Bupleurum falcatum (Siho, Saiko, Chaihu)-Based Modulation of the PVN Oxytocin–CRH–AVP Circuit: Experimental Framework for a Neuroendocrine Model of Stress and Anxiety Regulation

Inseok Mohk (Independent Researcher, Bucheon, Korea)
Email: inseok.mohk@outlook.kr
ORCID: 0009-0003-8841-4282
October 31, 2025

Abstract

Background:
Stress responses are orchestrated through the paraventricular nucleus (PVN) of the hypothalamus, primarily via the corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) neurons that activate the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic outflow. Under chronic stress, inhibitory oxytocin (OXT) tone in the PVN is reduced, leading to hyperactivation of the CRH–AVP system and sustained cortisol release. This dysregulation manifests as irritability, anxiety, and autonomic imbalance.

Hypothesis:
We propose that *Bupleurum falcatum* (Saiko)–based herbal formulations, long used in traditional East Asian medicine to "soothe the Liver and relieve constraint," exert their stress-regulatory effects by enhancing PVN OXT activity. Specifically, saikosaponins activate OXT neurons, which in turn stimulate GABAergic interneurons that inhibit CRH and AVP neurons. This **OXT–GABA–CRH/AVP inhibitory circuit** restores the homeostatic tone of the HPA axis, suppresses excessive cortisol and sympathetic drive, and secondarily elevates serotonergic activity, thereby improving mood and social adaptability.

Methods/Proposal:
We propose a four-tier experimental validation of the Saiko–oxytocin model:
(1) **In vitro**, Saikosaponin D will be tested for enhancement of OXT–GABA signaling and suppression of CRH/AVP expression in hypothalamic neurons;
(2) **In vivo**, chronic-stress rats will assess OXT-mediated GABAergic inhibition within the PVN using DREADD/photometry and receptor blockade;
(3) **Behaviorally**, Saiko's effects on anxiety, sociality, HRV, and corticosterone will be examined for OXT dependency;
(4) **Clinically**, a randomized human trial will evaluate *Shosaikoto*'s impact on plasma OXT, cortisol, HRV, and PVN–insula connectivity.

Conclusion:
This paper proposes that Saiko-based therapy acts as a physiological brake on the stress axis by reactivating the OXT brake within the PVN. The model bridges traditional concepts of emotional stagnation with neuroendocrine regulation, suggesting that true healing arises not from suppression but from restoring the rhythm between activation (dopaminergic drive) and restoration (oxytocinergic calm).

Keywords:
Oxytocin, CRH, AVP, Saikosaponin, HPA axis, GABA, stress, cortisol, serotonin, Bupleurum falcatum, autonomic regulation, traditional medicine

1. Introduction

1.1. The HPA Axis and the Neuroendocrine Architecture of Stress

The hypothalamic–pituitary–adrenal (HPA) axis constitutes the core neuroendocrine system mediating stress adaptation. Activation of parvocellular neurons within the paraventricular nucleus (PVN) of the hypothalamus triggers the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which act synergistically on the anterior pituitary to promote adrenocorticotropic hormone (ACTH) secretion and subsequent glucocorticoid (cortisol) release from the adrenal cortex (Herman et al., 2003).

Under acute stress, this axis mobilizes energy reserves and primes defensive responses, a mechanism critical for survival. However, chronic activation results in maladaptive outcomes, including hypercortisolemia, anxiety, irritability, and metabolic dysregulation (Sapolsky, 2004). CRH and AVP are both under tight inhibitory control by GABAergic interneurons in the PVN, and loss of this inhibition leads to sustained excitability of the stress circuitry.

1.2. Oxytocin as an Endogenous Brake of the Stress Axis

Oxytocin (OXT), synthesized in the parvocellular regions of the PVN, exerts potent inhibitory control over HPA activation (Neumann, 2008). OXT neurons engage GABAergic interneurons that synapse onto CRH- and AVP-expressing neurons, suppressing their firing under both basal and stress conditions (Windle et al., 2004; Yoshida et al., 2009).
Moreover, OXT dampens sympathetic outflow, enhances vagal tone, and fosters social approach and trust behaviors (Heinrichs et al., 2009; Zak et al., 2005). These features designate OXT as a neuropeptide of "calm and connection" (Uvnäs-Moberg, 2018).

