Antistress Pattern Induced by Oxytocin
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Repeated oxytocin injections cause lowered blood pressure, decreased cortisol levels, increased withdrawal latency, increased release of vagally controlled gastrointestinal hormones, and increased weight gain. Together, these effects form an antistress pattern. Nonnoxious sensory stimuli release oxytocin and induce an effect spectrum similar to the one caused by oxytocin injections.

Effects of oxytocin

Despite being the first peptide hormone to be identified and synthesized and despite being present also in males, the effects of oxytocin were long considered to be restricted to female reproductive behavior, i.e., the stimulation of uterine contractions during labor and milk ejection during lactation.

More recently, oxytocin has been shown to influence a variety of behaviors (it promotes sexual, maternal, and social behaviors) (2, 4, 11) as well as physiological and endocrine functions (the physiological and endocrine effects of oxytocin are the focus of this review).

As can be seen in the literature, many different and often opposing physiological and endocrinologic effects have been described in response to oxytocin. The complexity may be related to the fact that oxytocin can influence the same physiological or endocrinologic functions differently at different anatomic sites receiving oxytocinergic innervation. Therefore, depending on species, route of administration, dose given, time of observation, and other experimental factors, different effects in response to oxytocin may have been observed. From a functional point of view, the reason that oxytocin is able to induce such a variety of effects could be that it integrates physiological, endocrine, and behavioral functions in such different situations as birth, lactation, and sexual behavior.

Plasma levels of oxytocin normally vary between 10 and 100 fmol/l, and effects of oxytocin that are exerted by peripheral mechanisms can be induced following administration of oxytocin in amounts that raise plasma concentration to within this range. It is more difficult to decide what is a physiological dose of oxytocin following central administration. When oxytocin levels are measured in the cerebrospinal fluid (CSF), levels 5- to 10-fold higher than in plasma are normally found, but the concentration of oxytocin at its receptor sites is not known.
Effects of oxytocin may be observed following intracerebroventricular administration within a broad concentration range, i.e., from nanograms to micrograms per kilogram. Whether different types of oxytocin receptors are involved in the “low-” and “high”-dose effects of oxytocin is not known. Alternatively, a potentiating stimulus normally present when endogenous oxytocin is released may be lacking in experiments in which high amounts of exogenously administered oxytocin are needed to induce effects.

A short review of documented physiological and endocrine effects of oxytocin is given below. Thereafter, the oxytocin-mediated antistress effects, particularly when induced by repeated oxytocin injections or nonnoxious somatosensory stimulation, are described.

Cardiovascular effects

In rats, oxytocin (administered intrathecally) increases blood pressure and pulse rate by activation of the presynaptic sympathetic neurons in the spinal cord or, following intracerebroventricular administration, by influencing centre in the brain stem. However, sometimes a decrease in blood pressure is observed in response to oxytocin given intracerebroventricularly and, in primates or humans, administration of oxytocin always seems to be associated with decreased blood pressure. Electrical stimulation in the PVN, possibly resulting in oxytocin release, invariably leads to a lowering of blood pressure. Furthermore, intracerebroventricular administration of oxytocin may cause bradycardia by activation of a cholinergic mechanism in the DMX. Circulating oxytocin may also induce vasodilatation, particularly in cutaneous blood vessels.

Food intake and digestion

Oxytocin administered intracerebroventricularly in microgram amounts to male and nonlactating female rats has been shown to inhibit food intake for up to 3 h. However, oxytocin may also induce hyperphagia in female rats, particularly during lactation.

Digestion and metabolism

Oxytocin also stimulates acid secretion and the release of various gastrointestinal hormones such as cholecystokinin (CCK), somatostatin, and gastrin by activation of vagal fibers in the DMX. In addition, insulin release is promoted. These effects, which are induced by nanogram amounts of oxytocin given intracerebroventricularly, are blocked by atropine, suggesting they are mediated via cholinergic fibers. In addition, insulin and glucagon can be released by activation of oxytocin receptors in the pancreas.

Apparently, oxytocin has two opposite effects in the handling of nutrients. Insulin secretion and digestive function, and thereby storage of energy, are stimulated via a central action of oxytocin. In contrast, circulating oxytocin mobilizes energy by stimulating glucagon release, thereby increasing glucose levels.

