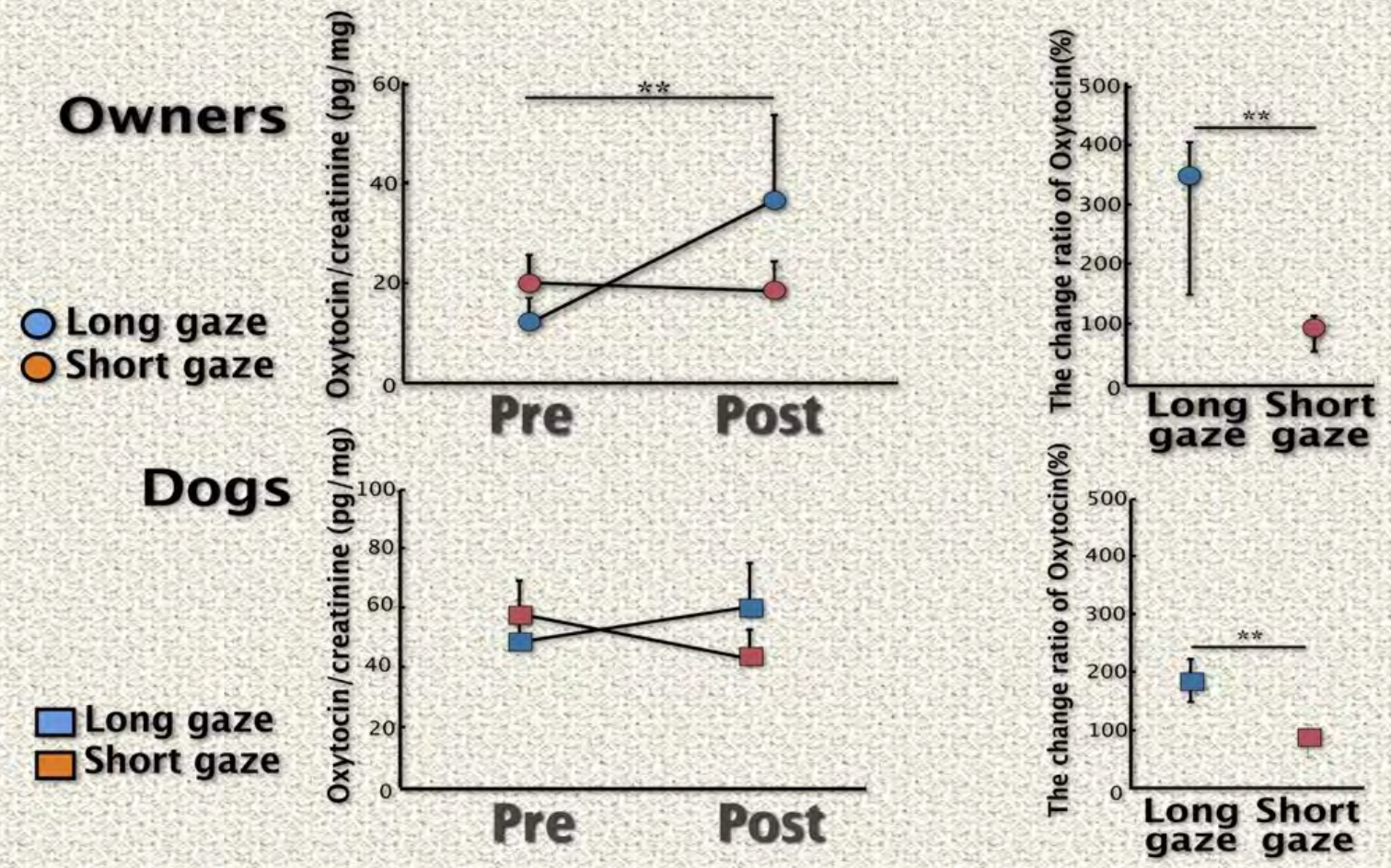
A, amygdala; pc, posterior cingulate; mp, mesial prefrontal/paracingulate gyrus; mt, middle temporal cortex; op, occipitoparietal junction; tp, temporal pole

