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Curcuminoids Rescue Long-Term Potentiation Impaired by Amyloid Peptide in Rat Hippocampal Slices

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KEY WORDS curcumin; LTP; memory; hippocampus; Alzheimer’s disease; curcuminoids

ABSTRACT Curcuminoids are vital constituent of turmeric, with therapeutic potential in the treatment of Alzheimer’s disease. Electrically, stimulus train-elicited plastic changes in hippocampal CA1 excitability were used as an experimental paradigm to study the effects of curcuminoid mixture and individual components on functional failure induced by Aβ peptide in vitro. Electrical stimulation was applied on Schaffer collaterals, and population spikes (PS) were recorded from stratum pyramidale. To induce long-term potentiation (LTP) of PS, primed burst stimulation (PBs) was used. Aβ peptide inhibited PS LTP induction. Sinking PS LTP due to Aβ peptide was rescued when curcuminoid mixture was applied before PBs only at lower dose (0.1 μM) resulting in PS potentiation to 127.42% ± 1.83% at 5 min and 123.98% ± 1.06% at 60-min post-PBs. Similarly, when bisdemethoxycurcumin was applied, PS LTP was induced and lasted only at a single dose (0.1 μM). Demethoxycurcumin was effective at a middle dose (1 μM), so that the PS amplitude was changed to 140.15% ± 2.68% and 129.82% ± 0.44% at 5 and 60 min, respectively. PS LTP was effectively induced in the presence of curcumin at middle and high doses (1 and 30 μM) with resultant PS LTP to 155.68% ± 1.23% and 127.72% ± 1.23%, respectively, at 60-min post-PBs. These results showed that curcuminoids can restore susceptibility for plastic changes in CA1 excitability that is injured by exposure to Aβ peptide and rescue sinking PS LTP in Aβ-peptide-exposed hippocampal CA1 neurons. Synapse 65:572–582, 2011. ©2010 Wiley-Liss, Inc.

INTRODUCTION Alzheimer’s disease (AD) is one of the most common forms of dementia (Blennow et al., 2006). There are certain established hallmarks of AD, such as deposition of extracellular amyloid plaques (also known as senile plaques) and intracellular neurofibrillary tangles (composed of paired helical filaments) in the brain of AD patients (Selkoe, 2001). Amyloid plaques are primarily composed of 40–42 residues long peptide (Aβ peptide), which is known to be a neurotoxic agent and causes substantial synaptic loss and neuronal cell degeneration (Roncarati et al., 2002; Selkoe, 2001). The processing and clearance of Aβ peptides are poorly understood, and there has been limited success with therapeutic options currently available. Newer options are being widely explored in this context. Medicinal plant-derived compounds have certain advantages associated with them, based on the fact that, usually, the parent crude extracts have long history of use, and derived compounds have complex stereochemical structures with multiple biological activities. Therefore, such compounds show therapeutic potential in different diseases (Corson and Crews, 2007; Gilani and Rahman, 2005; Schmidt et al., 2007), particularly, in conditions like dementias.

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where there is a wide room available for new drug development (Akhoundzadeh et al., 2003; Ghayur et al., 2008; Le Bars et al., 1997; Ng et al., 2006).

Turmeric (rhizomes of Curcuma longa) is a medicinal herb of global repute particularly famous in South Asia, where it is also used as a curry spice (Gilani et al., 2005; Goel et al., 2008). Turmeric is well known for its wide range of medicinal uses in different disorders, such as inflammation, asthma, epilepsy, gall bladder stones, wound healing, abdominal cramps, high cholesterol, congestion, and AD (Duke, 2002; Gilani et al., 2005; Kapoor, 1990; Nadkarni, 1986). The underlying pharmacological mechanism in most of these disorders, particularly, AD, is not clear yet.

