Human amygdala reactivity is diminished by the β-noradrenergic antagonist propranolol

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Background. Animal models of anxiety disorders emphasize the crucial role of locus ceruleus–noradrenergic (norepinephrine, NE) signaling, the basolateral amygdala (BLA) and their interactions in the expression of anxiety-like behavioral responses to stress. Despite clinical evidence for the efficacy of a β-noradrenergic receptor blockade with propranolol in the alleviation of anxiety symptoms and the secondary prevention of post traumatic stress disorder, preclinical evidence for a β-noradrenergic modulation of BLA activity in humans is missing.

Method. We combined functional magnetic resonance imaging in healthy volunteers with probabilistic mapping of intra-amygdalar responses to fearful, neutral and happy facial expressions to test the hypothesis that a β-noradrenergic receptor blockade with propranolol would inactivate the BLA.

Results. Consistent with our a priori hypothesis, propranolol diminished BLA responses to facial expressions, independent of their emotional valence. The absence of activity changes in probabilistically defined visual control regions underscores the specific action of propranolol in the BLA.

Conclusions. Our findings provide the missing link between the anxiolytic potential of propranolol and the biological basis of β-noradrenergic activation in the human BLA as a key target for the pharmacological inhibition of anxiety neurocircuitry. Moreover, our findings add to emerging evidence that NE modulates both the reactivity (sensitivity) and the operating characteristics (specificity) of the BLA via β-noradrenergic receptors.

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Introduction

National surveys suggest that up to 20% of the US adult population fulfil the DSM-IV-TR diagnostic criteria for one or more anxiety disorders in a 12-month period (Kessler et al. 2005). Current neurobiological models of anxiety disorders are amygdalocentric in form, with recent accounts incorporating a preponderance of bottom-up excitatory over top-down inhibitory influences on amygdala responses to stressful stimuli (Quirk & Gehlert, 2003; Amat et al. 2005). Indeed, one of the most replicated findings in functional magnetic resonance imaging (fMRI) studies of patients with anxiety disorders is amygdala hyper-activation to stressful stimuli (Etkin & Wager, 2007) and fMRI studies in healthy volunteers suggest that the hitherto most efficacious anxiolytic compounds act by reducing amygdala reactivity (Paulus et al. 2005; Arce et al. 2008; Murphy et al. 2009). Also heavily researched for its role in stress and anxiety disorders is the locus ceruleus (LC), a cluster of neurons within the dorsorostral pons, which provides the major source of central noradrenaline (norepinephrine, NE) (Redmond et al. 1976; Abercrombie & Jacobs, 1987; Bremner et al. 1996a, b; Sved et al. 2002; Itoi, 2008). The basolateral complex of the amygdala (BLA), comprising the lateral (LA) and basal (BA) nuclei, receives dense NE innervation from the LC (Asan, 1998). NE levels increase in the BLA in response to stressful stimuli (Galvez et al. 1996; Hatfield et al. 1999); the BLA, in turn, modulates LC-NE signaling via reciprocal projections (van Boekel et al. 2001). Thus, the BLA and LC appear to synergistically interact in promoting the NE response to stressful stimuli, which implicates the disinhibition of both in the pathology of...
anxiety disorders. There is indeed converging clinical evidence for a crucial role of LC-NE overdrive as an important substrate of anxiety disorders, particularly panic disorder (Redmond et al. 1976; Charney et al. 1990; Bremner et al. 1996b) and post traumatic stress disorder (PTSD) (Southwick et al. 1993, 1997). Consequently, one promising therapeutic strategy is to block LC-NE signaling via postsynaptic β-noradrenergic receptors with propranolol, which appears to be effective for the relief of anxiety symptoms (Granville-Grossman & Turner, 1966; Bonn & Turner, 1971; Stone et al. 1973; Hayes & Schulz, 1987) as well as the secondary prevention of PTSD (Pitman et al. 2002; Vaiva et al. 2003). Whereas animal studies suggest that propranolol might exert its anxiolytic effects by blocking LC-NE input to the BLA (Bufalari & Grace, 2007), there is still a paucity of information on how propranolol affects BLA activity in humans. In the present study, we thus combined fMRI in healthy volunteers with probabilistic mapping of intra-amygdalar responses to facial expressions (Amunts et al. 2005; Eickhoff et al. 2005, 2006, 2007) to test the hypothesis that a β-noradrenergic receptor blockade with propranolol would specifically diminish BLA activation. Support for this hypothesis would provide an important link between the anxiolytic potential of propranolol and the biological basis of β-noradrenergic activation in the BLA as a key target for the pharmacological control of anxiety neurocircuitry.

