Psychopharmacology (1999) 146:101–107

ORIGINAL INVESTIGATION

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Intensity dependence of auditory evoked potentials (AEPs) as biological marker for cerebral serotonin levels: effects of tryptophan depletion in healthy subjects

Received: 8 March 1999 / Final version: 25 May 1999

Abstract *Rationale:* The intensity dependence of the auditory evoked potentials (AEP) has been suggested to be a specific biological marker of central serotonergic activity. *Objective:* While previous studies used circumstantial evidence to support this hypothesis, we manipulated (decreased) cerebral levels of serotonin directly by using tryptophan depletion. *Methods:* Twelve healthy young subjects were investigated using placebo and two different amino acid mixtures in a double blind cross over design on three different occasions. AEPs recorded during tryptophan depletion were analyzed by dipole analysis and regional sources using methods published in the literature. *Results:* For none of the mixtures a significant effect of tryptophan depletion was found. There was a trend towards reduced intensity dependency after tryptophan depletion, especially in the right hemisphere. This reduction correlated with the amount of reduced tryptophan in plasma. *Conclusions:* The results indicate, in contrast to earlier indirect studies, that the intensity dependence of AEPs is not a specific marker of central serotonergic activity.

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Key words Tryptophan depletion · Serotonin · Electroencephalography · Auditory evoked potentials · Dipole analysis

Introduction

The central serotonergic system is assumed to be involved in the pathophysiology of various neuropsychiatric syndromes like depression, obsessive-compulsive disorder, and addiction. A variable that indicates the function of the central serotonergic system is of potential diagnostic, therapeutic and prognostic value for these syndromes. Yet the effects of changes of serotonergic transmission on the large-scale functions of the brain are notoriously hard to measure. Several measures have been suggested to be specific indicators of serotonergic neurotransmission that can be obtained invasively. The pharmacokinetics of serotonin in blood platelets, concentration of the metabolites of serotonin in cerebrospinal fluid and plasma or platelet contents of serotonin have been used as measures of presynaptic serotonergic neuronal function in vivo. Blood platelets, like central serotonergic neurons, are capable of taking up and storing serotonin (Meltzer and Arora 1991), but it is still questionable if the pharmacodynamics of serotonin in platelets are regulated in a sufficiently similar manner to those in central neurons, which can be regarded as a model for central serotonergic neurotransmission. The exact relation between platelet/plasma serotonin content and serotonergic neurotransmisson is still unknown (Maes and Meltzer 1995). Although concentrations in cerebrospinal fluid of 5-hydroxyindoleacetatic acid (5-HIAA), the major serotonin metabolite, seem to be the most reliable variable reflecting central serotonergic neurotransmission, it is difficult to draw any valid conclusions on central serotonin turnover on the basis of 5-HIAA in cerebrospinal fluid (Meltzer and Lowy 1987).

The intensity dependence of the N1 and P2 components of auditory evoked potentials (AEP) has also been suggested to be a specific biological marker of serotoner-

gic neurotransmission and thus to reflect cerebral functions which are mediated by serotonin (Hegerl and Juckel 1993). The great advantage of AEPs compared to these former mentioned indices of central serotonergic function is the non-invasiveness of the method (Murphy 1990). A facilitation of auditory brainstem potentials by serotonin depletion has been reported for the prosimian bush baby by Revelis et al. (1998). However, most studies investigating the relation between AEPs and serotonergic neurotransmission in humans focused on components generated in cortical areas. The AEP components N1 and P2 are generated in the primary auditory cortex (Pantev et al. 1990). The primary auditory cortex, Brodman areas 41 and 42, is densely innervated by serotonergic neurons and is, like other primary sensory areas, characterized by the high serotonin synthesis rate (Brown et al. 1979). The relation between central serotonergic neurotransmission and intensity dependence of the AEP components N1 and P2 was defined in the way that lower serotonergic neurotransmission leads to higher intensity dependence of AEP and vice versa (Hegerl and Juckel 1993).

Serotonin is presumed to modulate neuronal function of primary sensory areas by providing a stable and tonic preactivation level. The negative relationship between preactivation level and intensity dependence was argued to be a property found in some competitive neuronal networks where lateral inhibition occurs (Hegerl and Juckel 1993). Consequently, a greater neuronal activity is presumed if the level of preactivating serotonergic input is low and vice versa (Hegerl and Juckel 1993).