When curcuminoids (key constituents of turmeric) were tested for their acetylcholinesterase inhibitory activity, curcumin, which is the main constituent of the curcuminoid mixture (bisdemethoxycurcumin 3–5%, demethoxycurcumin 15–20%, and curcumin 75–80%), was found to be inactive or had little effect on acetylcholinesterase activity (Ahmed and Gilani, 2009). On the other hand, when studied in scopolamine-induced amnesia, curcuminoid mixture and all three individual components of the mixture were found equally effective in memory enhancement (Ahmed and Gilani, 2009). This suggests additional mechanism(s) besides acetylcholinesterase activity being responsible for their memory-enhancing effect. Recent study from our laboratory shows that curcuminoids enhance memory in rat model of AD through modulating PSD-95 and synaptophsyn expression levels (Ahmed et al., 2010). Moreover, a critical review of the literature revealed a trend to use curcumin and curcuminoid mixture interchangeably; but, based on the recent data from our lab as well as others, it was found that curcuminoid mixture and the individual components show different behavior in their activities at different doses (Ahmed and Gilani, 2009; Dairam et al., 2007).

Curcuminoids show multiple activities such as neuroprotection (Dohare et al., 2008), inhibitory effect on Aβ fibril formation (Kim et al., 2001), cellular survival against Aβ insult (Kim et al., 2005), and modulatory effect on amyloid precursor protein expression levels (Lin et al., 2008) and also found as potent inhibitors of the lipid peroxidation (Sreejayan and Rao, 1994). These activities of the curcuminoids are likely to ameliorate AD symptoms. Moreover, curcuminoids are known to clear Aβ by promoting uptake by macrophages in cell-culture system (Zhang et al., 2006). These studies indicate that curcuminoids may interfere with the formation of amyloid plaques and reduce the toxicity of Aβ, but it is unclear how curcuminoids affect synaptic plasticity. Although there is evidence for memory enhancing effect of curcuminoids in scopolamine-induced amnesia (Ahmed and Gilani, 2009), but how do they specifically enhance memory in AD model remains to be elucidated. The underlying mechanism might as well be a protective effect of curcuminoids against Aβ in AD, which needs to be investigated. For this purpose, long-term potentiation (LTP) impairment by Aβ in rat hippocampal slices serves as an excellent model to investigate. LTP is a form of synaptic plasticity known as a cellular model for certain forms of memory (Martin et al., 2000; Zakharenko et al., 2003). Aβ peptide, a neurotoxin, is known to impair LTP (Gong et al., 2006; Wang et al., 2004). We were interested in studying the effect of curcuminoids on Aβ-peptide-induced LTP impairment, in an attempt to provide cellular basis of memory enhancement in AD.

The foremost question to be addressed was whether the therapeutic effect of the curcuminoid mixture is primarily because of curcumin or the other components of the parent mix play a more significant role. Evidence suggests that curcuminoid mixture and the individual components show variation in their effects in different pharmacological activities (Ahmed and Gilani, 2009; Dairam et al., 2007; Kim et al., 2001; Zhang et al., 2008). Therefore, the effects of curcuminoid mixture and its individual components on LTP were studied.

**MATERIALS AND METHODS**

**Drugs and chemicals**

Amyloid beta peptide (1–40) and ibotenic acids were purchased from the Sigma Chemical Company, St. Louis, MO. Curcuminoids (>95% purity; having bisdemethoxycurcumin 4.15%, demethoxycurcumin 16.53%, and curcumin 79.52%) and its individual components, bisdemethoxycurcumin (78% purity), demethoxycurcumin (98% purity), and curcumin (98.35% purity) were generous gifts from the Sabinsa Group of Companies, 70 Ethel Road West, Unit 6, Piscataway, NJ 08854, USA. Purity of the curcuminoids and individual components was established by the Sam Labs, Bangalore, India (part of Sabinsa Group of Companies) through HPLC (Ahmed and Gilani, 2009). Working stocks of drug solutions were made on the day of experiment.

**Animals**

Experiments were performed complied with the rulings of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (NRC, 1996), and the protocol was approved from the Ethical Committee for Research on Animals (ECRA), Aga Khan University. Animals were given tap water ad libitum and a standard diet consisting of (g/kg): flour 380, fiber 380, molasses 12, NaCl 5.8, nutrivet L 2.5, potassium meta bisulphate 1.2, vegetable oil 38, fish meal 170, and powdered milk 150. For slice electrophysiology experiments, male Sprague–Dawley rats, 4–6 weeks of age and in the weight range of 120–150 g, were used.