Deficiency of OXT tone—whether due to chronic stress, social isolation, or trauma—results in disinhibition of the PVN stress network and hyperreactivity of the HPA axis. Such dysregulation manifests as heightened irritability, defensive vigilance, and difficulties in emotional containment—symptoms often addressed in traditional East Asian medicine as "Liver Qi stagnation."

1.3. Traditional and Pharmacological Perspectives on Saiko

Bupleurum falcatum (Siho, Saiko, Chaihu), the principal herb in classic formulas such as *Shosaikoto* (Xiaochaihu Tang) and *Saiko-ka-ryukotsu-borei-to*, has been prescribed for centuries

to “soothe the Liver,” alleviate irritability, and restore psychosomatic balance. In contemporary neuroendocrine terms, this symptom pattern aligns with chronic activation of the HPA axis and excessive sympathetic drive (Makino et al., 1999).

Experimental studies have demonstrated that Saiko-based formulas and their active components, saikosaponins A and D, attenuate corticosterone elevation and normalize stress-induced behavioral abnormalities in rodent models. Saikosaponin D, in particular, reduces CRH and AVP mRNA expression in the PVN and enhances central GABAergic tone.

Taken together, these findings suggest that the traditional “Liver-soothing” effect of Saiko may reflect a biochemical restoration of inhibitory control within the PVN. Specifically, we propose that Saiko enhances OXT signaling, which in turn suppresses CRH and AVP through a GABA-dependent pathway, thereby reinstating homeostatic balance in both the neuroendocrine and autonomic domains.

2. Hypothesis: The PVN OXT–GABA–CRH/AVP Inhibitory Circuit

2.1. Conceptual Overview

We hypothesize that *Bupleurum falcatum*–based formulations restore neuroendocrine stability by activating a **paraventricular oxytocin (OXT)–GABA–CRH/AVP inhibitory circuit**, which acts as a physiological brake on the stress axis. In this model, Saikosaponins—triterpenoid saponins uniquely enriched in *Bupleurum*—enhance OXT neuronal excitability within the PVN, leading to activation of local GABAergic interneurons. These interneurons, in turn, inhibit CRH- and AVP-producing parvocellular neurons, thereby attenuating adrenocorticotropic (ACTH) release, glucocorticoid secretion, and sympathetic tone.

This inhibitory network constitutes a **homeostatic loop** counterbalancing the excitatory drive of stress mediators. In acute stress, CRH and AVP dominate; in recovery, OXT and GABAergic inputs restore equilibrium. Chronic stress, however, suppresses OXT tone (Neumann, 2008; Windle et al., 2004), leading to unchecked CRH/AVP hyperactivity. Saiko’s pharmacological action is thus conceptualized as a restoration of this lost inhibitory tone.

2.2. Evidence for Oxytocin–GABA Mediation

Multiple lines of evidence support the proposed OXT–GABA linkage.
First, electrophysiological studies demonstrate that OXT facilitates GABAergic inhibitory postsynaptic currents (IPSCs) within the PVN (Boudaba et al., 2003). OXT receptor (OXTR) activation increases GABA release onto CRH neurons, suppressing their firing rate and reducing ACTH output under stress (Yoshida et al., 2009).
Second, chronic stress models show that OXT knockout or OXTR blockade enhances CRH mRNA expression and corticosterone release (Neumann, 2008). Conversely, OXT agonism or optogenetic activation of PVN OXT neurons reduces both CRH transcription and cortisol secretion (Jurek & Neumann, 2018).

This neurocircuit structure aligns with traditional pharmacological effects of Saiko, which decreases hypothalamic CRH and AVP mRNA (Makino et al., 1999) while normalizing GABAergic

tone. We therefore propose that Saiko acts at the **upstream node**—enhancing OXT signaling—to indirectly modulate both CRH and AVP output.

Beyond the PVN, OXT exerts reciprocal regulation with the monoamine systems. It enhances serotonergic tone in the dorsal raphe nucleus (DRN) (Yoshida et al., 2009).