Varying visual (VEP) and somatosensory (SEP) evoked potential responses were reported by Buchsbaum (1971) and von Knorring et al. (1978) by variation of stimulus intensity. Patients with affective psychoses showed divergent patterns of stimulus intensity dependence depending on whether they were responders or non-responders to lithium therapy (Hegerl et al. 1987, 1988, 1992a). The intensity dependence of AEPs has also been studied with regard to sensation seeking (Hegerl et al. 1989) and other personality traits (Hegerl et al. 1992b, 1995; Juckel et al. 1995), to lithium application in healthy subjects (Hegerl et al. 1990), and to suicidality (Juckel and Hegerl 1994). Since serotonergic function is assumed to be involved in these personality traits and drug effects as well, it was postulated that the intensity dependence of AEPs in fact reflects serotonergic functions (Hegerl and Juckel 1993). However, few studies exist on intensity dependence of AEPs after manipulation of the central serotonergic availability. An influence on intensity dependence of VEP by the serotonin agonist zimelidine (a serotonin reuptake inhibitor) has been reported (von Knorring and Johansson 1980), whereas no influence of fluvoxamine (also a serotonin reuptake inhibitor) on the intensity dependence of AEPs was found (Juckel et al. 1991). Alcohol ingestion increases serotonergic neurotransmission (review by Tollefson 1991) and a decrease of intensity dependence of AEPs was described in healthy subjects after acute alcohol consumption (Hegerl and Juckel 1993).

The present study aimed to study the intensity dependence of N1 and P2 AEP component dipole amplitude difference (ASF-slope) while manipulating the central serotonin content by using tryptophan depletion. According to animal and human studies tryptophan depletion leads to reduced central serotonin levels (Biggio et al. 1974; Gessa et al. 1975; Young et al. 1989; Nishizawa et al. 1997). Our hypothesis was accordingly that under tryptophan depletion intensity dependence of AEPs increases.

Material and methods

Subjects

Twelve subjects between 24 and 32 years (mean: 26.8 years, six women; six men) took part in the study. The subjects were paid students of the J. W. Goethe-University Frankfurt. Prior to inclusion in the study subjects underwent medical examination and laboratory tests of blood and urine to exclude physical or mental health problems. They were also screened for mental diseases in the family. Subjects with a history of chronic use of alcohol, nicotine or drugs were excluded. Finally an auditory test was administered to ensure normal hearing. The study was approved by the local ethics committee and all subjects gave written consent before the study was started.

Design

The study was a double-blind cross-over design with two different amino acid mixtures and one placebo mixture given on three different occasions with 1-week interval. On the day of investigation, only food with a low content of tryptophan was allowed. The two different amino acid mixtures, “Young 50” (Young et al. 1989) and “Moja” (Moja et al. 1988) were named after the first author describing the mixture. The placebo mixture was composed of orange juice, oat flakes and table salt to achieve consistency and taste similar as the amino acid mixtures. A cannula was placed intravenously to draw blood before and at hourly intervals after ingestion of the mixture. Levels of free and total tryptophan in plasma were measured (Viell et al. 1988). The electrophysiological investigations were done 4.5–5 h after application of the mixture.

AEP recordings

The auditory evoked potentials were recorded using a NeuroScan equipment with Synamps amplifiers (Neuroscan Inc., Hernon, USA). Twenty-eight electrodes were placed according to the extended 10-20 System (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2, A1, A2, FT9, FT10, TP9, TP 10, CP5, CP6, FC5, FC6), and additional four bipolar pairs of electrodes were placed to record horizontal and vertical EOG, EMG from the neck and ECG. The acoustic stimuli were presented using the STIM Hard- and Software (NeuroScan Inc.). 1000 Hz tones with duration of 30 ms were presented (10 ms raise and fall time). The interstimulus interval was randomized between 1600 and 2100 ms. The tones were applied binaurally by headphones using five different sound pressure levels (60, 70, 80, 90 and 100 dB SPL). The presentation sequence of the different levels was randomized, but identical for all subjects. Each level occurred with a frequency of 140 per study. The AEPs were recorded as ongoing EEG and digitized with a rate of 500 Hz. Prior to digitizing the EEG was bandpass filtered DC-70 Hz. To avoid the confounding influence of changes of vigilance the subjects were asked to open their eyes and perform eye blinking for 15 s after every 70th tone.