**Synapse**
Electrophysiology
Slice preparation
Slice electrophysiology was carried out as described earlier (Salmanzadeh et al., 2003) Rats were anesthetized with diethylether and decapitated, brain was removed, and the hippocampi were quickly dissected out. Transverse slices (400–450 μM) were prepared by vibroslicer (Campden Instrument, NVSLM1, Loughborough, UK) in cold 2–3°C artificial cerebrospinal fluid (ACSF) that contained (in mM): NaCl, 124; KCl, 4.4; KH₂PO₄, 1.25; MgCl₂, 2.06; CaCl₂ 2; NaHCO₃, 25; and glucose, 10 at pH 7.4. Slices were placed in an interface type-recording chamber perfused at a rate of 0.7–1 mL/min with ACSF continuously carbogenated (95% O₂ and 5% CO₂) at room temperature. The upper surface of slices was in contact with humidified stream (95% O₂ and 5% CO₂). After 1.5 h, temperature was slowly increased to 32°C.

Stimulation and recording
Fifteen minutes after electrode placement, constant current rectangular stimulus pulses (200 ms and 15–100 μA) were delivered by stimulus isolation unit (Nihon Kohden, SS-403J, Tokyo, Japan) through a bipolar stainless steel electrode, placed on stratum radiatum to stimulate Schaffer collaterals. Extracellular potentials were recorded with a glass micropipette filled with 2 M NaCl (2–5 MΩ), which was placed in stratum pyramidale of CA1 region. The distance between electrodes was about 1 mm. Signals were amplified by a microelectrode amplifier (Nihon Kohden, MEZ-8300, Tokyo, Japan), displayed on an oscilloscope (Yokogava, DL4200, Tokyo, Japan), and these signals were saved at 10 kHz sampling rate in computer hard disk for off-line data processing.

Experimental protocol
During 20 min after electrode placement (stabilization period), stimuli (25 μA and 0.1 Hz) were delivered. After the responses were stabilized, a baseline input–output curve was constructed at five different intensities (15–100 μA). The stimulus intensity that evoked an orthodromic population spike (PS) of 50–60% of the baseline maximum response was chosen for subsequent recording. The primed bursts stimulation (PBs) was used for LTP induction, which consisted of eight PBs, with a PB interval of 10 s. Each PB consisted of a single priming pulse followed 170 ms later by a burst of 10 pulses delivered at 100 Hz. After tetanus delivery, responses were again tested 60 min posttetanus. LTP was defined as an increase of at least 20% in the baseline PS amplitude, lasting at least 60 min after train stimulation.

Drug application
Drugs were prepared as stocks with rigorous shaking in distilled water and quickly stored at −20°C. Stocks were reconstituted on the day of experiment few minutes before addition to ACSF for the perfusion, which was started 25 min pretetanus and continued till the end of recording. Similarly, Aβ peptide was dissolved in distilled water, and its stock was stored at −20°C until it was used on the day of experiment.

Statistical Analyses
Data are expressed as mean ± standard error of the mean (SEM; n, number of experiments). Results were analyzed statistically using “Graph Pad Prism, San Diego, USA” software and taken as significant only if the P value was less than 0.05 using respective test (t-test or ANOVA where appropriate).

RESULTS
Effect of curcuminoids on baseline without Aβ peptide application
Baseline recording in the hippocampal slices was carried throughout at a stimulation rate of 0.1 Hz, and there was no frequency potentiation found at this rate in line with earlier study (Salmanzadeh et al., 2003). In a control group slices, baseline responses were stable for 80 min of recordings (101.68% ± 1.79%) when compared with the response recorded at the start (100% ± 1.34%; P = 0.235) as shown in Figure 2. In a separate set of experiments, we studied all compounds applied at a fixed dose of 1 μM after the stabilization of baseline without application of PB and continued until 80 min of the recording time (Figs. 3A–3E). After 80 min of curcuminoids application, baseline PS amplitude was significantly increased (P < 0.05) to 133% ± 1.83% compared to the vehicle-treated slices (101.68% ± 1.79%). Such increase in activity was not seen when bisdemethoxycurcumin or demethoxycurcumin was studied individually showing 87.24% ± 1.67% and 99.76% ± 3.39% response, respectively. Treatment with curcumin resulted in significant increase (P < 0.05) in PS amplitude (126.66% ± 1.88%) compared to the vehicle-treated group.
Curcuminoids application results in LTP induction in Aβ-peptide-exposed hippocampal slices Aβ impairs LTP induction