Release of pituitary hormones

Because oxytocinergic neurons project to the median eminence, oxytocin may be released into the hypthalamic pituitary portal system to influence the hormones produced in the anterior pituitary. Indeed, oxytocin given intracerebroventricularly stimulates prolactin release and, in addition, it has been shown to either stimulate or inhibit the secretion of growth hormone. A short-term release of adrenocorticotropic hormone and corticosterone has been demonstrated in rats, but in primates and humans the effect on these hormones is inhibitory.

Locomotor behavior

Low amounts of oxytocin [ng intracerebroventricularly (icv) or µg subcutaneously (sc)] change the activity from the periphery to the center of an open-field arena (an anxiolytic-like effect), whereas higher amounts of oxytocin (µg icv or mg sc) reduce the amount of locomotor behavior (a sedative effect).

Pain threshold

When given to conscious rats, oxytocin delays withdrawal latency to heat stimuli (tail-flick and hot-plate test) and also to mechanical stimuli. The effect can be induced by oxytocin given subcutaneously, but because similar effects are induced by 1,000-fold lower amounts of oxytocin given intracerebroventricularly, the effect is likely to be exerted centrally.

Kidney function and fluid balance

Oxytocin stimulates urinary Na excretion by inhibiting Na reabsorption in the distal tubule or collecting duct and also by stimulating Na excretion by a neural pathway. In addition, oxytocin inhibits salt appetite, which, together with the effects of oxytocin on kidney function, acts to reduce the Na content in the body.
Thermoregulation

Most studies regarding the effect of oxytocin on temperature indicate that oxytocin induces hyperthermia. Injection of small amounts of oxytocin directly into the anterior hypothalamus, the preoptic area, or the cerebral ventricles of rats leads to hyperthermia (8).

Oxytocin may also decrease the temperature of the skin of the tail by causing constriction of the vessels in this area. This effect of oxytocin is induced centrally and may be part of an energy-saving pattern (1). In contrast, circulating oxytocin may cause dilatation of cutaneous vessels, e.g., in the area overlying the mammary gland of lactating rats, to allow transfer of warmth from mother to pups (14).

Antistress effects of repeated administration of oxytocin

Repeated administration of oxytocin to rats causes an effect profile that in part differs from that induced by single injections (Table 1). These effects cannot be attributed to the direct effects of oxytocin, due to the short half-life of this substance (minutes), but to activation of secondary mechanisms, the nature of which is presently being explored. The effects are exerted centrally because they may be induced by intracerebroventricular administration of oxytocin. With subcutaneous administration, 1,000-fold higher doses are needed to induce the same effects. However, because 1–2‰ of a dose of oxytocin given peripherally passes the blood-brain barrier to reach the central nervous system, the effects in response to subcutaneous administration are also likely to be exerted centrally.

A 5-day period of daily oxytocin treatments (1 mg/kg sc or 1 µg/kg icv) causes the following effects. First, systolic and diastolic blood pressures are lowered by ~15 mmHg without affecting pulse rate. In males, blood pressure is normalized 10 days after the last oxytocin treatment, whereas in females differences between salinetreated controls and oxytocin-treated animals persist at this time point (6). Second, the withdrawal latency in the tail-flick test is increased and gradually declines to pretreatment values within 10 days. The sustained effect induced by repeated administration of oxytocin cannot be antagonized by the oxytocin antagonist as in the case of acutely oxytocin-induced elevation of withdrawal latency. Instead, naloxone temporarily inhibits the enhanced delay in withdrawal latency, suggesting that the activity of an endogenous opiate system has somehow been increased (7). Third, corticosterone levels are significantly lower and CCK levels are significantly higher than in saline-treated controls (10). Fourth, female rats experience a slow, spontaneous weight gain (13). This effect occurs without an increase in food intake, suggesting that the effect is due to metabolic changes favoring the storage of energy.