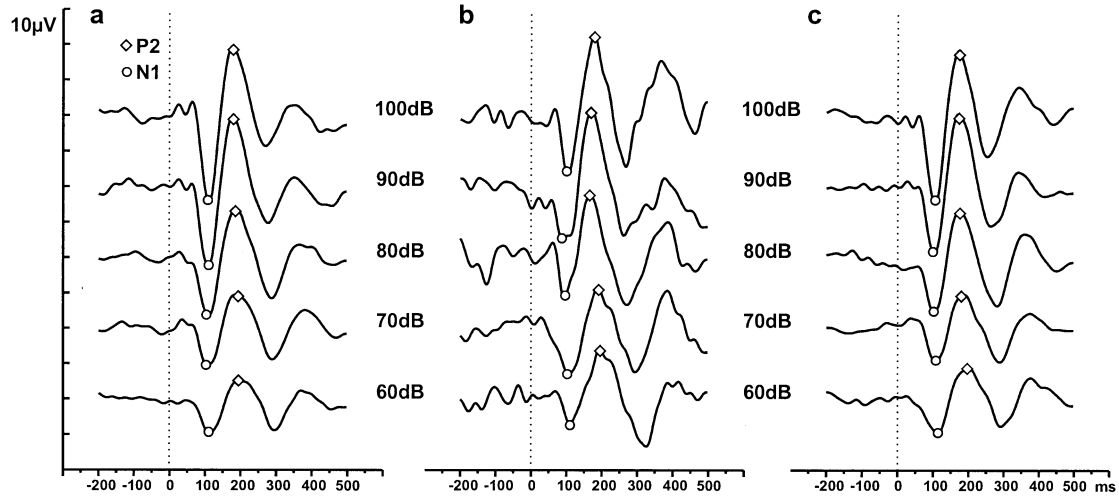

Fig. 1a–c EP waveforms during acoustical stimulation at five intensities recorded from electrode Cz (vertex) in one subject after **a** placebo, **b** Young 50, and **c** Moja mixture application. With increasing loudness of the auditory stimulus the peak to peak amplitude difference between N1 and P2 is augmented (intensity dependency of AEPs). Stimulus onset is at 0 ms (*dotted line)*

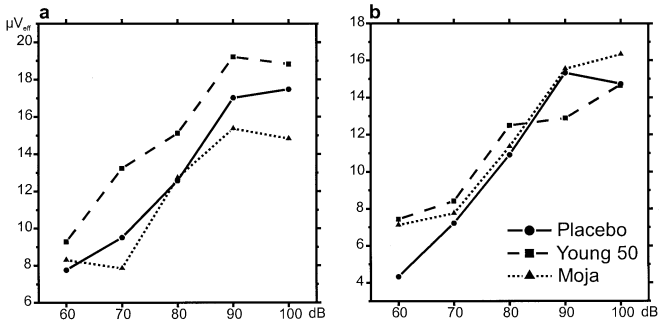

Fig. 2a, b Diagram showing peak to peak amplitude difference in relation to loudness level for right (**a**) and left (**b**) tangential dipole for the three different mixtures applied for the same subject as in Fig. 1. Mean slopes for placebo: right: 2.45, left: 2.60, for Young 50: right: 2.40, left: 1.75, and Moja: right: 1.65, left: 2.9 (μV_{eff}/10 dB)

EP analysis

For each EEG epoch containing an acoustical stimulus, a baseline correction for the data 200 ms prior to the stimulus was performed. To avoid artefacts all epochs containing data exceeding ±50 µV in any channel (except for ECG and EMG channels) 200 ms prior to and 500 ms after the stimulus were excluded from further analysis. For 60 dB 71±26, 70 dB 67±27, 80 dB 64±28, 90 dB 62±27, and for 100 dB 51±27 sweeps (mean and SD) were gained as free of artefacts. The average EP for each loudness level was determined separately for each subject and day of investigation (Fig. 1).

