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Extremely Low Doses of Oxytocin Reduce Pain Sensitivity in Men

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The effect of extremely low doses of oxytocin (vapor) on the perception of pain (pricking of the finger) is studied on 48 healthy volunteers. Inhalation of oxytocin vapor from the standard solution in doses producing a sensation of smell lowers pain threshold by 56.5%. Inhalation of oxytocin vapor creating no sense of smell has a lower hypalgesic effect. The oxytocin-induced hypalgesia is consistent with reduction in the heart reactivity to pain.

Key Words: *oxytocin; hypalgesia; pain*

Previously, we found that some compounds creating the sense of smell (odogens) [5] change the activity of the autonomic nervous system and the sensitivity of the olfactory analyzer [3]. On the basis of these findings it was hypothesized that odogens may modulate the perception of pain.

It was reported that parenteral administration of oxytocin (OT) produces an analgesic effect [6]. In the present study we examined the effect of extremely low (nanomolar) doses of OT applied as an odogen on the perception of pain by young healthy men.

MATERIALS AND METHODS

Forty-eight 18-24-year-old volunteers were enrolled in the study. Observations were carried out against the background of usual psychoemotional and physical activity of each individual during two preceding days, in the absence of changes in the nasal breathing, 1.5-2.5 h after the last meal, and a 2-h abstention from smoking.

A volunteer was lying on a couch with a high head-rest, wearing ear caps and a light-proof mask. Prior to the test, differential rheogram was recorded in a 4-RG-1-M apparatus and an EK 4T-02 electrocardiograph. The results were analyzed using Statgraphics software.

We studied how the subjective perception of pain caused by the pricking of the finger changes after inhalation of vapor from distilled water and an aqueous solution of OT in concentrations inducing and not inducing a sensation of smell. Pain was induced by pricking the 4th then the 3rd finger on the right hand with the use of a blood lancet.

The standard aqueous solution of OT (5 IU/ml, Gedeon Richter, 16 volunteers) and freshly prepared OT solution of a subthreshold concentration (0.02 IU/ml,

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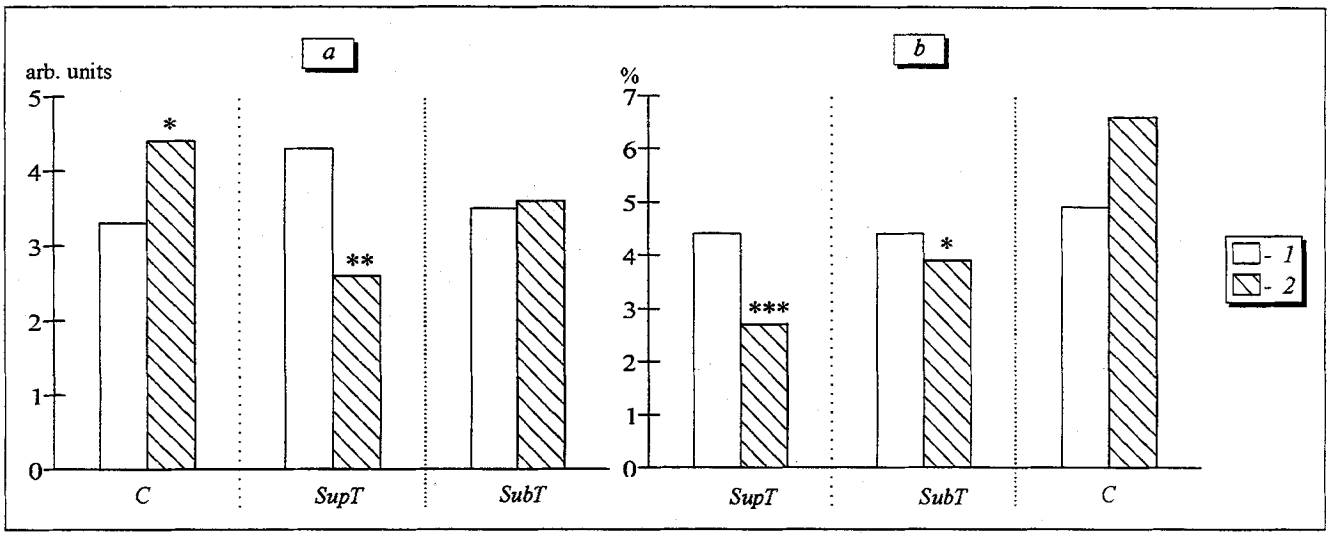