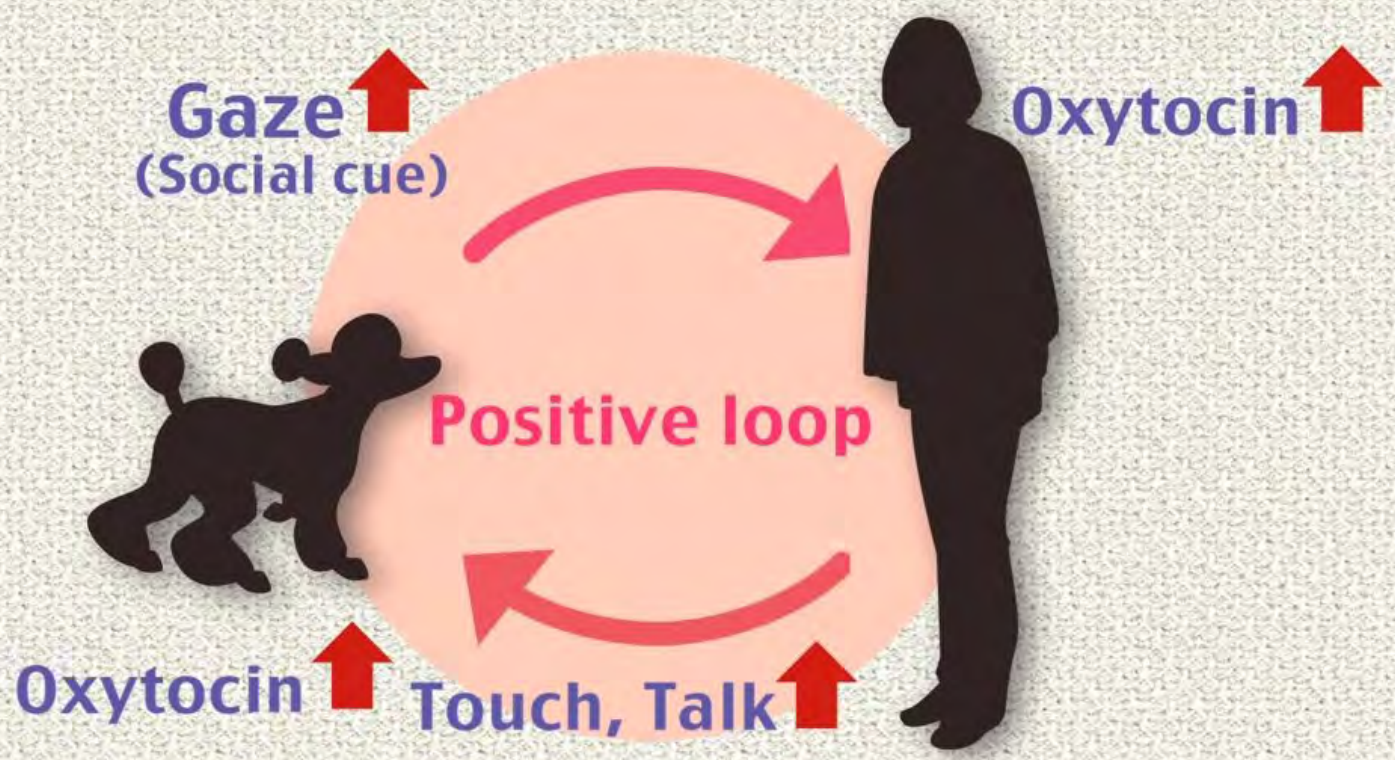
Bartels & Zeki, 2004

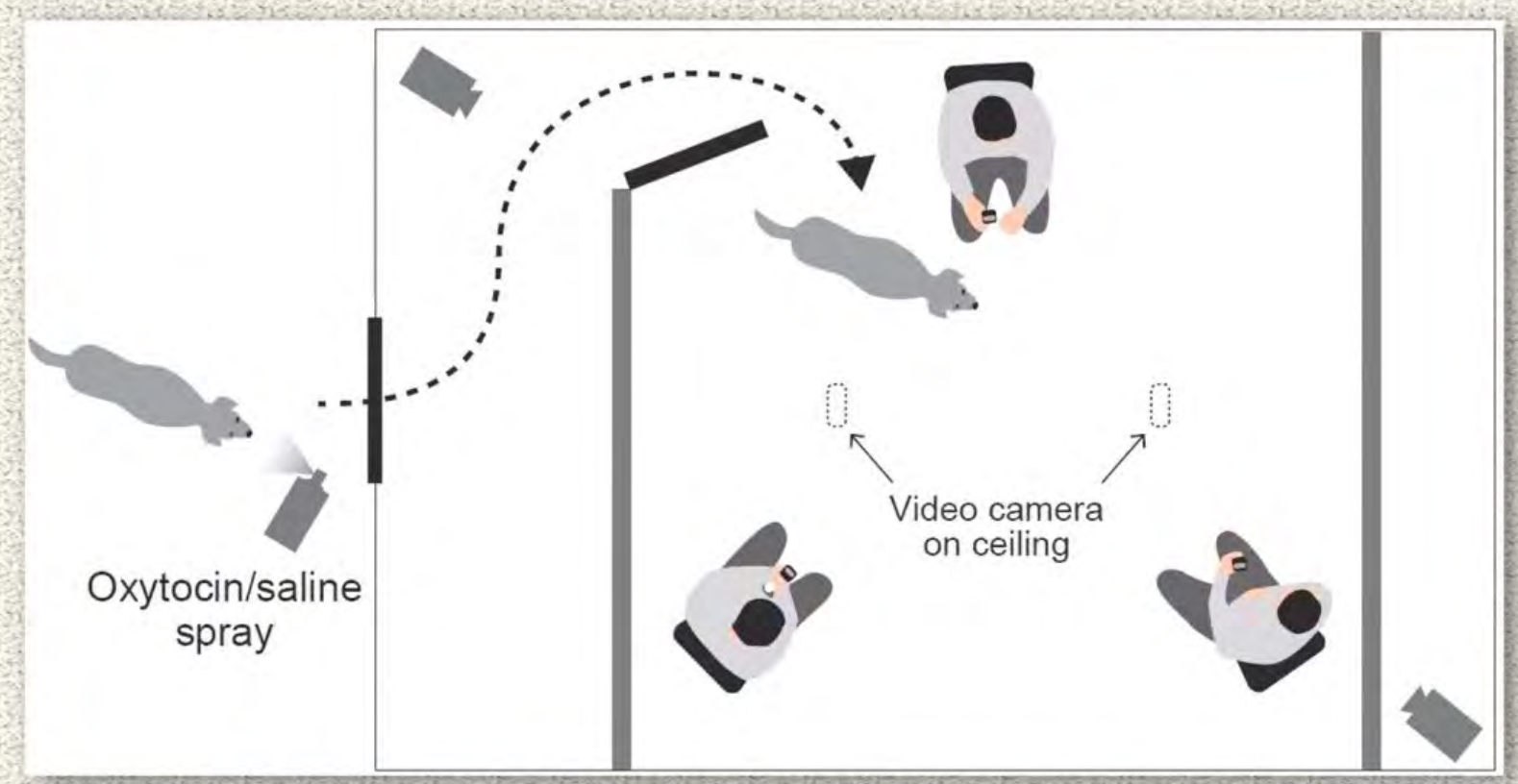
NAGASAWA, M., MITSUI, S., EN, S., OHTANI, N., OHTA, M., SAKUMA, Y., ONAKA, T., MOGI, K. & KIKUSUI, T. 2015. Social evolution. Oxytocin-gaze positive loop and the coevolution of human-dog bonds. *Science,* 348**,** 333-6.dx.doi.org/10.1126/science.1261022