On the basis of a grand average EP over all subjects, all sessions, and all loudness levels a mean dipole model was estimated using the commercial software BESA (Scherg and Von Cramon 1985). Prior to dipole analysis data were low pass filtered with 20 Hz. In each hemisphere two regional sources were defined each with two tangential and one radial dipole, which were fitted with the constraint of interhemispheric symmetry for localization and direction of dipoles for the time epoch 60–120 ms after the stimulus occurrence (residual variance 1.65%). For each subject and each session the results of the mean dipole model were used as starting point for the individual dipole fitting of the average waveform for each subject (over session and loudness). In this individual step only the orientation of the dipoles was fitted. The remaining unexplained variance was on average 4.1±1.1%. This "individual" dipole model was used for determining the results for each session and each loudness level for each subject for the vertical tangential and the radial dipole. In this step the residual variance was on average 9.5±6.7%. The peak latency for N1 was determined as the most negative value in a window between 55 and 140 ms poststimulus and for P2 as the most positive value in a window between 130 and 250 ms. For that latency, the amplitude of vertical tangential and radial dipole was determined for each hemisphere for N1 and P2. Then the peak to peak amplitude between these both components was calculated. A diagram was drawn of the peak to peak amplitude in relation to loudness level and mean slope of the line connecting these values calculated (amplitude stimulus-intensity function (ASF)-slope) (Fig. 2). Thus for each subject and session a mean intensity dependence slope was calculated for both the tangential vertical and the radial dipole. To ensure comparability with previous studies the methodology followed published literature (Hegerl and Juckel 1993, 1994; Juckel et al. 1994). For a discussion of the applied dipole model see Hegerl and Juckel (1994) and Juckel et al. (1994).

Statistical analysis

For evaluation of confirmatory statistical effects of tryptophan depletion on ASF-slope a three-way ANOVA for repeated measurements was performed. Factors were a) dipole: tangential and radial, b) hemisphere: right and left and c) mixture: placebo, Young 50 and Moja. For descriptive reasons, a Wilcoxon-paired test was performed with regard to ASF slope between placebo and depletion condition for each hemisphere and each dipole. The relation of free and total tryptophan level in plasma at the time of the AEP measurement to the tryptophan level before application of the mixture was calculated and logarithmically transformed to ensure normal distribution. This variable of the extent of the tryptophan depletion was finally correlated with intensity dependence of the AEP (ASF slope) using Pearson linear correlation.

Results

Influence of tryptophan depletion on the plasma level of tryptophan

At the time of AEP measurement free and total tryptophan levels in plasma were reduced to approximately

Table 1 Three-way ANOVA for effect of tryptophan depletion on ASF-slope using dipole analysis. *IA* interaction between factors

Factor	*df*	*F*-value	*P*-value
Dipole (tangential, radial)	1, 11	14.67	0.003
Hemisphere (right, left)	1, 11	1.91	0.194
Mixture (placebo, Young 50, Moja)	2, 22	2.49	0.106
IA: Dipole×hemisphere	1, 11	0.45	0.514
IA: Dipole×mixture	2, 22	0.57	0.571
IA: Hemisphere×mixture	2, 22	2.57	0.099
IA: Dipole×hemisphere×mixture	2, 22	0.51	0.610

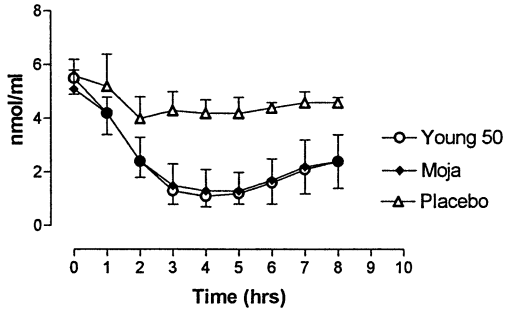

Fig. 3 Free L-tryptophan in plasma following administration of amino-acid mixtures according to Moja et al. (1988) and Young et al. (1989), and after placebo mixture (mean and SD)