Methods and materials

Subjects

A total of 18 healthy right-handed adults (nine females, nine males; mean age 23 years; age range 19–31 years) volunteered after giving written, informed consent. The study had full ethical approval and was carried out in compliance with the latest revision of the Declaration of Helsinki. Subjects were screened for MRI compatibility and determined to be free of current or past medical (including respiratory or allergic illness), neurological or psychiatric disorders (including nicotine, drug or alcohol abuse) by medical history and diagnoses according to the Structured Clinical Interview for DSM-IV-TR (APA, 2000). Volunteers were naive to prescription-strength psychoactive medication (including propranolol for treatment of ‘exam nerves’) (Brewer, 1972) and had not taken over-the-counter psychoactive medication in the past 4 weeks. Neuropsychological screening included the Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 1995) to estimate verbal IQ based on lexical decisions, the Rey Auditory Verbal Learning Test; (RAVLT) Rey, 1941; German adaptation by Helmstaedter et al. (2001) to assess verbal learning and memory and the Trail Making Test (TMT; Raitan, 1958) to examine motor speed and visual attention. Facial emotion recognition was assessed with the Facial Expressions of Emotions: Stimuli and Test (FEEST; Young et al. 2002). Volunteers had a mean verbal IQ of 118 ± 11 and showed average to above-average performance in the RAVLT, TMT and FEEST (data not shown). They were instructed to maintain their regular bedtimes and wake times throughout the study period and to abstain from caffeine and alcohol intake on the day before an fMRI scan.

Study design

The rationale of the present study was to measure the effects of the non-specific β-noradrenergic antagonist propranolol with a face perception fMRI paradigm in healthy volunteers, in a within-subject, double-blind, placebo-controlled design (see also Paulus et al. 2005; Arce et al. 2008; Onur et al. 2009). Subjects were scanned at identical times in two separate sessions, at least 1 week apart. According to the scan protocol, four subjects were completed in 60-min intervals, starting at 10:00 hours and finishing at 14:00 hours; until they were scanned, subjects were placed in a quiet room with reading materials. In view of the pharmacokinetics of propranolol (time to peak plasma concentration, 1–2 h; elimination half-life, 3–4 h), subjects received one pill containing either verum or a lactose placebo 1.5 h before the fMRI scans. We administered a 40-mg single oral dose of propranolol in analogy to fMRI studies, where this dose was found to alter neural responses to verbal stimuli (Strange & Dolan, 2004, 2007). The order of verum/placebo administration was completely counterbalanced across subjects. Blood pressure (BP) was measured at verum/placebo administration and plasma samples and BP were taken immediately before a fMRI session. Consistent with our previous studies, propranolol produced trend-to-significant decreases in systolic and diastolic BP (Hurlemann et al. 2005). After oral administration, propranolol is a lipophilic alkaline compound that is almost completely absorbed. Approximately 60–70% of the drug is metabolized during its first pass through the liver and 30–40% is bioavailable. Inter-individual variation in the degree of first-pass metabolism contributes to the differences in propranolol plasma levels after oral administration of equivalent doses (Wood et al. 1978). Consequently, we determined individual propranolol plasma levels in each subject by high-performance liquid chromatography (for a detailed synopsis of analytical
procedures, see Hurlemann et al. 2005); the resulting plasma levels were as follows: mean = 39.2 μg/l; S.E.M. = 8.53 μg/l.