2.3. Mechanistic Schema

The following sequence summarizes the proposed pathway:

Saikosaponin D → PVN OXT neuron activation → ↑GABAergic inhibition → ↓CRH & AVP output → ↓ACTH / ↓Cortisol / ↓Sympathetic tone → ↑Serotonin tone (DRN) → Emotional stability & homeostasis.

This cascade provides a mechanistic bridge between molecular pharmacology and traditional pathophysiology. In East Asian medicine, emotional constraint and irritability are interpreted as a "Liver Qi stagnation" pattern—characterized by excessive sympathetic arousal and poor emotional regulation. Our model redefines this phenomenon as a manifestation of **OXT deficiency and CRH–AVP disinhibition**, a biologically plausible correlate of the ancient diagnostic framework.

3. Mechanistic Framework: From PVN Modulation to Systemic Homeostasis

3.1. The Stress–Recovery Loop within the PVN

The paraventricular nucleus (PVN) is a convergence hub where stress, emotion, and visceral states are integrated (Herman et al., 2003). Within this microcircuit, CRH and AVP neurons initiate the HPA cascade, while OXT and GABAergic interneurons provide inhibitory counterbalance.
Under acute threat, glutamatergic and noradrenergic afferents activate CRH and AVP neurons, leading to the release of ACTH and cortisol. Once the stressor is removed, feedback inhibition via glucocorticoid receptors, GABA, and OXT restores baseline tone (Ulrich-Lai & Herman, 2009).

However, in chronic stress or social isolation, this inhibitory feedback becomes blunted. Diminished OXT release reduces GABAergic inhibition and disinhibits CRH/AVP neurons, producing sustained hypercortisolism and sympathetic hyperactivity (Neumann, 2008; Jurek & Neumann, 2018). The system enters a maladaptive steady state characterized by *persistent alertness and affective rigidity*—a biological correlate of the "Liver Qi stagnation" pattern described in traditional medicine.

3.2. Saikosaponin-Induced Modulation of PVN Circuits

Saikosaponin D (SSD), a triterpenoid saponin from *Bupleurum falcatum*, is known to modulate neuronal excitability through multiple molecular targets. In vitro studies indicate that SSD enhances intracellular calcium influx in specific hypothalamic neurons and potentiates OXT release. Concurrently, SSD upregulates glutamic acid decarboxylase (GAD67) expression, suggesting reinforcement of GABAergic tone.

Thus, SSD appears to act as a **neuro-modulatory amplifier**, preferentially facilitating the OXT–GABA inhibitory axis while suppressing CRH–AVP overactivity. This dual modulation effectively lowers cortisol levels, restores heart rate variability, and mitigates behavioral indices of anxiety and irritability.
In rodent models, administration of Saiko-containing formulas reduced plasma corticosterone, normalized ACTH response, and restored social approach behavior (Makino et al., 1999.

3.3. Integration Across the Autonomic and Monoaminergic Systems

At the systemic level, PVN modulation reverberates across both autonomic and affective networks.
OXT neurons project to the nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus, where they increase parasympathetic output and promote vagal cardiac tone (Porges, 2011; Thayer et al., 2012). The resulting **autonomic rebalancing** reduces heart rate and blood pressure while increasing baroreflex sensitivity.

Simultaneously, OXT enhances serotonergic activity in the dorsal raphe nucleus (Yoshida et al., 2009) and inhibits CRH-mediated suppression of serotonin release (Lowry et al., 2005). This mechanism links endocrine stability to emotional resilience. Enhanced serotonergic tone promotes patience, emotional containment, and optimism—core affective dimensions often impaired in stress-related disorders (Cools et al., 2011).

Hence, the Saiko–OXT pathway can be conceptualized as an **endocrine-to-affective bridge**: restoring HPA inhibition not only lowers physiological arousal but also reestablishes emotional flexibility and social connectedness.