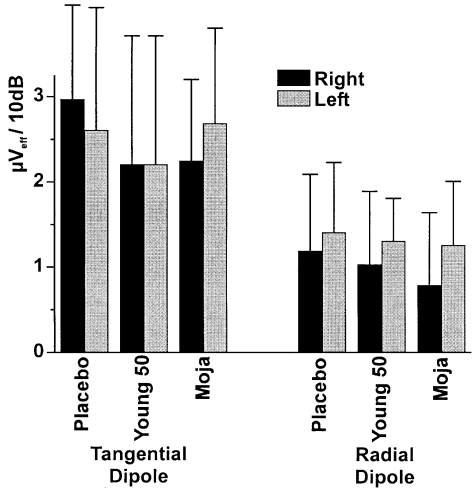

Fig. 4 Mean and SD of the ASF slope (see Fig. 2) separated for factors dipole (tangential, radial), hemisphere (right, *black bars*; left, *grey bars*) and mixture (placebo, Young 50, Moja)

30% (mean). The nadir of plasma levels of tryptophan occurred between 2.5 and 5.5 h after mixture application (Fig. 3).

Influence of tryptophan depletion on AEPs

A significant positive correlation between relative amount of free tryptophan in plasma and ASF slope was observed for the tangential dipole in the right hemisphere (r=0.46; P<0.01; n=42, Fig. 5a), in the left hemisphere no correlation was detected (r=0.23; P>0.10; n=42, Fig. 5b). For the radial dipole, no significant correlations were observed (right: r=–0.11, left: r=–0.04). Similar results were obtained for the correlation between ASF slope and total tryptophan in plasma (not presented here).

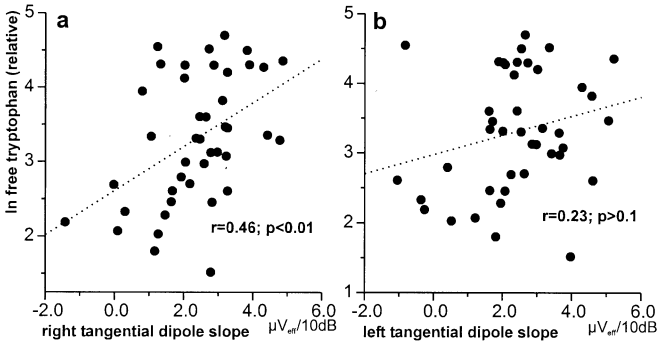

Fig. 5a, b Correlation between relative free tryptophan in plasma and ASF-slope (see Fig. 2) of tangential dipole in the right (**a**) and left (**b**) hemisphere

Discussion

The hypothesis that intensity dependence of AEPs is a specific marker for serotonergic neurotransmission could not be confirmed by the present study. Only a trend towards a decrease of intensity dependence of N1/P2 amplitude difference (ASF-slope) could be demonstrated for the right hemisphere after tryptophan depletion. This finding contradicts reports that decreased serotonergic neurotransmission leads to increased intensity dependence of AEPs (Hegerl and Juckel 1993). Before we can conclude that the intensity dependence of AEPs does not appear to be a specific marker of serotonergic neurotransmission, several critical issues regarding the present study have to be discussed.

The reduced level of free tryptophan after tryptophan depletion of 70% is comparable to other studies using tryptophan depletion to influence serotonergic functions in the brain. Recently, Carpenter et al. (1998) and Williams et al. (1999) reported that the nadir of the CSF level of serotonin and 5-HIAA, respectively, was reached hours after plasma nadirs. In the present study AEP recordings were done approximately 2 h after the plasma nadir was reached and 5 h following ingestion of the TRP-free amino acid drink. Together with data from