**FMRI paradigm**

The fMRI paradigm consisted of a pseudorandom series of movies obtained from 10 professional actors (five females, five males), who in each clip displayed a fearful, neutral or happy facial expression in a standardized fashion (for emotion ratings by independent judges, see van der Gaag et al. 2007; for online exemplification of movies, see Kukolja et al. 2008). In previous fMRI studies, these stimuli evoked unbiased, i.e. equally robust, amygdala responses (van der Gaag et al. 2007), making them an ideal imaging probe to assess the potential qualitative and/or quantitative changes in amygdala responsivity associated with pharmacological manipulations (Kukolja et al. 2008; Onur et al. 2009). Moreover, we used dynamic instead of static stimuli for higher ecological validity; in everyday life, during social interactions, genuine dynamic and not static facial displays serve as the primary conveyors of social-emotional information (Hurlemann et al. 2008; see also Hasson et al. 2004; Reinders et al. 2006). We thereby adapted an approach also used in recent single-neuron recording studies of the primate amygdala; this approach accounts for the fact that primates never see static facial displays in their natural habitat (Kuraoka & Nakamura, 2007). Each movie had a duration of 3 s and was repeated twice, resulting in 30 stimulus presentations per condition. Movies occurred at a rate of one every 13.2 s (7.8–18.6 s) over a period of approximately 20 min. A fixation cross was interspersed between each movie. During fMRI scanning, subjects were engaged in a gender judgment task requiring appropriate push-button responses. Stimulus delivery and behavioral response recording was carried out using Presentation12 (Neurobehavioral Systems Inc., USA).

**FMRI acquisition**

An Avanto MRI system (Siemens, Germany) operating at 1.5T and the parallel acquisition technique ‘generalized autocalibrating partially parallel acquisitions’ were used to obtain T2*-weighted echoplanar (EPI) images with blood-oxygen-level-dependent (BOLD) contrast (TR, 2.70 s; TE, 40 ms; matrix size, 64 × 64; pixel size, 3 × 3 mm²; slice thickness, 1.8 mm; distance factor, 50%; FOV, 192 mm; flip angle, 85°; 39 axial slices). Based on our a priori hypothesis the 39 slices were oriented centrally to the amygdala. A total of 550 volumes were acquired; the first five volumes were discarded to allow for T1 equilibration effects. Stimuli were presented with liquid crystal display video goggles. In addition, high-resolution anatomical magnetic resonance images were acquired (T1-weighted 3D MPRAGE) to exclude potential T1-sensitive brain abnormalities.

**FMRI data analysis**

The image pre-processing was performed using Matlab7 (The MathWorks Inc., USA) and Statistical Parametric Mapping version 5 (SPM5) (http://www.fil.ion.ucl.ac.uk/spm). The EPI images were corrected for head movement between scans by an affine registration (Ashburner & Friston, 2003) involving a two-pass procedure, by which images were initially realigned to the first image of the time series and subsequently realigned to the mean of all images after the first step. After completing the realignment, the mean EPI image for each subject was computed and spatially normalized to the Montreal Neurological Institute (MNI) template (Evans et al. 1992; Collins et al. 1994; Holmes et al. 1998) using the ‘unified segmentation’ function in SPM5 enabling the match of tissue classes of every subject with tissue probability maps in MNI space (Ashburner & Friston, 2005). Briefly, this algorithm is based on a probabilistic framework that enables the combination of image registration, tissue classification and bias correction within the same generative model. The resulting parameters of a discrete cosine transform, which define the deformation field necessary to move the subjects’ data into the space of the MNI tissue probability maps (Evans et al. 1994), were then combined with the deformation field transforming between the latter and the MNI single subject template. The ensuing deformation was subsequently applied to the individual EPI volumes. All images were hereby transformed into standard stereotaxic space and resampled at 2 × 2 × 2 mm voxel size. The normalized images were spatially smoothed using an 8-mm FWHM Gaussian kernel. Methodological studies suggest no benefit from smaller smoothing kernels, when probabilistic mapping of intra-amygdalar responses is intended (Hurlemann et al. 2008).

