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Oxytocin Levels Inversely Correlate With Skin Age Score and Solar Damage

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ABSTRACT

Background: Studies have shown oxytocin (OT) and its carrier protein neurophysin 1 are found in the epidermis. The oxytocin receptor, which is found on human fibroblasts has been shown, when activated by oxytocin, to inhibit senescence-associated secretory phenotype (SASP). SASP activation induces the release of proinflammatory cytokines which contribute to skin aging. Therefore, its inhibition by oxytocin would constitute a protective mechanism. This pilot study was designed to explore clinical evidence of oxytocin levels correlating to the skin's appearance in subjects.

Methods: Oxytocin levels, facial photographs, and lifetime sun exposure questionnaires from six female subjects aged 48–61 years old were analyzed. A skin age score (SAS) was determined for each subject and was compared to the expected average SAS for each subject based on their age to determine a percentage in change, if any. A reduction in SAS would indicate more youthful appearing skin than the average person of that age.

Results: All subjects had at least some reduction in SAS score as compared to their expected score. An almost linear relationship of SAS reduction as related to OT levels was found, showing a correlation of more youthful appearing skin with higher OT levels.

Conclusions: This study links previously published evidence of oxytocin's protective role against inflammatory cytokine release in the skin with clinical evidence of OT levels correlating with SAS scores. Furthermore, it shows OT is likely inducing a protective function in the epidermis in the case of sun exposure and possibly with intrinsic aging.

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INTRODUCTION

The epidermis has an obvious role of protecting us from the environment, but recent research is revealing some new functions. Keratinocytes have been shown to secrete oxytocin (OT) in response to an ATP analogue in a dose-dependent manner.[1] Oxytocin is a neuropeptide which is involved with milk ejection, uterine contractions, behavior, memory, social bonding, and mental state.[1,2,3,4] Oxytocin has also been shown to be involved with muscle regeneration, cardiovascular regulation, and osteocyte-adipocyte balance.[4] In fact, both OT and its carrier protein neurophysin 1 are synthesized in keratinocytes.[1]

The oxytocin receptor (OTR) is a seven-membrane spanning receptor that is coupled via various G-protein isoforms to different signaling pathways, allowing it to have various physiologic functions in different cell types.[2,5,6] The OTR is expressed on human fibroblasts.[2,5] This receptor is internalized after binding with OT and is transported to the cell nucleus.[5] Once in the cell nucleus, OT effects gene regulation.

Oxytocin binding to its receptor on fibroblasts has been shown to suppress senescence-associated secretory phenotype (SASP).[4] When not suppressed, SASP promotes a low-level chronic inflammatory state by releasing proinflammatory cytokines such as interleukin (IL)-6, IL-1, chemokines, growth factors, and extracellular matrix-remodeling proteases.[4] This leads to aging of the skin. Therefore, OT binding would have a protective, anti-inflammatory effect through its suppression of SASP and in turn its prevention of inflammatory cytokine release.[4]

This study attempts to establish a link between OT levels and clinical evaluation of the skin. Of interest, is whether or not a higher OT level correlates to more youthful appearing skin. Knowing that the appearance of the skin is not only due to intrinsic factors, we also evaluated the amount of lifetime sun exposure for each study subject as an indication of the amount of extrinsic or environmental aging.

METHODS

A chart review was performed in an IRB-exempt study, revealing six female subjects aged 48–61 years old who qualified to be included. All were average BMI and non-smokers. Fitzpatrick skin types II–IV were included. Exclusionary criteria included any cosmetic procedures such as neurotoxin injections, dermal filler injections, chemical peels, laser treatments, or any other

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TABLE 1.

Sun Exposure Questions	
Question	**Value Assigned**
Do you use sunscreen daily? If so, what SPF? When did you start this habit?	Yes = 0 No = 1
How much sun did you get as a child and young adult?	Minimal = 1 Moderate = 2 Extreme = 3
Have you ever used a tanning booth? If so, how many times?	Never = 0 1-2 times = 1 3-5 times = 2 6 or more times = 3

cosmetic rejuvenation treatments in the six months prior to the participant's recorded OT level. Other exclusionary criteria included the use of any topical or cosmetic treatments with any active ingredient such as retinoic acid, retinol, salicylic acid, glycolic acid or antioxidants. Sunblock usage was allowed. Subjects were not on any hormone supplements.