Pup attachment
Oxytocin
Oxytocin
Nurturing behavior


Wolf
Short Gaze Group
Long Gaze Group
Number of dogs
0
2
4
6
8
10
12
0
20
40
60
80
100
120
Duration of dog's gaze (sec)

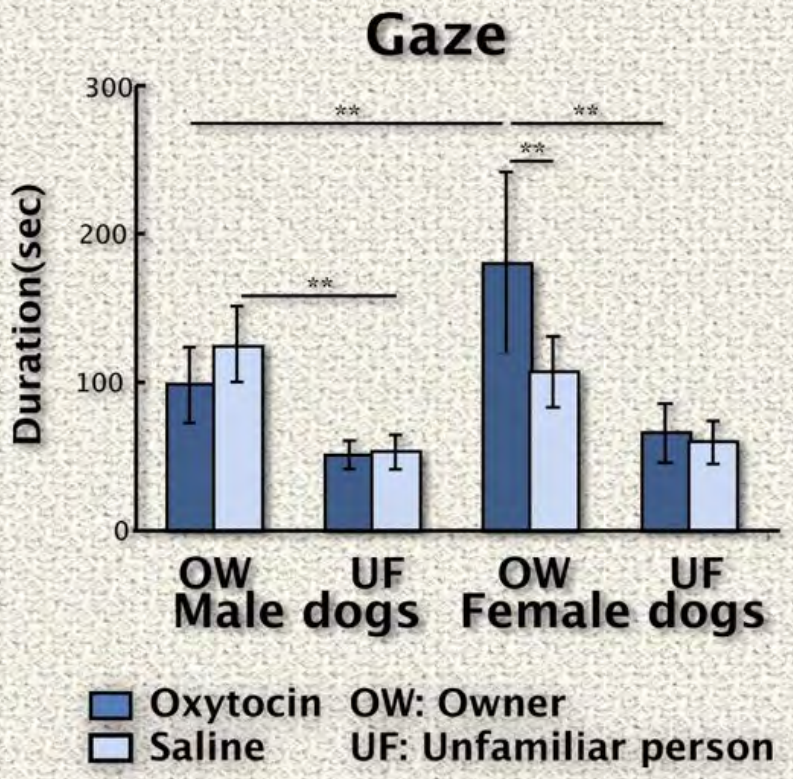

Owners
Long gaze
Short gaze
Oxytocin/creatinine (pg/mg)
60
40
20
0
**
Pre
Post
The change ratio of Oxytocin(%)
500
400
300
200
100
0
**
Long gaze
Short gaze
Dogs
Long gaze
Short gaze
Oxytocin/creatinine (pg/mg)
100
80
60
40
20
0
Pre
Post
The change ratio of Oxytocin(%)
500
400
300
200
100
0
**
Long gaze
Short gaze