The three conditions (fearful, neutral and happy) were modeled by means of reference waveforms, which correspond to stick functions placed at the onset of the stimuli convolved with a hemodynamic response function (Friston et al. 1995). A design matrix comprising contrasts of alternating intervals of the different trials, the time derivative and movement parameters were created. Specific effects were assessed by applying appropriate linear contrasts to the parameter estimates of the experimental trials, resulting in t statistics for each voxel. These formed
statistical parametric maps [SPM(T)] of differences between the three conditions. SPM(T)-statistics were interpreted in light of the theory of probabilistic behavior of Gaussian random fields. Propranolol-induced effects on neural activations across fearful, neutral and happy conditions were assessed by a second-level analysis constituting a random effects model. For each simple effect in any of the two treatment sessions (placebo, propranolol) and the three conditions. A β-noradrenergic receptor blockade with propranolol abolished left BLA responses; (b) relative signal changes in the BOLD response of activated clusters within the primary visual cortex (visual area V1). Amplitudes and latencies of minima and maxima of the V1 hemodynamic response profile were not affected by propranolol, which argues against a global homogeneous drug effect on the BOLD signal. Error bars indicate S.E.M. CA, cornu ammonis; CM, centromedial amygdala; L, left hemisphere; P, posterior; PLC, placebo; PRO, propranolol; R, right hemisphere; SF, superficial amygdala.

Fig. 1. (a) Activation map resulting from the placebo-minus-propranolol contrast (calculated across fearful, neutral and happy conditions) in a probabilistic region of interest (ROI) analysis of the amygdala; (i) propranolol inactivated the left basolateral amygdala (BLA) (Montreal Neurological Institute coordinates x, y, z = −28, −12, −10, respectively); (ii) plotted are the relative signal changes in the blood-oxygen-level dependent (BOLD) response of the activated voxels for each of the two treatment sessions (placebo, propranolol) and the three conditions. A β-noradrenergic receptor blockade with propranolol abolished left BLA responses; (b) relative signal changes in the BOLD response of activated clusters within the primary visual cortex (visual area V1). Amplitudes and latencies of minima and maxima of the V1 hemodynamic response profile were not affected by propranolol, which argues against a global homogeneous drug effect on the BOLD signal. Error bars indicate S.E.M. CA, cornu ammonis; CM, centromedial amygdala; L, left hemisphere; P, posterior; PLC, placebo; PRO, propranolol; R, right hemisphere; SF, superficial amygdala.

Results
To assess potential behavioral effects of propranolol on response accuracy and reaction times, comparisons were made between the propranolol and placebo
treatment session. However, separate condition (fearful, neutral and happy) × treatment session (propranolol, placebo) repeated measures ANOVA yielded neither main nor interaction effects on the behavioral indices (all \( p \) values > 0.05). We measured an overall reaction time of 1.33 s ± 0.54 s and an overall response accuracy of > 95%. Driven by our a priori hypothesis, the fMRI analysis was based on probabilistically defined ROI within the left and right amygdalae. Relative to placebo, propranolol attenuated left amygdala responses across the three conditions (MNI coordinates \( x, y, z = -28, -12, -10 \), respectively, \( p < 0.001 \), uncorrected; \( p < 0.05 \), FWE-corrected; probability, 70%). Among the amygdala subregions, the left BLA, specifically its posterior portion bordering the amygdala-hippocampal junction was identified as the most likely candidate site for the action of propranolol (Figs 1a and 2). A subsequent analysis revealed no significant association between higher propranolol plasma levels and lower BLA responsivity (MNI coordinates \( x, y, z = -32, 02, 020 \), respectively \( p = 0.003 \), uncorrected; \( p = 0.27 \), FWE-corrected). Given the potential influence of a \( \beta \)-noradrenergic receptor blockade with propranolol on cerebral hemodynamics, one important consideration is the differentiation between regional drug effects on neural activity or global drug effects on the BOLD signal per se. To exclude the latter, we analyzed the relative signal change profile in the primary visual cortex (visual area V1). Specifically, we determined the relative signal change throughout stimulus onset to the end of the hemodynamic response function (for a similar approach see Paulus et al. 2005; Onur et al. 2009). This analysis demonstrated that propranolol affected neither the amplitudes nor the latencies of minima and maxima of the V1 hemodynamic response. A comparison of standard deviations did not reveal any significant differences either (Fig. 1b). This analysis was complemented by an additional probabilistic ROI analysis of V1, such that V1 neural responses to faces underwent the same FWE-corrected probabilistic ROI analysis as did BLA neural responses to faces. Again, no significant influence of propranolol was found in the control region. Together, these results suggest that propranolol may act by modulating a face-responsive neural circuitry rather than by globally altering the BOLD signal per se. To identify further face-responsive regions showing altered activation under propranolol treatment, we extended our analysis to the whole brain; however, correction for multiple comparisons yielded no supra-threshold activations in any contrast.