3.4. Summary of Mechanistic Interactions

Level	Primary Mediators	Effect of Saiko (Proposed)
Molecular	↑ OXT release, ↑ GABA synthesis, ↓ CRH/AVP mRNA	Restores inhibitory control of stress axis
Circuit	PVN OXT–GABA–CRH/AVP loop	Dampens HPA excitability and sympathetic tone
Systemic	↓ Cortisol, ↑ HRV, ↑ Vagal tone	Autonomic and endocrine stabilization
Behavioral	↓ Irritability, ↓ Anxiety, ↑ Sociality	Emotional calmness and resilience

4. Experimental Proposal: Testing the Saiko–OXT Hypothesis

4.1. Rationale

The proposed hypothesis — that *Bupleurum falcatum* (Saiko) exerts its neuroendocrine stabilizing effect by enhancing oxytocinergic inhibition of CRH/AVP neurons in the PVN — can be empirically tested through converging lines of evidence.
A comprehensive validation requires examining molecular, circuit, and behavioral outcomes following Saiko administration and determining whether these effects are mediated by oxytocinergic signaling.

We therefore outline a four-tiered experimental framework integrating **in vivo**, **ex vivo**, and **translational** approaches. In subsequent experiments, the Saiko intervention will employ a **standardized hot-water extract of *Bupleurum falcatum*** or **purified saikosaponin A/D** or Standardized *Shosaikoto* extract to ensure reproducibility and pharmacological specificity.

4.2. Tier 1: Molecular and Cellular Validation (in vitro)

Objective:

To determine whether Saiko intervention enhances OXT neuron activity and GABAergic transmission while suppressing CRH/AVP expression in hypothalamic cultures.

Methods:

- **Cell model:** Primary hypothalamic neuron cultures obtained from Sprague–Dawley rat pups (P0–P2).
- **Interventions:** Treatment with SSD (1, 10, 50 μM) versus vehicle for 24 hours.(or hot-water extract of Bupleurum falcatum or standardized Shosaikoto extract)
- Readouts:
    - OXT and CRH mRNA levels via qRT-PCR.
    - OXT and AVP release quantified by ELISA.
    - GAD67 protein levels assessed via Western blot.
    - Intracellular calcium dynamics measured by Fluo-4 AM imaging.

Expected outcome:

Saiko intervention will increase OXT expression and GAD67 while reducing CRH/AVP mRNA. This would support the hypothesis that Saiko enhances inhibitory (OXT–GABA) tone within the hypothalamus.

4.3. Tier 2: Circuit-Level Confirmation (in vivo)

Objective:

To visualize whether Saiko intervention increases OXT neuron activity and strengthens GABAergic inhibition on CRH/AVP neurons in the PVN.

Methods:

- **Animal model:** Adult male Wistar rats exposed to chronic restraint stress (2 hours/day for 14 days).
- **Groups:** Control, stress + vehicle, stress + Saiko intervention(for example, Saikosaponin D (20 mg/kg, oral)), stress + Saiko intervention + OXT receptor antagonist (L-368,899).
- Techniques:
    - Immunofluorescence labeling for OXT, GAD67, CRH, AVP.
    - In situ hybridization for OXT and CRH mRNA.
    - Fiber photometry recording of OXT neuron calcium activity (using AAV-OXT-Cre × GCaMP6s).
    - Optogenetic or chemogenetic validation (hM3Dq/hM4Di DREADDs) to selectively manipulate OXT neuron activity.

Expected outcome:

Saiko intervention will increase OXT neuronal firing and local GABAergic tone, resulting in suppression of CRH/AVP neuron activity and normalization of corticosterone levels. Antagonizing OXT receptors will abolish this effect, confirming OXT mediation.

4.4. Tier 3: Behavioral and Physiological Correlates

Objective:

To link neural modulation to behavioral and systemic outcomes.

Methods:

- Behavioral tests:
  - Elevated plus maze (anxiety-like behavior).
  - Social interaction test (affiliative behavior).
  - Tail suspension or forced swim test (despair index).
- Physiological markers:
  - Serum corticosterone, ACTH, and heart rate variability (HRV).
  - Telemetry-based autonomic recordings for vagal tone (Porges, 2011).
- Pharmacological controls:
  - OXT antagonist and CRH receptor antagonist to isolate pathway specificity.

Expected outcome:

Saiko will reduce anxiety-like and irritability behaviors, enhance social engagement, increase vagal HRV, and reduce serum corticosterone.
These effects will be blocked by OXT antagonism, confirming pathway dependency.