In conclusion, acute administration of oxytocin to rats can be followed by a short-lasting increased activity in the sympathoadrenal system and an increased activity in the hypothalamic pituitary adrenal (HPA) axis (8). In contrast, the long-term effects caused by oxytocin, particularly following repeated administration, are always consistent with a lowered sympathoadrenal tone and activity in the HPA axis as well as with an elevated vagal nerve tone, enhanced digestive and anabolic activity, and behavioral calm, suggesting that one important effect of oxytocin is to integrate an antistress pattern that actually runs counter to the effects caused by corticotropin-releasing factor (CRF) and vasopressin (two other regulatory peptides produced in the PVN). This effect pattern forms an antithesis to the previous-

| TABLE 1. Comparison between effects of oxytocin injections and 5-min abdominal stroking |
|---------------------------------------------|---------------------------------------------|
| Effect of Oxytocin (1 mg/kg sc and 1 µg/kg icv) | Effect of Abdominal Stroking (40 strokes/min for 5 min) |
| Blood pressure | Decrease | + | + |
| Locomotor behavior | Decreased locomotor activity | + | + |
| Pain threshold | Increased latency to heat stimulation | o | o |
| | Increased latency to mechanical stimulation | + | + |
| Tail skin temperature | Decrease | + | + |
| Effect on vagal hormones | + | + |

sc, Subcutaneous; icv, intracerebroventricular. o, Effect is reversed by an oxytocin antagonist (whereas other effects are not).
ly identified fight-flight response (10) (Fig. 1).

**Oxytocin effects in response to nonnoxious somatosensory stimulation**

Several types of innocuous stimuli, such as touch, warm temperature, vibration and electroacupuncture, and stroking (i.e., stroking the abdomen of conscious rats at a frequency of 40 strokes/min), increase oxytocin levels in plasma and, in particular, in CSF (1, 10). These stimuli also induce an antistress pattern similar to the one caused by noxious and the latter by nonnoxious sensory stimuli or by equivalent "psychological" stimuli. GI, gastrointestinal.

**Oxytocin effects in response to suckling**

The effects of oxytocin in connection with suckling in lactating animals are complex. It is well known that oxytocin is released into the circulation in response to the suckling stimulus, causing milk ejection. Milk ejection is, however, also accompanied by an oxytocin-mediated increased blood flow to the skin overlying the mammary gland and by a rise of glucagon and glucose levels in response to elevation of circulating oxytocin levels, allowing transport of nutrients to the mammary gland. These effects of oxytocin in the circulation are all part of the physiological mechanism involved in the transfer of energy from mother to offspring (14).

However, the antistress pattern of oxytocin is also induced. Thus, in lactating women, each suckling episode is followed by a fall in blood pressure and cortisol levels and a release of gastrointestinal hormones. Breastfeeding women were also found to be calmer than the nonpregnant, nonbreastfeeding control women. The level of calm correlates with oxytocin levels, suggesting a role for oxytocin in this adaptation (11, 14).

**Oxytocin-induced attachment and health-promoting or antistress effects by social interaction**

In various animal experimental models, oxytocin has been shown to facilitate bonding or attachment (mother-infant or female-male) or simply to increase the amount of social contact between individuals (4, 11, 14, 15). A specific bond between individuals or an increased wish or need for contact (in opposite terms, a lowered level of suspicion or aggression) also has interesting physiological consequences in the sense that it invites repetitive exposure to friendly interaction involving tactile or other kinds of sensory or psychological stimuli. With the assumption that oxytocin is repeatedly released by sensory or equivalent stimuli exchanged in social interaction, experiments in which oxytocin is repeatedly administered should result in a similar situation. If so, lowered sympathoadrenal activity, enhanced vagal nerve activity leading to anabolic metabolism and possibly to growth, as well as relaxation should be induced (10). Indeed, there is extensive literature indicating that good relationships and social support have positive effects on health. In particular, the risk for cardiovascular disease seems to be decreased (13).

In conclusion, oxytocin has a broad range of
behavioral, endocrine, and physiological effects. Oxytocin seems to integrate patterns of effects in various interactive situations such as birth, lactation, and sexual and other kinds of social behavior. The antistress effects caused by oxytocin, particularly in response to repeated exposure to nonnoxious sensory stimuli, may have health-promoting effects.

References

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