The next step was to see if application of Aβ affects baseline. When Aβ peptide (500 nM) was applied at baseline in slice preparation, there was no change ($P > 0.05$) in baseline responses after 80 min of recording (106.74% ± 1.77%) when compared with the control group (101.68% ± 1.79%), indicating that Aβ peptide had no effect on baseline responses (Figs. 4A and 4B), which is in agreement with the earlier report (Wang et al., 2004).

Our next question was to investigate what is the effect of Aβ application on LTP induction. PB was applied after baseline recordings were obtained. In untreated slices (control group), PB elicited induction of PS LTP to 149.07% ± 2.41% at 5 min after PB application and was maintained to 131.09% ± 0.79% after 60 min, but in the presence of Aβ peptide (500 nM), PB was unable to induce PS amplitude potentiation (112.92% ± 1.18%) and PS amplitude at 60-min post-PB amplitude was 101.26% ± 1.92%. Thus, these findings show that application of Aβ peptide, 25 min before the PB, impaired both induction and maintenance/expression of LTP (Figs. 4C and 4D).

Effect of curcuminoid mixture on Aβ-peptide-induced LTP impairment

When curcuminoid mixture and Aβ peptide were applied before the application of PB, it was evident that curcuminoids at the dose of 30 μM prevented LTP induction, and, surprisingly, this treatment resulted in suppression of the response that shifted PS amplitude even below baseline (PS amplitude after 60 min of PB application was 59.78% ± 1.23%) as shown in Figure 5A. At lower dose (1 μM), however, there was an initial increase in the response (146.71% ± 2.82% at 5-min post-PB application) for short period, but later on, there was inhibition of LTP, so that, at the end of 60 min recording after HFS, the PS amplitude (62.03% ± 0.98%) was significantly ($P < 0.01$) below baseline (Fig. 5B). Further reduction in the dose to 0.1 μM resulted in recovery of Aβ-induced LTP impairment (Figs. 5C and 5D). The PS amplitude was 127.42% ± 1.83% and 123.98% ± 1.06% at 5 and 60 min of PB, respectively ($P < 0.01$) at 0.1 μM, when compared with the group where only Aβ peptide was applied (101.26% ± 1.92%).

Effect of individual components of curcuminoids on Aβ-peptide-induced LTP impairment

Study on the individual compound showed bisdemethoxycurcumin application at the dose of 30 μM caused in an increase in PS amplitude initially to 159.97% ± 4.93% at 5-min post-PB application, but the response was not sustained and resulted in suppression of response below baseline at 60-min post-PB (87.42% ± 0.74%) as shown in Figure 6A. At the dose of 1 μM, bisdemethoxycurcumin caused LTP induction (155.02% ± 4.53%) but later suppression of the PS below baseline (75.99% ± 4.77%) as shown in Figure 6B. Further decrease in the dose to 0.1 μM, bisdemethoxycurcumin like parent curcuminoid mixture was able to completely rescue LTP, resulting in LTP induction (139.98% ± 1.31%), and maintenance PS amplitude was 130.17% ± 1.05% ($P < 0.01$) when compared with the group where Aβ peptide was applied alone (Fig. 6). Bisdemethoxycurcumin was the most effective for its effect on the induction of LTP in a way that it showed effect at broad range of doses.