Gaze
(Social cue)
Oxytocin
Positive loop
Oxytocin
Touch, Talk


Oxytocin/saline
spray
Video camera
on ceiling

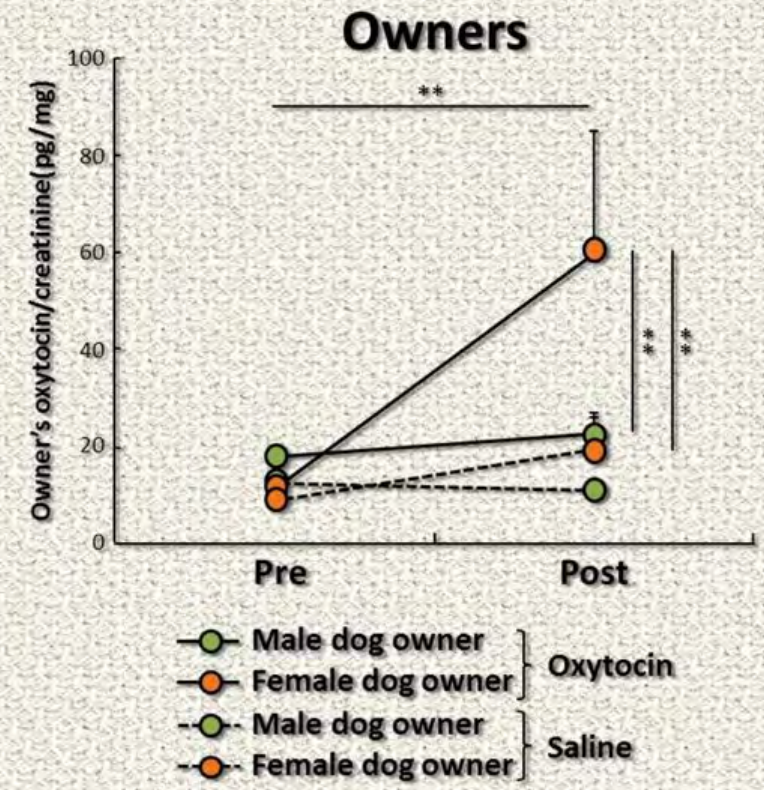

UF
OW
Oxytocin

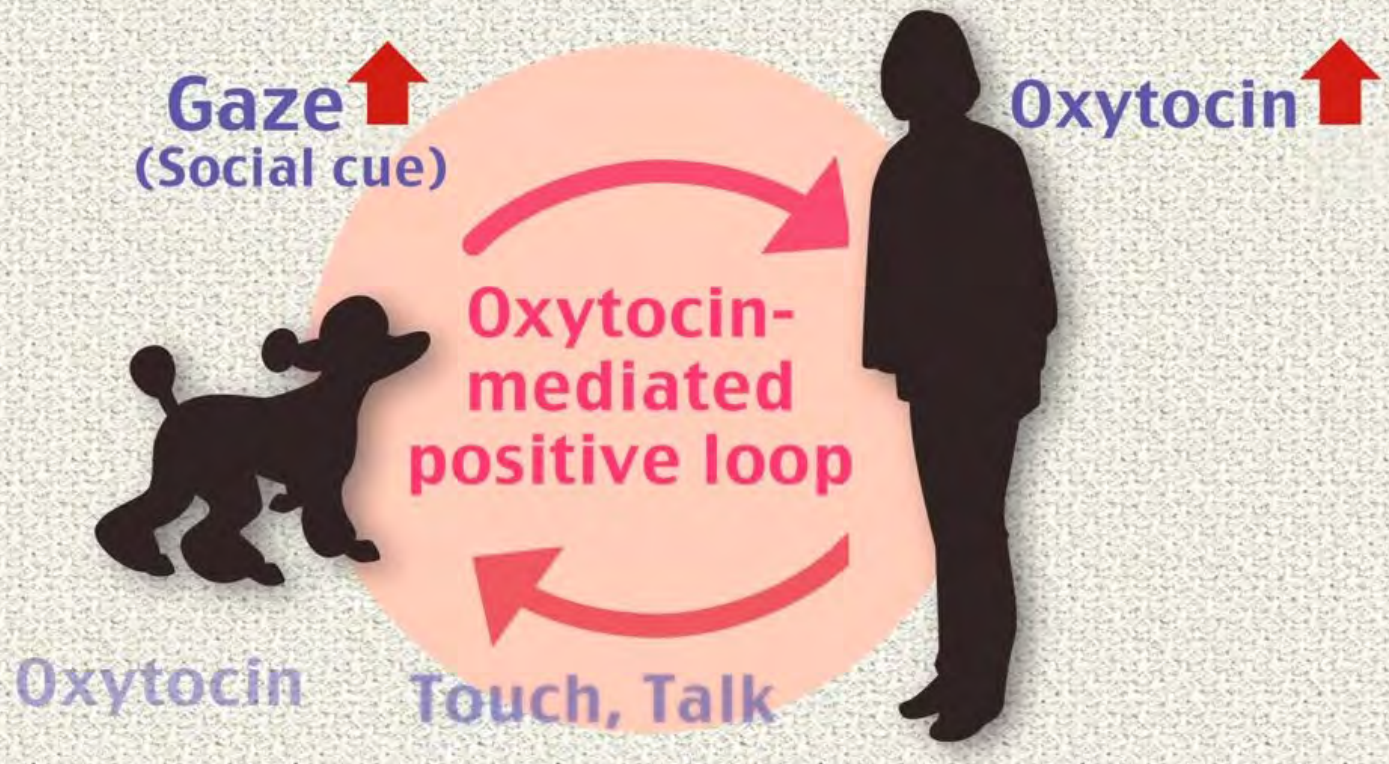

Saline
OW
UF

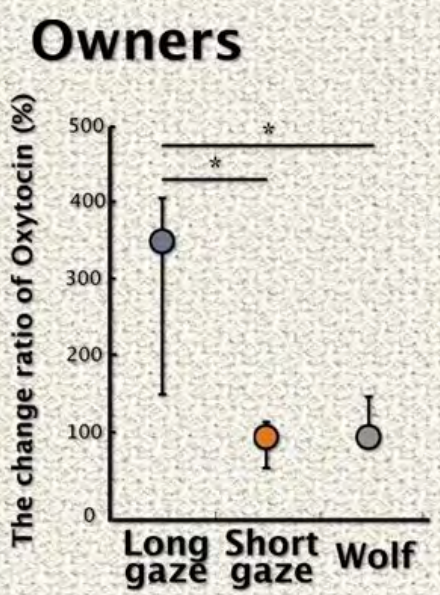

Gaze
Duration(sec)
300
200
100
0
**
**
**
**
OW
UF
OW
UF
Male dogs
Female dogs
Oxytocin
Saline
OW: Owner
UF: Unfamiliar person