Subjects had a lifetime sun exposure history (Table 1) recorded and had been photographed using a medical imaging camera and software system (Canfield Scientific, Parsippany, NJ). A skin age score (SAS)[7] was calculated along with a lifetime sun exposure score. Since the SAS tends to be a linear relationship for those between 31 and 71 years of age with the SAS correlating with chronologic age,[7] an estimated change of SAS was calculated assuming the subject's age as their expected SAS score:

Estimated % change of SAS =
[(Subject's age – SAS) / Subject's age] x 100

The sun exposure score was calculated by assigning a value to the sun exposure questions as shown in Table 1.

Oxcytocin levels were measured from 24-hour urine samples. Analysis was done by Meridian Valley Labs (Tukwila, WA). Samples were collected and processed as per Meridian Valley Lab's protocol.

RESULTS

The lifetime sun exposure questionnaire revealed that all subjects, except for subject 4, used sunblock daily and had been doing so for decades. The remainder of the questions were answered as shown in Table 2.

Oxytocin levels ranged from 86 pmol/24hr to 306 pmol/24hr. SAS scores ranged from 23 to 53, and sun exposure scores ranged from 1 to 7. (Table 3 and Figure 1)

The two subjects with the highest OT levels had the greatest

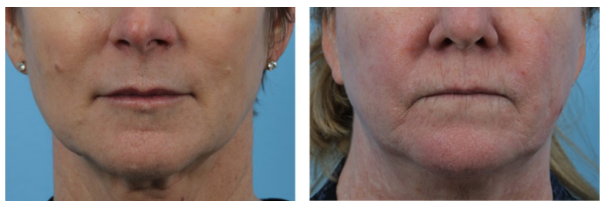
TABLE 2.

Sun Exposure Responses		
Subject	**How much sun did you get as a child and young adult?**	**Have you ever used a tanning booth? If so, how many times?**
1	Moderate	6 times
2	Minimal	1 time
3	Minimal	No
4	Extreme	Often for years
5	Extreme	5 times
6	Minimal	No

TABLE 3.

Oxytocin Levels, Skin Age Score and Sun Exposure Score per Participant						
Subject	**Age (yrs)**	**Fitzpatrick**	**OT pmol/ 24hr**	**Skin Age Score**	**Estimated change in SAS based on age**	**Sun Exposure Score**
1	52	III	216	28	-46%	5
2	48	II	101	34	-29%	2
3	61	II	115	53	-13%	1
4	53	II	120	47	-11%	7
5	57	II	306	23	-60%	5
6	58	IV	86	42	-26%	1

FIGURE 1. Left: Patient 5 with high OT level and high estimated reduction in SAS, who reported a strong sun lifetime exposure history. Right: Patient 3 with a low OT level, low estimated reduction in SAS, who reported a minimal sun lifetime exposure history.



estimated SAS reduction in spite of having two of the highest sun exposure scores. The two subjects with the lowest reported sun exposure scores had the lowest and third lowest OT levels. They also had two of the SAS scores that were most in line with their age, or with little reduction from the predicted value. All subjects had at least some reduction in SAS as compared to their expected score.

When the percentage of SAS reduction is plotted against the subject's OT level, there is almost a linear relationship showing the higher a subject's OT level, the greater the reduction in SAS she had. (Figure 2) This appears to be independent of the subject's lifetime sun exposure level.

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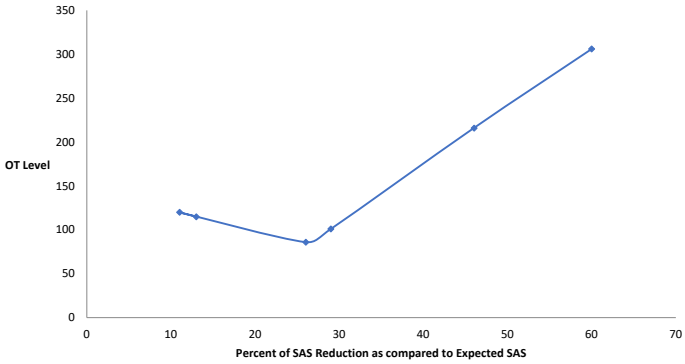
FIGURE 2. A comparison of SAS reduction to OT levels. SAS reduction was calculated using subject's actual SAS and their expected SAS. Expected SAS was assumed to correlate with the subject's age. A higher percentage of reduction corresponds to a more youthful appearing epidermis.



