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De-masking oxytocin-deficiency in craniopharyngioma and assessing its link with affective function

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ABSTRACT

Despite the high prevalence of panhypopituitarism and diabetes insipidus in patients with craniopharyngioma (CP), little is known about the functioning of the neuropeptide oxytocin in these patients. This is of special interest as tumor-associated lesions often impair sites critical for oxytocin production and release, and affective dysfunction in CP links with elsewhere reported prosocial, antidepressant and anxiolytic oxytocin effects. Using a prospective study-design, we tested whether oxytocin is reduced in CP-patients, and whether altered oxytocin levels account for affective and emotional dysfunction. 26 adult CP-patients and 26 healthy controls matched in sex and age underwent physical exercise, a stimulus previously shown to induce oxytocin release. Baseline and stimulated salivary oxytocin levels, as well as empathy, depression and anxiety scores were measured. Results showed that patients overall did not present with lower baseline oxytocin levels than controls ($F[1,30] = 0.21$, $p = 0.649$), but baseline oxytocin levels were indeed reduced in patients with hypothalamic damage, as assessed by MRI-based grading ($F[2,9.79] = 4.54$, $p = 0.040$). In response to exercise-induced stimulation, *all* CP-patients showed a blunted oxytocin-release compared to controls ($F[1,30] = 9.36$, $p = 0.005$). DI was not associated with oxytocin levels. Regarding affective function, unexpectedly, higher *baseline* oxytocin was related to higher trait anxiety ($b = 2.885$, $t(43) = 2.421$, $p = 0.020$, CI[.478; 5.292]); the positive link with higher depression failed to reach statistical significance ($b = 1.928$, $t(43) = 1.949$, $p = 0.058$, CI[−0.070; 3.927]). A blunted *oxytocin-release* was linked with higher state anxiety ($b = -0.133$, $t(43) = -2.797$, $p = 0.008$, CI [-0.230; −0.037]). Empathy was not associated with oxytocin measures. In conclusion, we observed reduced baseline oxytocin levels only in CP-patients with hypothalamic damage. Exercise-induced stimulation de-masked an oxytocin-deficiency in all CP-patients. Baseline oxytocin levels and stimulated OT-responses might have different effects on affective function, which should be considered in future substitution paradigms.

1. Introduction

Craniopharyngiomas (CP) are rare epithelial tumors arising along the path of the craniopharyngeal duct with an overall incidence of 0.13 cases per 100,000 person-years (Bunin et al., 1998). Though histologically benign, they are associated with a high degree of morbidity. This is due to their disadvantageous location, growth pattern, and the consequences of their surgical and radiotherapeutical treatment. Up to 85% of patients suffer from hormonal deficiencies because of damage to the pituitary gland (Duff et al., 2000). About 95% show suprasellar extensions, putting basally-located hypothalamic nuclei at risk (Karavitaki et al., 2005), commonly resulting in hypothalamic dysfunction such as hyperphagia, obesity, and severe homeostatic imbalances (Karavitaki et al., 2006; Müller, 2014; Wijnen et al., 2017). Treatment of these tumors includes routine screenings of hypothalamic-pituitary endocrine axes, and if necessary, pharmacological substitution of the hormones affected. Current clinical practice, however, does not assess the neurohypophyseal hormone oxytocin (OT). This is the case although there is both indirect and direct evidence for impairment of OT in CP.

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First, indirect evidence comes from CP-patients often showing anatomical lesions which in theory should affect both OT-production and –release: OT is produced in the same hypothalamic nuclei (supraoptic and paraventricular nuclei, SON/PVN) and released from the same pituitary region (posterior pituitary gland) as anti-diuretic hormone (ADH). This hormone, responsible for the sensation of thirst and renal re-absorption of free water, is known to be deficient in at least one third of CP-patients (DeVile et al., 1996; Karavitaki et al., 2005). ADH-imbalances then result in the symptoms of diabetes insipidus (DI). Yet, while clinical tests and pharmacological substitution for DI are hallmarks of CP-treatment, OT is currently neither measured nor substituted in clinical routine.

Second, in addition to these anatomical parallels, psychoemotional impairment in CP-patients mirrors some of the assumed functional effects of OT. Previously only known for its role in child birth, there is now a rapidly growing body of literature linking OT with empathy and psychopathology: It has been shown to improve the ability to empathize in healthy people and enhance social awareness in patients of the autism spectrum (Feeser et al., 2015). Lower endogenous OT has also been linked with higher anxiety levels in children (Carson et al., 2015), while intranasal OT administration appears to buffer amygdala activation in response to fear-inducing stimuli in healthy adults (Kirsch et al., 2005) as well as reduce fear reactivity (Labuschagne et al., 2010) and improve self-representations in patients with anxiety disorder (Guastella et al., 2009). OT also increases attention to happy stimuli in depressed patients (Domes et al., 2016), possibly representing a new treatment option for depressive symptoms (Neumann and Landgraf, 2012). Mirroring these OT-effects, CP-patients show increased psychosocial morbidity (Pereira et al., 2005): Psychopathological symptoms include depression, anxiety and social withdrawal, as well as greater harm avoidance and fatigability both in childhood-onset as well as adult CP-patients (Karavitaki et al., 2005; Karavitaki et al., 2006; Müller, 2014; Roemmler-Zehrer et al. 2017; Wijnen et al., 2017). The causes for affective impairment in CP may certainly be multi-factorial. Particularly the effect of concomitant obesity should not be underestimated. However, it is tempting to assume that at least some of the known difficulties are attributable to currently undiagnosed OT insufficiencies.