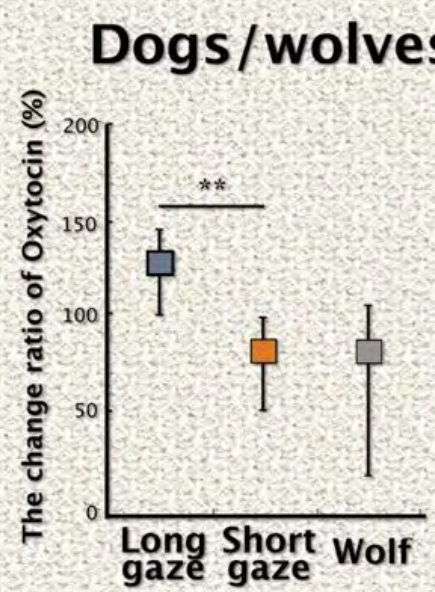

UF
OW
Oxytocin

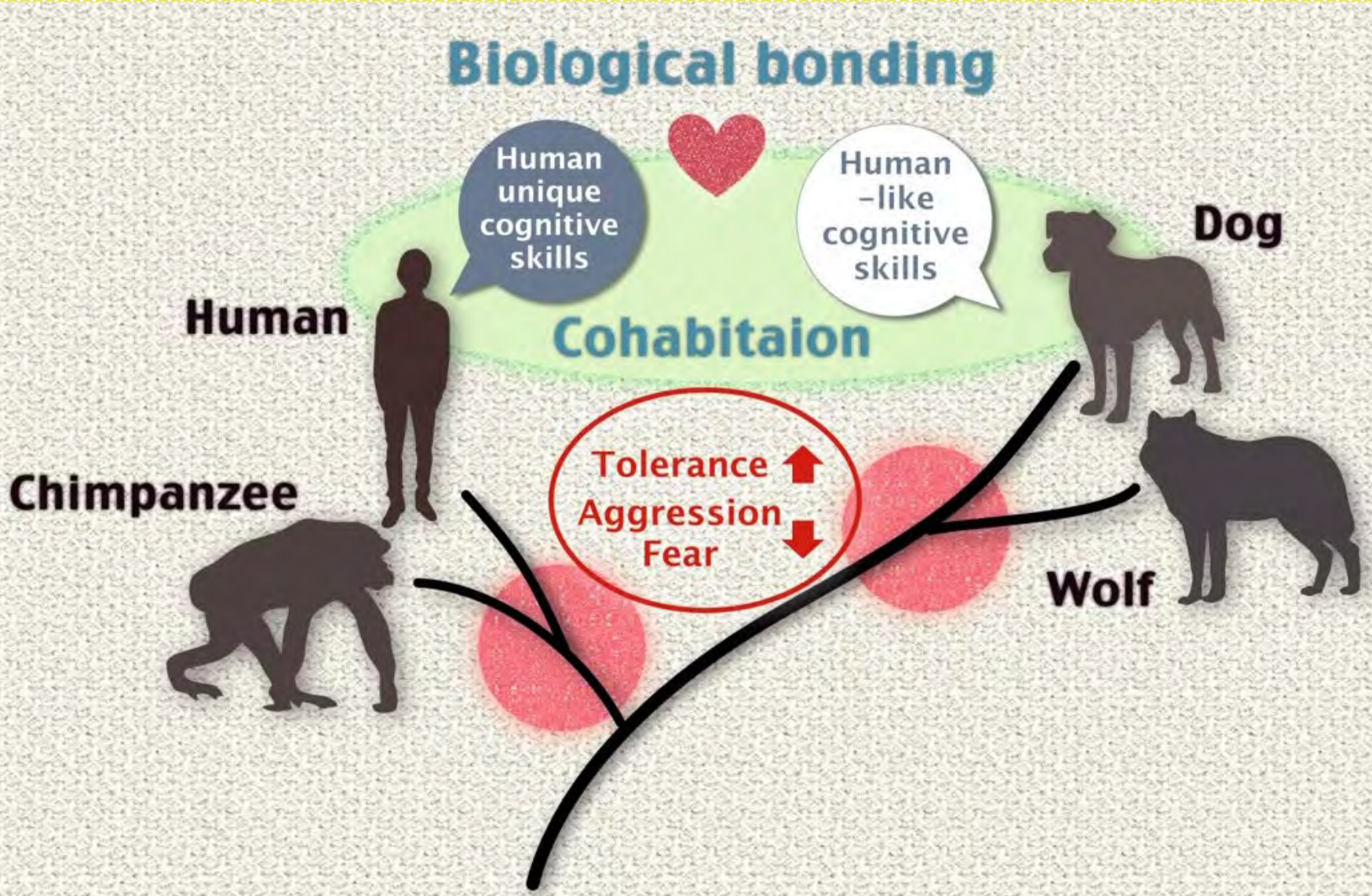

Saline
OW
UF


Owners
Owner's oxytocin/creatinine(pg/mg)
100
80
60
40
20
0
**
**
**
Pre
Post
Male dog owner
Female dog owner
Oxytocin
Male dog owner
Female dog owner
Saline

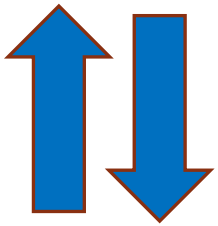

Gaze
(Social cue)
Oxytocin
Oxytocin-
mediated
positive loop
Oxytocin
Touch, Talk


Owners
The change ratio of Oxytocin (%)
500
400
300
200
100
0
*
*
Long gaze
Short gaze
Wolf


Dogs/wolves
The change ratio of Oxytocin (%)
200
150
100
50
0
**
Long gaze
Short gaze
Wolf


Biological bonding
Human unique cognitive skills
Human -like cognitive skills
Cohabitaion
Human
Chimpanzee
Dog
Wolf
Tolerance
Aggression
Fear