4.5. Tier 4: Translational Human Correlates

Objective:

To assess whether Saiko-based formulas modulate oxytocin levels, cortisol, and autonomic balance in human subjects.

Design:

- **Participants:** 60 adults with mild anxiety and elevated stress biomarkers (salivary cortisol >1 SD above mean).
- **Design:** Double-blind, randomized, placebo-controlled 8-week trial.
- **Intervention:** Standardized *Shosaikoto* extract (7.5 g/day) vs. placebo.
- Outcome measures:
  - Plasma oxytocin and cortisol (ELISA).
  - Heart rate variability (HRV) via ECG.
  - Self-reported stress and irritability scales (STAI, POMS).
  - fMRI resting-state functional connectivity between PVN–amygdala–insula circuits (Craig, 2002; Feldman, 2017).

Expected outcome:

Saiko treatment will increase plasma OXT, reduce cortisol, and enhance vagal tone (high-frequency HRV).
fMRI will show strengthened PVN–insula coupling (interoceptive calm) and reduced amygdala reactivity.
This would represent a translational validation of the proposed OXT-mediated homeostatic mechanism.

4.6. Summary of Experimental Predictions

Level	Methodology	Predicted Saiko Effect	Antagonist Reversal (OXT Blockade)
Cellular	qPCR, ELISA, Western blot	↑ OXT, ↑ GAD67, ↓ CRH/AVP	Yes
Circuit	Fiber photometry, IHC, DREADDs	↑ OXT firing, ↑ GABA, ↓ CRH/AVP	Yes
Behavioral	Anxiety/social tests	↓ Anxiety, ↑ Social interaction	Yes
Physiological	HRV, cortisol assays	↑ Vagal tone, ↓ Cortisol	Yes
Human	Plasma OXT, fMRI connectivity	↑ OXT, ↓ Cortisol, ↑ HRV	Yes

5. Discussion and Perspectives: Restoring the Motivation–Rest Cycle

5.1. Integrating the OXT–CRH Axis into Modern Stress Theory

Contemporary stress models emphasize the HPA axis and sympathetic activation but often overlook the counter-regulatory oxytocin–GABA system. Integrating this inhibitory axis reshapes our understanding of stress resilience.
Whereas glucocorticoid feedback provides delayed endocrine inhibition, OXT offers rapid, context-sensitive neural inhibition—a *real-time brake* on overactivation.

This insight invites a shift from unidimensional suppression of stress hormones to **dual-axis regulation**, targeting both excitatory (CRH/AVP) and inhibitory (OXT/GABA) arms for optimal resilience. Saiko-based interventions may therefore serve as prototypes for *bidirectional adaptogens*—agents that do not merely blunt stress but restore its natural self-limiting rhythm (Makino et al., 1999; Kawashima et al., 2004).

5.2. Translational and Clinical Implications

From a translational standpoint, the Saiko–OXT framework provides a neurobiological explanation for the long-recognized clinical efficacy of *Shosaikoto* and related formulas in treating irritability, anxiety, and psychosomatic disorders.
It suggests that the therapeutic target lies not only in suppressing cortisol but in enhancing oxytocin-mediated GABAergic restraint—thereby unifying endocrine, emotional, and social dimensions of recovery.

Moreover, the concept has broad implications for modern mental health paradigms:

- **For anxiety and depression:** Restoring OXT–GABA tone may enhance emotional regulation and stress coping without inducing sedation.
- **For psychosomatic disorders:** Strengthening OXT's visceral regulation may improve autonomic balance, vagal tone, and interoceptive awareness (Craig, 2002; Porges, 2011).

These effects converge on the restoration of **homeodynamic rhythm**—a state in which physiological and affective systems oscillate flexibly between activation and rest.

5.3. Limitations and Future Directions

While the proposed mechanism integrates multiple strands of neuroendocrine evidence, several uncertainties remain.

- Direct measurement of OXT neuron activation by Saikosaponins in vivo remains to be empirically confirmed.
- The precise receptor targets and signaling pathways mediating Saiko's effects on OXT neurons are still unknown.
- Translational studies in humans are limited by the complexity of measuring central OXT dynamics and individual differences in receptor polymorphisms.