Demethoxycurcumin showed comparable induction of PS amplitude (131.93% ± 1.64% and 140.15% ± 2.68% at 30 and 1 μM, respectively, at 5 min post-PB application), but was able to maintain Aβ-induced impairment of LTP (129.82% ± 0.44%) only at the dose of 1 μM (Figs. 7A–7D). At other two doses studied (30 and 0.1 μM), PS amplitude was 109.66% ± 0.91% and 104.43% ± 0.89%, respectively, at 60-min post-PB, thus showing that it could not recover Aβ-induced LTP impairment (Fig. 7).

Curcumin at 30 and 1 μM showed LTP induction with resultant values of 149.92% ± 1.46% and 140.3% ± 1.57% and maintenance values of 127.72% ± 1.23% and 155.68% ± 1.23%, respectively, but this effect was not evident at the lower dose (0.1 μM),
where the extent of response amplitude change was 100.14% ± 1.03% at 60 min (Figs. 8A–8D). This was contrary to our observations with parent curcuminoid mixture or low dose of bisdemethoxycurcumin (Figs. 5 and 6). Curcumin was the most effective compound for its effect on the maintenance of the LTP.

*Synapse*
DISCUSSION

LTP is a form of synaptic plasticity, which is known to provide cellular basis for certain forms of memory (Martin et al., 2000; Zakharenko et al., 2003). LTP can be divided into two obvious forms; early- and late-LTP. Early-LTP does not involve protein synthesis and is expressed through receptor modification and increase in the number of receptors in postsynaptic terminal, whereas late-LTP involves protein synthesis (Raymond, 2007). Amyloid plaques, which are deposited in the brain of AD patients, are composed of Aβ, which is highly neurotoxic and known to impair LTP (Gong et al., 2006; Wang et al., 2004). Curcuminoid is a mixture of three individual components, which are important constituent of turmeric (Ahmed and Gilani, 2009; Goel et al., 2008). The curcuminoid mixture was studied here in order to investigate the effect on LTP that was impaired by Aβ peptide. Interestingly, curcuminoid mixture at the high dose used in this study (30 μM), when coadministered with Aβ peptide, did not show any significant effect on LTP induction, which was impaired by Aβ, while at the lower dose (1 μM), it did show a rescuing effect on the initial phase of LTP. The rescuing effect of curcuminoid mixture on LTP impaired by Aβ decayed with time. Further reduction in the dose to 0.1 μM resulted in LTP induction as well as maintenance of the PS amplitude. It is important to emphasize that the dose of curcuminoid mixture, which increased baseline excitability of neurons, caused a decrease in PS amplitude after PB application. This

Fig. 4. Aβ peptide impaired LTP in rat hippocampal slices: (A) Effect of Aβ on baseline (n = 4). B: Representative responses of last 5 min from each group show comparison of vehicle and Aβ-peptide-treated slices after 80 min of recording. C: Field potential recording was carried out in control group (n = 6) and in Aβ group (n = 5) in which Aβ peptide (500 nM final concentration) was applied for 25 min before application of primed burst (PB) and perfused until the recording was terminated after 60 min of PB application. D: Graph showing PS potentiation where PS amplitude at 5 and 60 min after PB application is plotted as bar diagram. A, place where Aβ peptide was applied. Arrow indicates where PB as high-frequency stimulation (HFS) protocol was applied. **P < 0.01 using ANOVA followed by Tukey's multiple comparison test, when compared with the Aβ-peptide group. Insets represent the actual recording traces, which are displayed at the top; given numbers are the places where these were picked. Scale bars shown. C, control group tracings; P, peptide group tracing; PS, population spike.
suggested that the suppressive effect is specific for the pathways activated after PB application. At the lower dose of 0.1 μM, curcuminoid mixture rescued LTP completely, and this dose was quite relevant from the clinical point of view, as the desired plasma concentration can be achieved with oral dosing in humans (Baum et al., 2008). Similarly, bisdemethoxycurcumin showed dose-dependent inverse relationship on the induction of LTP. This inhibitory effect on the induction of LTP at high doses could be because of either nonspecific effect on different pathways or might be a toxic effect, which needs further studies.