Hormone alters behavior

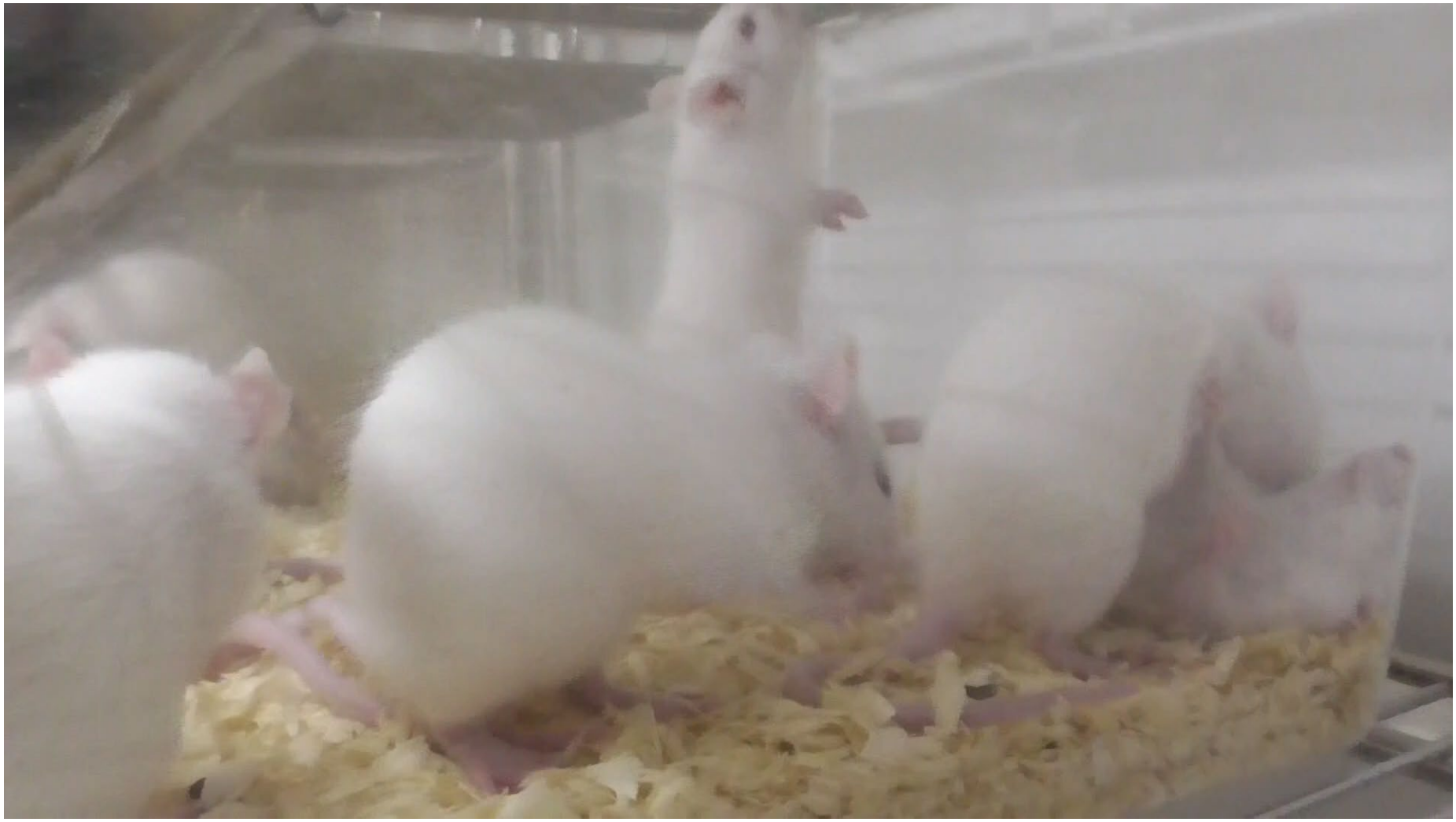


Behavior defines hormone action

Motherhood; reflex ovulation; attachment; Trust…

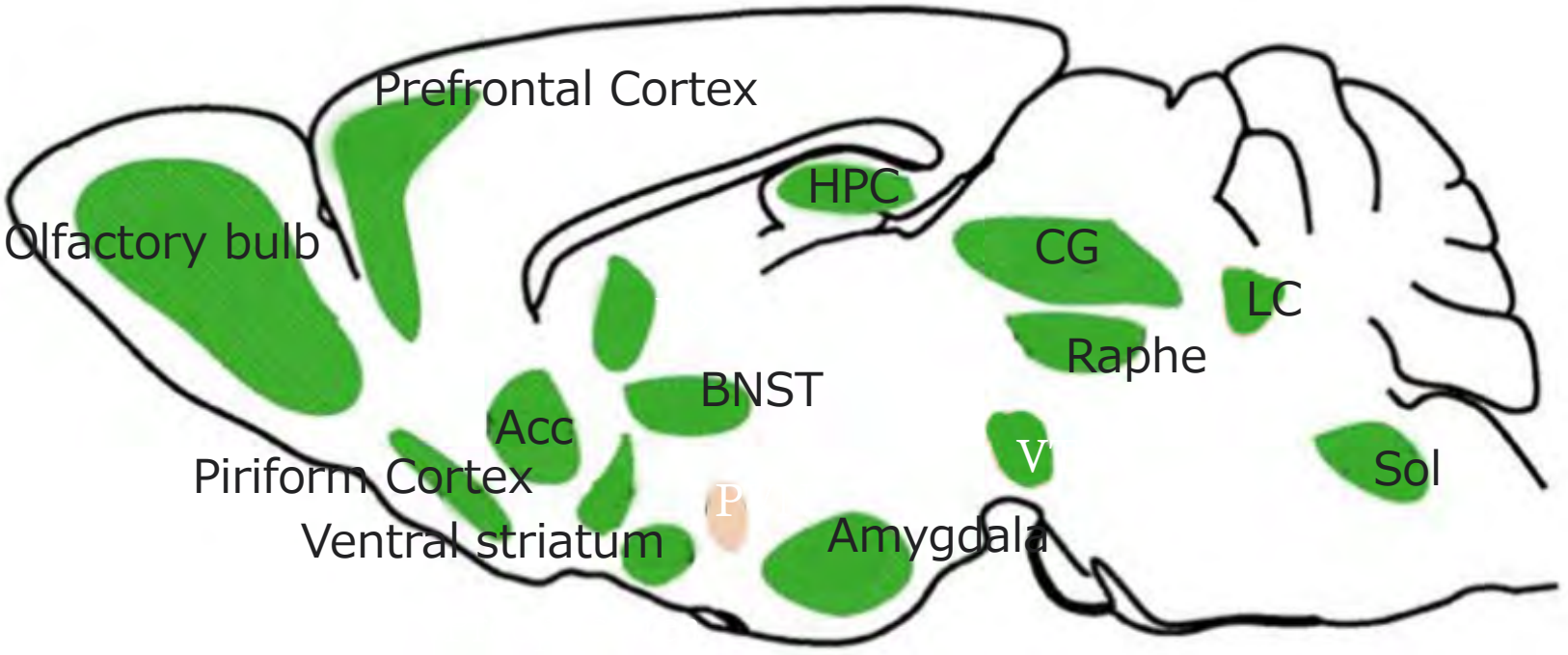

匹分数 オス メス
離乳日
メモ

“Rough and Tumble Play” Day 22

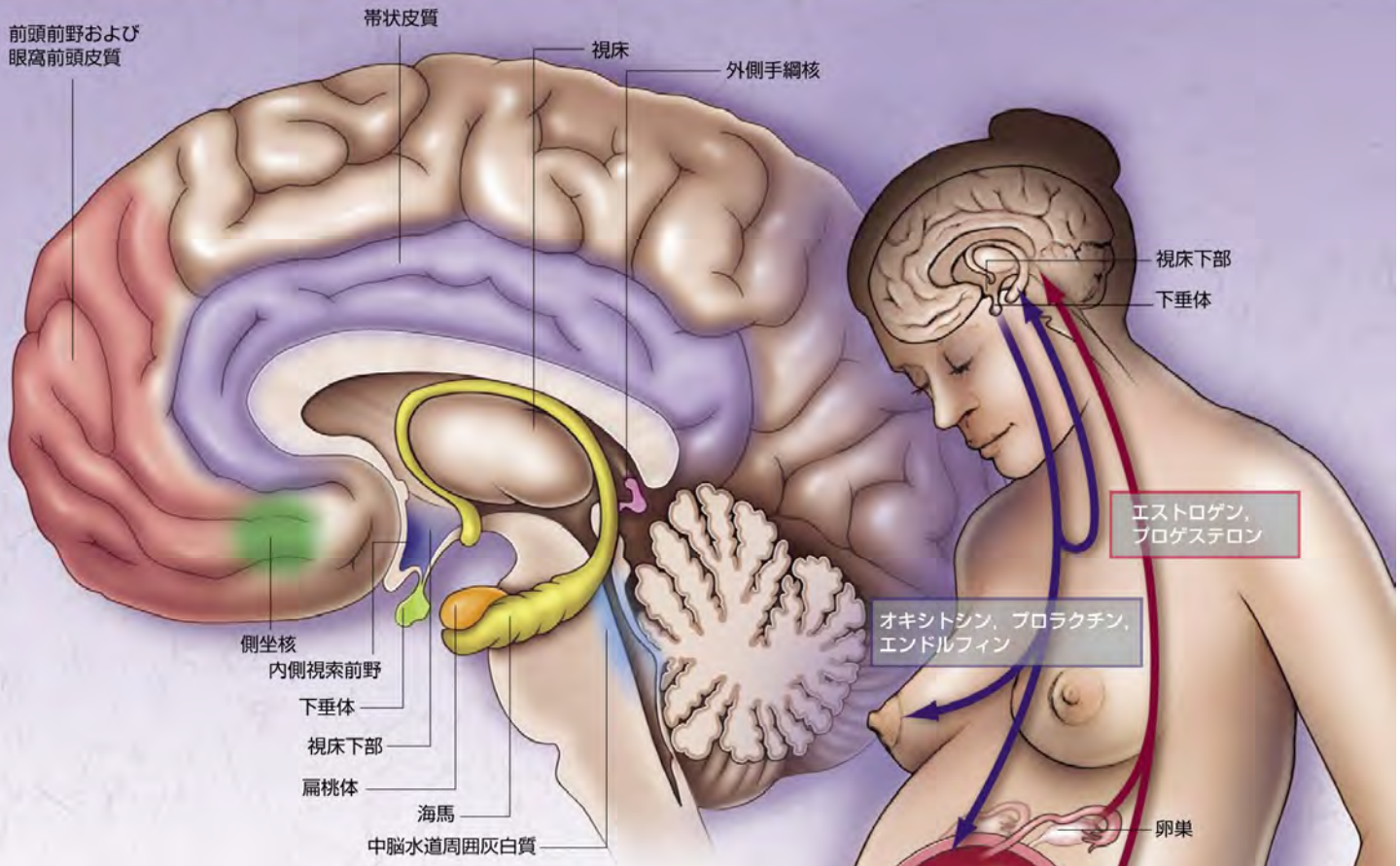



50.7
COM
FREQUENCY
HET
FREQ DIV
VOLUME

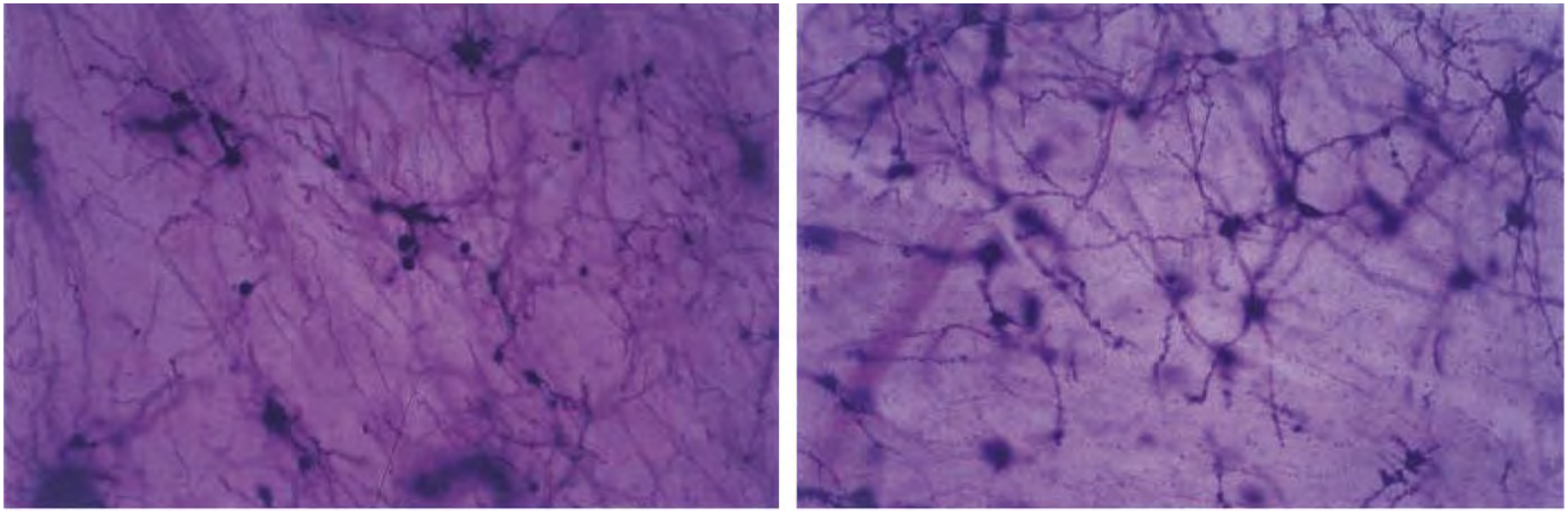
Oxytocin Receptor Expression in Mouse Brain



妊娠で変化する脳



妊娠中，卵巣と胎盤は女性の生殖ホルモンであるエストロゲンとプロゲステロンを大量に分泌する。視床下部と下垂体は分娩時の子宮の収縮を誘発するオキシトシン，乳腺を刺激するプロラクチン，分娩時の苦痛を和らげるエンドルフィンを分泌する。動物の研究からこれらの物質がさまざまな形で女性の脳に影響することがわかってきた。例えば基本的な母性反応を制御する視床下部の内側視索前野では，エストロゲンとプロゲステロンによってニューロンの細胞体が大きくなるようだ。同様に記憶と学習を司る海馬では，ニューロンの分枝が増えて表面積が増加する。オキシトシンも海馬を刺激する。他にも帯状皮質，前頭前野，眼窩前頭皮質，側坐核，扁桃体，外側手綱核，中脳水道周囲灰白質などの脳領域が母性行動とかかわっている。