DISCUSSION

The known role of OT has been expanding recently through research. Oxytocin has been proven to be produced and released by keratinocytes.[1,2,6] A study by Deing et al showed that skin which was caressed prior to a sample being taken for analysis had significantly higher OT levels as compared to unstimulated skin, showing that tactile stimulation of the skin is one signal which causes OT release.[2] This shows that physical contact and affection increase OT levels.

Human fibroblasts have been shown to express the OTR.[2,5] OT binding to its receptor on fibroblasts inhibits the SASP phenotype, thus also inhibiting cellular senescence through preventing the release of proinflammatory cytokines, resulting in an anti-inflammatory effect.[4] In effect, OT has a protective, anti-inflammatory effect on the skin which could protect it from changes associated with photo and possibly intrinsic aging.

This pilot study shows that there is a clinical correlation between OT levels and the SAS of a subject. High OT levels of several patients, in spite of strong lifetime sun histories, correlated with more youthful skin and significantly lower SAS scores than expected. The reverse was also true with multiple patients whose lifetime sun histories showed a lower risk of solar damage having relatively higher SAS scores along with lower OT levels. This shows that higher levels of OT translate to a less inflammatory environment and more youthful looking skin. This may be a protective mechanism against photo aging, intrinsic aging, or both. Although this study is small, and OT levels are likely to vary over time, an almost linear relationship was found between the OT level and percent of SAS reduction as compared to the expected SAS for a subject.

Piecing all of this together leads to the conclusion that there is a complex oxytocin social exchange system that not only effects behavior, memory, social bonding, and mental state, but links them to the preservation of a more youthful appearance. This more youthful appearance may in turn be interpreted by others as the subject being young, healthy and possibly a more attractive subject for social interaction. More positive social interaction and exchange of affection may in turn help to raise OT levels, thus creating a positive re-enforcement loop.

The epidermis and central nervous system have a common embryologic origin, both being derived from the ectoderm layer. Therefore, it is not surprising that the epidermis is linked through neuropeptide signaling not only to mental state of that person but is also sending signals to others through the protection and enhancement of its skin. This protection and more youthful appearance will convey a sign of fertility to the opposite sex, thereby leading to procreation and more offspring, possibly with a positive social attitude. Humans are social creatures, and this complex OT Social Exchange System deserves further study.

DISCLOSURES

The author has no declared conflicts of interest.

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REFERENCES

1. Denda S, Takei K, Kumamoto J, et al. Oxytocin is expressed in epidermal keratinocytes and released upon stimulation with adenosine 5′-[γ-thio] triphosphate in vitro. *Exp Dermatol* 2012; 21(7):535-537.
2. Deing V, Roggenkamp D, Kühnl J, et al. Oxytocin modulates proliferation and stress responses of human skin cells: implications for atopic dermatitis. *Exp Dermatol* 2013; 22(6) 399-405.
3. Denda M, Takei K, Denda S. How does epidermal pathology interact with mental state? *Med Hypotheses* 2013; 80(2): 194-196.
4. Cho S, Kim A, Kim J, et al. Oxytocin alleviates cellular senescence through oxytocin receptor-mediated extracellular signal-regulated kinase/Nrf2 signalling. *Br J Dermatol* 2019; 181(6): 1216-1225. Doi: 10.1111/bjd. 17824. Epub 2019 Jun 23.
5. Kinsey C, Bussolati G, Bosco M, et al. Constitutive and ligand-induced nuclear localization of oxytocin receptor. *J Cell Mol Med* 2007; 11(1): 96-110.
6. Lotti T, Hautmann G, Panconesi E. Neuropeptides in skin. *J Am Acad Dermatol* 1995; 33(3): 482-496.
7. Guinot C, Malvy D, Ambroisine L, et al. Relative contribution of intrinsic vs extrinsic factors to skin aging as determined by a validated skin age score. *Arch Dermatol* 2002; 138: 1454-1460.

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