Future work should employ chemogenetic manipulation, advanced imaging, and personalized pharmacogenomics to further elucidate how Saiko modulates the OXT–GABA–CRH/AVP axis across individuals and contexts.

References

- Berridge, K. C., & Kringelbach, M. L. (2015). Pleasure systems in the brain. *Neuron, 86*(3), 646–664.

- Boudaba, C., Szabó, K., & Tasker, J. G. (1996). Physiological mapping of local inhibitory inputs to the hypothalamic paraventricular nucleus. *Journal of Neuroscience, 16*(22), 7151–7160.

- Cools, R., Nakamura, K., & Daw, N. D. (2011). Serotonin and dopamine: Unifying affective, activational, and decision functions. *Neuropsychopharmacology, 36*(1), 98–113.

- Craig, A. D. (2002). How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews Neuroscience, 3*(8), 655–666.

- Dayan, P., & Huys, Q. J. M. (2008). Serotonin in affective control. *Annual Review of Neuroscience, 31*, 95–126.

- Dietrich, A. (2004). Neurocognitive mechanisms underlying the experience of flow. *Consciousness and Cognition, 13*(4), 746–761.

- Everitt, B. J., & Robbins, T. W. (2016). Drug addiction: Updating actions to habits to compulsions ten years on. *Annual Review of Psychology, 67*, 23–50.

- Fields, H. L., & Margolis, E. B. (2015). Understanding opioid reward. *Trends in Neurosciences, 38*(4), 217–225.

- Heinrichs, M., von Dawans, B., & Domes, G. (2009). Oxytocin, stress, and social behavior. *Annals of the New York Academy of Sciences, 1167*(1), 114–126.

- Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo–pituitary–adrenocortical axis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 29*(8), 1201–1213.

- Jurek, B., & Neumann, I. D. (2018). The oxytocin receptor: From intracellular signaling to behavior. *Physiological Reviews, 98*(3), 1805–1908.

- Lowry, C. A., et al. (2005). Modulation of serotonergic systems by corticotropin-releasing factor and urocortin. *Pharmacology & Therapeutics, 107*(3), 405–424.

- Montague, P. R., Dayan, P., & Sejnowski, T. J. (1996). A framework for mesencephalic dopamine systems based on predictive Hebbian learning. *Journal of Neuroscience, 16*(5), 1936–1947.

- Neumann, I. D. (2008). Brain oxytocin: A key regulator of emotional and social behaviours in both females and males. *Frontiers in Neuroendocrinology, 29*(1), 81–89.

- Porges, S. W. (2011). The Polyvagal Theory: Neurophysiological Foundations of Emotions, Attachment, Communication, and Self-Regulation. W. W. Norton.

- Sapolsky, R. M. (2004). *Why Zebras Don't Get Ulcers* (Updated ed.). Holt.

- Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology, 80*(1), 1–27.

- Schultz, W. (2016). Dopamine reward prediction-error signalling: A two-component response. *Nature Reviews Neuroscience, 17*(3), 183–195.

- Thayer, J. F., Åhs, F., Fredrikson, M., Sollers, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies. *Neuroscience & Biobehavioral Reviews, 36*(2), 747–756.

- Uvnäs-Moberg, K. (2018). The Oxytocin Factor: Tapping the Hormone of Calm, Love, and Healing (Updated ed.). Da Capo.

- Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience, 10*(6), 397–409.

- Windle, R. J., Shanks, N., Lightman, S. L., & Ingram, C. D. (1997/2004). Oxytocin attenuates stress-induced c-fos expression in hypothalamus and amygdala. *Endocrinology, 138*(2), 987–995; see also 2004 follow-ups.

- Yoshida, M., Takayanagi, Y., Inoue, K., et al. (2009). Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons. *Journal of Neuroscience, 29*(7), 2259–2271.

- Zak, P. J., Kurzban, R., & Matzner, W. T. (2005). Oxytocin is associated with human trustworthiness. *Nature, 435*(7042), 673–676.

- Zubieta, J. K., et al. (2005). Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *Journal of Neuroscience, 25*(34), 7754–7762.