大きくなるニューロン　未婚のラットの内側視索前野にあるニューロンの細胞体（左）は妊娠ラットのもの（右）よりかなり小さい。妊娠ホルモンは出産後に母性が必要となる前にあらかじめ内側視索前野のニューロンを活性化させるため，タンパク質の合成と活性が促進される。

Department of Physiology
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- Masakatsu Kato
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- Yasuhiko Kondo
- Chitose Orikasa
- Tomohiro Hamada
- Nobuyuki Tanaka
- Hirotaka Ishii
- Yin Chengzhu
- Momoko Kobayashi
- Sunil Dhungel
- Mikiko Koyama
- Dilip Rai
- Sumiko Usui
- Chiaki Suzuki

Past…:
- Ishwar S Parhar (Monash)
- Tomoko Soga (Monash)
- Takashi Kitahashi (Monash)
- Satoshi Ogawa (Monash)
- Qing Xue (Dalian)
- Shun Sato (Neurosurgery)
- Yoshie Hiraizumi (Gynecology)
- Ichiro Nishimura (Kikkoman)
- Kai Xiao (Shenyang)
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- Ryoko Shibata (Ajinomoto)
- Ryoiti Kiyama (AIST)
- Shinji Hayashi (Yokohama)
- Korehito Yamanouchi (Waseda)
- Donald W Pfaff (Rockefeller)
- Bruce S McEwen (Rockefeller)
- Miho Nagasawa (Azabu)
- Takefumi Kikusui (Azabu)
- Kazushige Touhara (Tokyo)

JSPS Grants-in-aid for Scientific Research (18390070; 18659061; 22390043 &c) ; MEXT Grant for Scientific Research on Priority Area “Mechanism of Sexual Differentiation” (1686210); Strategic Grant to Promote Research at Private Universities, MEXT (S0801035)…