Discussion

In accord with our a priori hypothesis, the present study shows that a 40-mg single oral dose of propranolol reduces human BLA responses to fearful, neutral and happy facial expressions. The absence of activity changes in the probabilistically defined V1 control region underscores the specific action of propranolol in the BLA. Our results are consistent with quantitative autoradiography studies in the rat brain, which identified the BLA as the amygdala subregion with the highest availability of \( \beta \)-noradrenergic receptors (Rainbow et al. 1984). Thus, the present study translates evidence for an interventional significance of a \( \beta \)-noradrenergic receptor blockade with propranolol as a ‘switch-off’ of the BLA from rats (Buffalari & Grace, 2007) to humans.

Using an analogous fMRI study design, we recently modeled a stress-induced BLA response bias towards fearful faces by potentiating NE signaling with a 4-mg single oral dose of the NE transporter antagonist

Fig. 2. Presented are sections through the cytoarchitectonic probability map of the laterobasal subregion of the amygdala (blue) in anatomical Montreal Neurological Institute space (\( x, y, z \) coordinates indicate distances (mm) from the anterior commissure in the mediolateral, rostrocaudal and dorsoventral directions, respectively) (Amunts et al. 2005; Eickhoff et al. 2005, 2006, 2007). Column 1 (sagittal sections) lists the \( x \) coordinates, column 2 (coronal sections) the \( y \) coordinates and column 3 (horizontal sections) the \( z \) coordinates of the smallest (borders) and largest areas covered by the map.
reboxetine (Onur et al. 2009). It thus appears from our series of studies that NE modulates both the reactivity (sensitivity) and the operating characteristics (specificity) of the BLA. Under propranolol conditions and reduced NE input, the BLA is inactive, whereas it is active under placebo conditions and moderate NE input, and hyperactive under reboxetine conditions and elevated NE input. Together, these data converge on NE as a key modulator of BLA response sensitivity. In addition, BLA response specificity appears to vary as a function of NE in that reboxetine-induced elevation of NE increased BLA responses to fearful faces but decreased BLA responses to neutral faces (Onur et al. 2009), perhaps by preferentially augmenting the signal:noise ratio for fearful faces at the cost of neutral faces (see also Woodward et al. 1991; Berridge & Waterhouse, 2003; Aston-Jones & Cohen, 2005) and thus converting the BLA into a ‘fear module’. Based on our findings, we suggest that elevations of NE evoked by stressful stimuli elicit a shift in BLA responsivity towards these stimuli. One scenario would be that those BLA neurons that are activated by elevations of NE project to downstream target areas to promote stress-related plasticity in these target areas (Morilak et al. 2005; Buffalari & Grace, 2007).

Key among the BLA projection areas is the hippocampus (Young et al. 1994; Pitkanen et al. 2000), which orchestrates declarative memory formation (Scoville & Milner, 1957). Evidence from behavioral and fMRI studies in healthy volunteers indicates that pre-treatment with a 40-mg or 80-mg single oral dose of propranolol abolishes an amygdala-dependent enhancement of hippocampal plasticity during declarative memory encoding (Strange et al. 2003; Strange & Dolan, 2004; Hurlemann et al. 2005; van Stegeren et al. 2005, 2008) and consolidation (Cahill et al. 1994; van Stegeren et al. 1998) of stressful stimuli. Propranolol infusions into the rat BLA impair dentate gyrus long-term potentiation (Ikegaya et al. 1997) as well as (re)consolidation of fear inhibitory avoidance (Liang et al. 1986) and spatial maze learning (Hattfield & McGaugh, 1999; Przybylsawski et al. 1999), whereas intra-LA infused propranolol disrupts reconsolidation but not consolidation of conditioned fear (Debiec & LeDoux, 2004). Consistent with these findings, propranolol has been reported to erase conditioned fear responses in rats (Rodriguez-Romaguera et al. 2009) and humans (Kindt et al. 2009). Together, these studies provide intriguing translational evidence for a key role of β-noradrenergic activation in the BLA in mediating the influence of stress on declarative and non-declarative memory formation. Consequently, current conceptually driven approaches concerning the use of propranolol for the secondary prevention of PTSD (Pitman et al. 2002; Vaiva et al. 2003) emphasize its efficacy as an antagonist of exuberant LC-NE input to the BLA under conditions of traumatic stress, serving to forestall over-learning and over-(re)consolidation of declarative (Hurlemann, 2008) and non-declarative memories (Debiec & LeDoux, 2006; Kindt et al. 2009; Rodriguez-Romaguera et al. 2009) of emotional trauma.