behavioural and animal studies at that time window (e.g., Biggio et al. 1974; Gessa et al. 1975), this suggests that a sufficiently low plasma level of tryptophan was reached to reduce tryptophan uptake in the brain and consequently also serotonin synthesis at the time of AEP recordings. However, it is a crucial issue whether tryptophan depletion actually leads to reduced serotonin synthesis in the brain. In rats, reduced tryptophan levels in plasma and brain and reduced serotonin levels in brain after tryptophan depletion have been reported (Gessa et al. 1975) as well as reduced 5-HIAA in simian liquor (Biggio et al. 1974; Young et al. 1989). Tryptophan depletion also seems to influence cerebral serotonin levels and serotonergic neurotransmission in humans. Nishizawa et al. (1997) found lower rates of serotonin synthesis after tryptophan depletion by using positron emission tomography (PET). The effect of tryptophan depletion on endocrinological parameters also support this hypothesis: melatonin secretion (tryptophan is the precursor of melatonin) was reduced in healthy subjects after tryptophan depletion (Zimmermann et al. 1993). Indirect measures of central serotonin activity have also been shown to be influenced by depletion of tryptophan. Cognitive functions like learning and memory were shown to be selectively impaired by tryptophan depletion (Park et al. 1994; Riedel et al. 1999). Furthermore, it is assumed that serotonin plays a major part in the modulation of human behavior (Young et al. 1988) and tryptophan depletion was demonstrated to increase behavioural aspects like aggression and impulsivity (Cleare and Bond 1995; Moeller et al. 1996). Mood has also been modulated by serotonin, and several studies indicate that depressive symptoms appear or increase after tryptophan depletion in depressive patients (e.g. Smith et al. 1997). In the present study tryptophan depletion, especially Moja mixture, resulted in a change in various behavioral parameters, e.g. in increased anger and depressive mood (Schmeck et al. 1998). In summary, these studies suggest strongly that tryptophan depletion influences tryptophan and serotonin content in the brain as well as the cerebral functions that are modulated by serotonin.

Even though electrophysiological recordings were done when minimal tryptophan levels in plasma had already been present for 2 h, it cannot be ruled out that the effect of the tryptophan depletion on serotonergic neurotransmission occurs later. However, the studies mentioned above gained their results during the same time window as in the present study.

It is reasonable to speculate that the discrepant results in the present study compared to previous reports may depend on some methodological differences regarding application of dipole estimation. However, recording parameters and analysis steps were strictly consistent with those described in earlier studies. Nevertheless, the same analysis procedure was used as in the initial reports in which no dipole estimation was performed, but more straightforwardly the amplitudes at the electrode Cz was calculated. When using this less complicated analysis, the result was not different to the one using dipole analysis.

Even though we found no significant effects of tryptophan depletion on intensity dependence of AEPs a trend towards reduced intensity dependence after tryptophan depletion was apparent, which, as mentioned before, is contrary to the stated hypothesis based on earlier indirect studies. There is evidence that in depressive patients who exhibit a relapse of depressive symptoms after tryptophan depletion a decrease of glucose metabolism occurs, whereas in patients not showing any relapse of depressive symptoms, glucose metabolism increases (Bremner et al. 1997). It could be speculated that brain response on tryptophan depletion, resulting in serotonin reduction, depends on the current state of the serotonergic system. Thus tryptophan depletion may lead to different patterns of brain activation depending on whether healthy subjects or patients in different states of their disease are studied. On the other hand, Hegerl et al. (1996) studied the effect of alcohol, a serotonergic agonist, on healthy subjects and reported a decreased intensity dependence of AEPs (Hegerl et al. 1996). This was expected according to the hypothesis, contradicting the differentiated response in healthy and ill subjects.

The application of fenfluramine, a serotonin reuptake inhibitor and releaser, leads to an increased glucose metabolism in the right hemisphere compared to placebo application (Mann et al. 1996), supporting our results of a different response to changes in serotonergic tonus in the left and right hemispheres.

According to this line of argument, we conclude that our results are methodologically valid and that tryptophan depletion in fact results in a change of central serotonergic activity.

In animal studies on evoked potentials, evidence exists that other neurotransmitters, e.g. noradrenaline, play an important role in the generation of auditory evoked potentials, although evoked components generated by acoustical odd-ball paradigms seem to be stronger modulated by these neurotransmitters compared to the earlier components P1 and N1 (Pineda and Swick 1992; Swick et al. 1994). To what extent other neurotransmitters are involved in the modulation of the intensity dependence of middle latency AEPs cannot be resolved by the present study, but they may play a crucial role (Juckel et al. 1996).

Compared to previous reports which draw conclusions indirectly between central serotonergic activity and intensity dependence by studying diseases in which the serotonergic system is supposed to be involved, we tried to manipulate directly the availability of serotonin in the brain. We argue that this ought to be a more valid method for the investigation of the relation between central serotonergic activity and intensity dependence of auditory evoked potentials. The results of the present study lead us to the conclusion that the intensity dependence of the AEP N1/P2 amplitude is not a specific marker of serotonergic neurotransmission.

Acknowledgements We thank D. E. J. Linden for helpful discussion.

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