Fig. 1. *a*) Intensity of pain after the first (*1*) and second (2) pricking of the finger in control group (*C*) and after inhalation of suprathreshold (*SupT*) and subthreshold (*SubT*) concentration of vapor from an aqueous solution of oxytocin. **p*<0.05, ***p*<0.01 compared with the first prick; *b*) changes in the duration of the cardiac cycle in response to the first (*1*) and second (2) prick compared with the baseline level. *SubT* and *SupT*) changes caused by sub- and suprathreshold concentrations of oxytocin vapor, respectively. *C*) control, **p*<0.05 compared with changes after the first prick; ****p*<0.01 compared with the control.

16 volunteers) were applied as odogens. Distilled water (Pfizer) was used as the control (16 volunteers).

The odogen was proposed 30 sec after first pricking and was inhaled for 30-40 sec.

The volunteer signalled the intensity of pain by bending the 2nd finger (no bending indicated no pain, 10 bendings indicated unbearable pain) and by a visual-analogous scale [4] after the end of test. The estimations obtained by both scales proved to be similar.

RESULTS

In the control group, the second prick (after inhalation of water vapor) was perceived as more painful (by 33%) by 62.4% of the volunteers, indicating sensitization to pain.

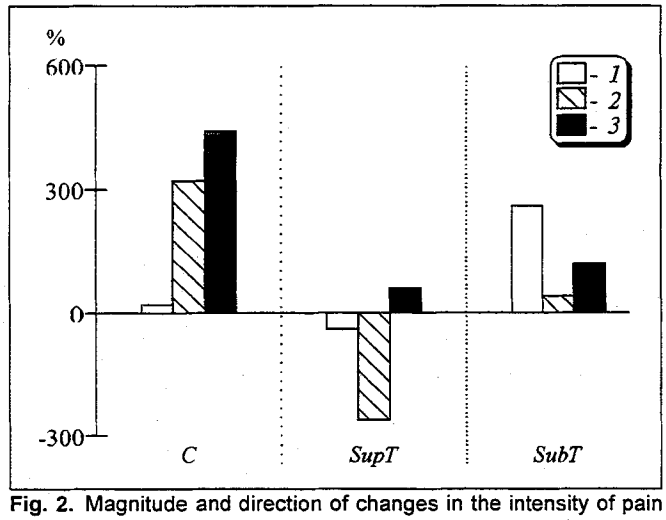

Fig. 2. Magnitude and direction of changes in the intensity of pain after the second prick expressed as a percentage of the pain intensity after the first prick in sympatho- (*1*), normo- (2), and parasympathotonics (*3*). Symbols are the same as in Fig. 1.

Inhalation of oxytocin vapor (OTv) reduced the sense of pain by 56.5% of the initial level in the majority of volunteers (87.5%). Analgesia was not achieved in any of the volunteers even after 40 sec of inhalation of OTv.

Inhalation of subthreshold concentrations of OTv reduced pain in 43.8% of the volunteers. Others (56.2%) reported increased pain, although to a lesser extent than in the control (Fig. 1, *a*).

The duration of cardiac cycles determined as the interval between two peaks on a rheogram was chosen as an objective parameter of pain. The results obtained with the use of this parameter (Fig. 1, *b*) were consistent with subjective estimations of pain: pronounced changes in the cardiac cycle in response to the second prick were observed in the control group, their intensity decreased after inhalation of OTv, the decrease being lower in the volunteers proposed subthreshold concentrations of OTv.