The present study extends evidence of a β-noradrenergic inhibition of BLA responses during stress–memory interactions to the perceptual domain. Our observation that propranolol globally decreased BLA responses to faces independent of their emotional valence may be indicative of a broader role of β-noradrenergic activation of the amygdala in the perception of facial motion beyond the extraction of emotion. This underscores the view that the amygdala is tuned to respond to dynamic social–environmental changes (Labar et al. 2003; Adolphs & Spezio, 2006; Fitzgerald et al. 2006; van der Gaag et al. 2007). Reduced amygdala responses to (static) facial expressions have also been reported for the anxiolytics lorazepam, which enhances γ-aminobutyric acid (GABA) signaling via the benzodiazepine-GABAA receptor (Paulus et al. 2005), and escitalpram, which potentiates 5-HT (serotonin) signaling by blocking 5-HT reuptake via the 5-HT transporter (Arce et al. 2007). It thus appears from these studies that independent of whether dynamic or static face stimuli are used to evoke amygdala activation, inhibition of this activation is the basic principle of anxiolytic drug action.

In contrast to 5-HT re-uptake inhibitors, benzodiazepine derivatives have the advantage of rapid onset of anxiolytic action; however, their chronic administration is limited by sedation, tolerance and dependence. Propranolol has traditionally been used by psychiatrists to treat performance anxiety (particularly stage fright in musicians) (Brantigan et al. 1982; Tyrer 1988), test anxiety (Faigel, 1991), anxiety in dental phobic patients (Liu et al. 1991) and avoidance behavior in panic disorder patients (Ravaris et al. 1991). Other studies, however, failed to find robust effects of propranolol on subjective anxiety in phobic subjects (Fagerstrom et al. 1985) or expression of cued fear conditioning in healthy volunteers (Grillon et al. 2004). The observation that propranolol improved cognitive ability under stressful conditions (Faigel, 1991; Alexander et al. 2007) suggests potential use of the drug as an adjunct to exposure-based cognitive-behavioral therapy (CBT) for anxiety disorders. Specifically, diminishing excessive stress during repeated exposure with propranolol could reduce drop-out rates in CBT (Rodriguez-Romaguera et al. 2009). Considering evidence-based medicine criteria,
propranolol is indicated to treat lithium-induced tremor, antipsychotic-induced akathisia/tardive dyskinesia, withdrawal syndromes and (auto)aggressive behavior with temper outbursts (Kornischka et al. 2007).

Limitations
In the present study, we combined conventional fMRI with cytoarchitectonic probability maps to make an initial attempt at subdivision-level investigation of the effects of propranolol on the human amygdala. One limitation is the relatively low field strength of the MRI system (1.5T), which complicates the probabilistic assignment of activation sites to histologically defined amygdala subregions. To account for the fact that the centers of these subregions are <1 cm apart, we chose a rather narrow slice thickness of 1.8 mm (pixel size, centers of these subregions are amygdala subregions. To account for the fact that the centers of these subregions are <1 cm apart, we chose a rather narrow slice thickness of 1.8 mm (pixel size, 3 × 3 mm2). Nevertheless, the accuracy of subdivision-level investigation of drug effects on amygdala function could be further refined by employing MRI systems with field strengths of 3T or higher and a slice thickness of 1 mm or less. Moreover, future investigations might adopt resting state BOLD or arterial spin labelling techniques to better differentiate between local and global effects of propranolol treatment.

Conclusion
The present study provides the missing link between the anxiolytic potential of propranolol and the biological basis of β-noradrenergic receptor activation in the BLA as a key target for the pharmacological control of anxiety neurocircuitry. In combination with our previous study (Onur et al. 2009), the present study suggests a key role of NE in modulating both the reactivity (sensitivity) and the operating characteristics (specificity) of the BLA via β-noradrenergic receptors.

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Declaration of Interest
None.

References