In contrast to the anatomical and psychopathological parallels, direct evidence for the impairment of OT in CP is scarce. A single case study indicated that intranasal OT in a child with CP did improve the child's desire for socialization and affection towards her family (Cook et al., 2016). A recent study in childhood onset CP suggests that OT-levels and positive treatment effects of OT administration might be hypothalamic lesion-dependent: basal salivary OT-levels did not differ between patients and healthy controls, neither at baseline, nor 1 h after intake of a standardized meal (Daubenbüchel et al., 2016). Baseline levels were only lower in a small subgroup of patients with anterior hypothalamic damage (N = 6). Subsequent administration of OT in this subgroup improved the previously impaired ability to categorize negative emotions (Hoffmann et al., 2017). Normal OT-levels at baseline, however, have not been found consistently. A recent study reported reduced salivary OT-levels at baseline and reduced empathic abilities in patients with anterior hypopituitarism, including 9 CP-patients, compared to healthy controls (Daughters et al., 2017). In this case, however, extent of hypothalamic lesion was not controlled for.

As OT-effects in vivo likely rely on short-acting release in response to certain cues such as stress, touch, sexual stimulation or emotion perception (Bartz et al., 2011; de Jong et al., 2015; Meyer-Lindenberg et al., 2011; Wotjak et al., 2001), it appears reasonable to perform a stimulation when measuring OT, similar to stimulation tests used for diagnosis of other endocrine dysfunction. This way, not only baseline levels but also the responsiveness of the OT-system can be assessed, demasking a possibly underlying deficiency more reliably. In the current study, we therefore aimed to assess OT and its link with affective function in CP-patients by measuring OT-levels both at baseline and after stimulation. Since we wanted a paradigm easily applied in clinical routine, we chose a simple physical exercise regimen as stimulation method, since exercise has previously been shown to stimulate OT-release (de Jong et al., 2015). Regarding OT-measurements, we chose to collect salivary OT, a method validated in various previous studies (Daubenbüchel et al., 2016; Daughters et al., 2017; de Jong et al., 2015; Fujii et al., 2016; Grewen et al., 2010). Using a more direct representation of central OT-levels, i.e. OT in cerebrospinal fluid (CSF), would present a technique too invasive for daily clinical practice. Furthermore, while the underlying mechanisms are still unclear, it has been shown that central and peripheral OT-levels are closely interconnected: administration of OT in the periphery (intravenously and intranasally) leads to elevated OT-levels in CSF (Freeman et al., 2016; Striepens et al., 2013) as well as to changes in centrally generated behaviours (Bartz et al., 2011; Heinrichs and Domes, 2008; Meyer-Lindenberg et al., 2011). In addition, it has been shown recently that peripheral OT can even cross the blood brain barrier back into the brain, directly affecting OT-levels in CSF (Lee et al., 2017) although it remains to be shown if endogenous OT from peripheral sources can cross the blood brain barrier and therefore influence CSF levels.

We nonetheless deem salivary OT to provide a non-invasive and feasible window into the functioning of the OT-system in our participants.

We expected saliva OT-levels at baseline to be lower in CP compared to healthy controls (HC), especially in patients with hypothalamic damage or symptoms of DI. We further expected patients to present with a blunted OT-response to physical exercise. Lastly, we wanted to assess the functional relevance and possible treatment implication of OT in this patient group. We expected that reduced OT-levels would be linked with reduced empathy and that it would at least partially explain affective dysfunction, with lower OT levels being linked to higher anxiety and higher depression scores on clinically established questionnaires.

2. Subjects and methods

2.1. Participants

Patients were recruited from the Neuroendocrine Outpatient Unit of the Max-Planck Institute of Psychiatry (MPIP) and the Endocrine Department of the Medical Clinic IV, Ludwig Maximilian University, Munich, Germany. Eighty eligible patients aged 18–65 years were identified by the local electronic databases and invited both by letter and phone to participate in the study. Reasons for non-participation were: letters did not reach their recipient (n = 5), not interested in the study in general (n = 4), high effort to participate in the study (n = 10), living too far away (n = 19), not having the time to participate due to work-related or personal liabilities (n = 16). Finally, N = 26 patients participated in this study. N = 26 controls were recruited by public advertising and were only included if they had not been using hormonal contraceptive medication during the previous 6 months before study. They were rewarded with 50€ for participation. Patients and controls were matched in sex (50% women in each group) and age (patients: 39.7 ± 12.1 years, controls: 36.7 ± 12.8 years). Patients and controls also reported similar habits regarding smoking, drinking, and physical exercise. Patients, however, had higher BMI-values than healthy controls (patients: 30.6 ± 8.5 kg/m^2, controls: 25.2 ± 6.5 kg/m^2; $p = 0.012$). Statistical analyses included corrections for this difference. For further clinical characteristics of CP-patients, see Table 1.

The prospective study was approved by the local ethics committee (#712-15) and conducted in accordance with the 2013 Declaration of Helsinki. All participants gave their written informed consent.

2.2. Oxytocin measurements

52 participants arrived at the outpatient unit of the MPIP at 8:30