Assuming that the OTv-induced decrease in the sensitivity to pain is due to stimulation of the olfactory cells and does not depend on the amount of the compound in the upper respiratory tract, we compared changes in the pain sensitivity in persons with high and low smell thresholds.

According to the sensitivity to the odor from an OT solution, 16 volunteers were subdivided into 3 groups: 7 individuals (43.8%) with a high threshold (0.156 IU/ml and higher), 4 individuals (25%) with a medium threshold (0.078 IU/ml), and 5 individuals (31.2%) with a low threshold (0.039 IU/ml).

A relationship between the hypalgesic effect of subthreshold concentrations of OTv and sensitivity to the odor of OTv was revealed: the decrease in pain sensitivity after the second prick relative to the first prick in the volunteers with a low threshold was 31.7±5.1%, while in volunteers with a high threshold it was 75±18.1% ($p<0.05$).

In order to assess the relationship between subjective perception of pain and activity of the autonomic nervous system the volunteers were assigned into groups according to the predominance of sympathetic and parasympathetic innervation [1]. There were no significant differences in pain sensation of sympatho-, normo-, and parasynpathotonics after the first prick.

In the control series of observations, sensitization to repeated pain was 3.2- and 1.9-fold higher in parasympathotonics and normotonics, respectively, than in sympathotonics. Since the thresholds for this odogen were consistent with the activity of the autonomic nervous system [3], we hypothesized that the analgesic effect of nanomolar concentrations of OT depends on this factor.

In parasympathotonics, the hypalgesic effect of OTv was 1.4-fold as high as that in sympathotonics (Fig. 2). Presumably, this was due to a greater reduction in the sense of pain after inhalation of OTv, since the sensitivity to pain after the first prick was similar in all the volunteers.

Analysis of the duration of the cardiac cycle revealed a relationship between heart reactivity and activity of the autonomic nervous system, but not the concentration of OTv (Fig. 3).

Since the reduction in pain sensitivity was not determined by the dose of OT but by the threshold of the sensitivity to the OT smell and the activity of the autonomic nervous system, it can be concluded that the hypalgesic effect of OTv is realized via the olfactory analyzer. The mechanism whereby the effect of extremely low doses of OTv is realized via the olfactory epithelium differs from that operating after parenteral administration of OT.

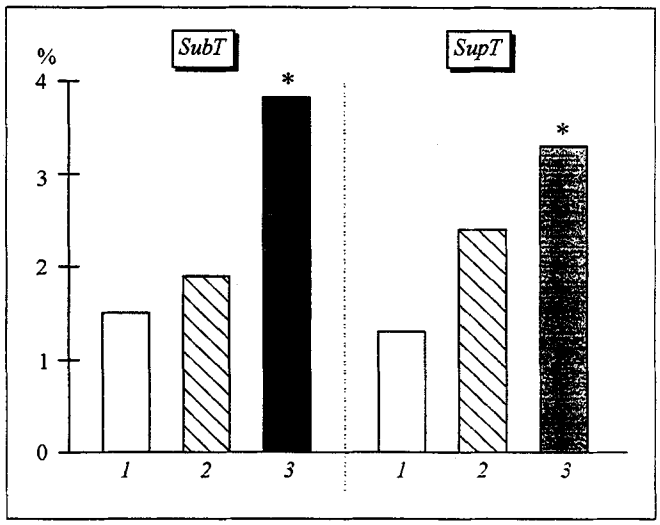

Fig. 3. Changes in the duration of cardiac cycle in response to subthreshold (*SubT*) and suprathreshold (*SupT*) concentrations of odogen in sympatho- (*1*), normo- (*2*), and parasympathotonics (*3*). *$p<0.05$ in comparison with sympathotonics.

It is likely that the lowering of pain threshold by nanomolar concentrations of OTv is caused by such a redistribution of the activity of the CNS structures which is accompanied by a decrease in the sympathotonic activity and an increase in the parasympathotonic activity caused by stimulation of the olfactory receptors.

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