Bisdemethoxycurcumin was the only compound effective at all three doses in the LTP induction. Demethoxycurcumin was effective in rescuing Aβ-peptide-induced LTP impairment at a single dose of 1 μM, while curcumin was effective at high doses (30 and 1 μM). Curcumin in opposition to the curcuminoid mixture and bisdemethoxycurcumin did not suppress PS amplitude below baseline. Curcumin was the most effective compounds as opposed to other constituents for its effect on the maintenance of LTP for 60 min after PB application, though not effective at lowest dose like curcuminoid mixture, but it was the only compound, which showed sustained effect on the maintenance response for 60 min at two doses. The rescuing effects of curcumin were demonstrated at relatively high doses. Now the question is what oral dose will produce corresponding plasma levels and what plasma level can produce same response in vivo needs to be studied in future.

Hence, based on these observations, it is concluded that curcuminoid mixture plays an important role in the modulation of LTP.
role in different phases of LTP, possibly due to the presence of curcumin, as curcumin was the only compound that showed effectiveness at two doses. The effect of curcumin and/or curcuminoid mixture on Aβ-induced LTP impairment provides possible cellular basis for the memory-enhancing effect of these compounds. Curcumin was devoid of any suppressive effect on LTP as opposed to the curcuminoid mixture, which demonstrated suppressive effect at high doses. It was observed that curcuminoids did not show LTP induction, particularly, in the initial phase of LTP, which plays complex but essential role in learning (Raymond, 2007). Here, in this case, comparison of curcuminoid mixture with bisdemethoxycurcumin, which demonstrated rescuing effect at early-LTP at comparable dose (Figs. 5A and 6A), clearly showed that bisdemethoxycurcumin had better effect in LTP induction. Furthermore, need arises to investigate bisdemethoxycurcumin as individual compound if it is more effective in memory-enhancing effect as well by the virtue of its specific effect on LTP induction compared to the curcuminoid mixture or curcumin.

Our observation that curcuminoid mixture and individual compounds have variable effect at different doses is somewhat difficult to interpret. It did not show a linear dose-dependent effect at different doses; however, our observations are consistent with observations by the other investigators. Several reports suggest that these compounds have tendency of showing different effects at different doses (Aggarwal and Sung, 2009; Lim et al., 2001; Ono et al., 2004; Yang et al., 2005). The effect of curcuminoids on initial phase of LTP is complex, possibly mediated through ryanodine receptors or through protein kinase C (PKC), as their dual effect on PKC...
is already known (Mahmoud, 2007). Curcumin is also known to upregulate cyclic AMP response element binding protein (CREB) (Li et al., 2009), which is also a key modulator of late-LTP. CREB upregulation potentiates the late phase of LTP and could be the reason why curcumin showed higher degree of effectiveness in case of Aβ-peptide-impaired LTP. Finally, curcuminoids have been found to be safe and well tolerated at high doses (Cheng et al., 2001; Lao et al., 2006; Shoba et al., 1998), this further adds to their merit.

To summarize, this study is the first of its type showing the comparative effect of curcuminoid mixture and individual components on LTP. Curcuminoid mixture along with bisdemethoxycurcumin was found effective at the lowest dose, whereas, later being effective at broad range of doses on LTP induction, but could not maintain this response at each dose for 60 min. This might explain the usefulness of bisdeme-thoxycurcumin in memory but not like curcumin, which was the most effective for its effect on the maintenance of the LTP in a way that it was the only compound effective at two doses. This explains the useful effect of curcumin in memory and unravels one of the few possible underlying mechanisms to explain the memory enhancing effect of curcumin in different models, although there is a need to further investigate in different in vivo models. This also demands the in vivo LTP studies to find whether this rescuing effect is achieved or not, and to provide in vivo dosing patterns, this will help in understanding the rational dose selection for humans. Curcumin as well as bisdemethoxycurcumin add merits to the parent curcuminoids on Aβ-peptide-induced impairment in LTP. Additionally, curcumin has been found to be useful in different models of neuroprotection (Bala et al., 2006; Kumar et al., 2007; Tang et al., 2009; Wang et al., 2008; Zhao et al., 2008). These findings suggest that
Curcuminoid mixture possesses multiple pharmacological properties that can be helpful in providing pharmacological basis for the medicinal use of curcuminoids in AD.

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