Brief Communication

Fibroblast growth factor-2 alters the nature of extinction

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These experiments examined the effects of the NMDA-receptor (NMDAR) antagonist MK801 on reacquisition and re-extinction of a conditioned fear that had been previously extinguished before injection of fibroblast growth factor-2 (FGF2) or vehicle. Recent findings have shown that relearning and re-extinction, unlike initial learning and extinction, do not depend on NMDAR activation. Three experiments demonstrated that FGF2 prevents the switch from NMDAR-dependent to NMDAR-independent reacquisition and re-extinction, suggesting that FGF2 may lead to the partial erasure of the original fear memory. These findings add to a growing body of work suggesting that FGF2 may be a novel pharmacological enhancer of exposure therapy for humans with anxiety disorders.

Fibroblast growth factor-2 (FGF2) is a neurotrophic factor that regulates neural development, regenerative plasticity, and neurogenesis (Unsicker et al. 1991). Recently, systemic FGF2 has been shown to enhance long-term memory for contextual fear (Graham and Richardson 2009a, 2010a) and extinction of conditioned fear in rats (Graham and Richardson 2009b, 2010b). Extinction occurs when a conditioned stimulus (CS) is repeatedly presented in the absence of the unconditioned stimulus (US), which substantially reduces conditioned fear responding. The finding that fear often returns after extinction when the CS is presented in a different context to that of extinction (renewal) (Bouton and Bolles 1979a), or when a mild unsignaled stressor precedes the test (reinstatement) (Bouton and Bolles 1979b), has led to the widely-held belief that extinction involves the formation of a new context-specific CS–no US memory that inhibits the (intact) original fear memory.

Our recent studies suggest that FGF2 does not facilitate the formation of a context-specific extinction memory. Specifically, FGF2-treated rats show significantly attenuated reinstatement and renewal (Graham and Richardson 2009b, 2010b), even when control rats are given double the amount of extinction training to equate the strength of extinction between FGF2-treated and control rats. This suggests that FGF2 may change the quality of extinction, possibly by weakening the original fear memory. The present experiments assessed this possibility behaviorally by exploiting recent findings regarding the molecular substrates underlying re-extinction, which refers to the process of relearning extinction following reacquisition of fear to an extinguished cue. Converging evidence strongly suggests that initial extinction and re-extinction do not depend on the same neural or molecular mechanisms. For example, unlike initial extinction, re-extinction is not impaired by NMDAR antagonists MK801 or DL-APV (Laurent et al. 2008; Langton and Richardson 2009, 2010). These experiments suggest that relearning to inhibit fear does not depend on NMDAR activity.

The present experiments assessed the effect of MK801 on the re-extinction of conditioned fear that had been extinguished with FGF2 or its vehicle. If FGF2 simply enhances context-dependent new learning during extinction, then re-extinction in FGF2-treated rats, as in vehicle-treated rats, should be

NMDAR-independent. However, if treatment with FGF2 alters the nature of extinction, then these rats may not exhibit this transition. Rats were 23 days of age at the start of all experiments; rats this age exhibit adult-like extinction (Kim and Richardson 2010). In Experiment 1, rats were fear conditioned with two white-noise CS and footshock US pairings on day 1. On day 2 rats received 45 CS-alone extinction trials, immediately followed by 0.02 mg/kg body weight FGF2 or vehicle. On day 3 rats were given one CS-US pairing during reacquisition training. On day 4 rats received 0.1 mg/kg body weight MK801 or saline, and 10 min later they received 45 CS-alone re-extinction trials. On day 5 rats were tested for re-extinction retention, involving a 1 min adaptation period followed by a 2 min CS presentation. Rats were scored for the percentage of time spent freezing during the adaptation period (pre-CS), and the CS presentations at extinction, reacquisition, re-extinction, and test as an index of fear (Fanselow 1980). Table 1 presents the experimental timeline for all experiments.

There were no group differences in pre-CS freezing prior to extinction training (i.e., no significant main effects or interaction; $P_s \geq 0.15$; see Table 2 for pre-CS freezing for all experiments). Furthermore, all groups exhibited similar levels of conditioned fear and similar rates of extinction; an extinction-drug by re-extinction-drug by extinction block mixed-design analysis of variance (ANOVA) revealed a significant effect of block ($F_{(8,432)} = 60.42$, $P < 0.0001$), with no effects of group or interaction ($P_s \geq 0.07$; Fig. 1A). In addition, all groups exhibited similar levels of extinction retention, as there were no group differences in pre-CS or CS-elicited freezing during reacquisition ($P_s \geq 0.16$; Table 2; Fig. 1B). This is consistent with previous findings that vehicle-treated rats exhibit comparable levels of extinction to FGF2-treated rats following a large number of extinction trials (Graham and Richardson 2009b, 2010b).

During re-extinction training MK801-treated rats exhibited significantly less pre-CS freezing than saline-treated rats; an ANOVA revealed a significant effect of re-extinction drug ($F_{(1,54)} = 8.9$, $P = 0.004$), but no effect of extinction drug and no interaction of the two on pre-CS freezing prior to re-extinction training ($P_s \geq 0.43$; Table 2). During re-extinction training, CS-elicited freezing decreased across blocks for all groups (Fig. 1C); an extinction-drug by re-extinction drug by re-extinction block mixed-design ANOVA revealed a significant effect of block ($F_{(8,432)} = 32.68$, $P < 0.0001$). There was also a significant effect of re-extinction drug ($F_{(1,54)} = 75.9$, $P < 0.0001$), due to rats given MK801 exhibiting significantly less freezing

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during re-extinction training. There was no effect of extinction drug and no significant interaction ($P_s \geq 0.53$). The findings that MK801-treated rats exhibited reduced freezing throughout re-extinction is consistent with previous reports (Lee et al. 2006; Chan and McNally 2009; Langton and Richardson 2009) that MK801 induces hyperactivity and reduces freezing.

An ANOVA revealed no significant effects of extinction drug or re-extinction drug on pre-CS freezing prior to test ($P_s \geq 0.49$). However, there was a significant interaction ($F_{(1,54)} = 6.32$, $P = 0.015$), due to FGF2-treated rats that received MK801 prior to re-extinction exhibiting higher pre-CS freezing than FGF2-treated rats that received saline prior to re-extinction ($t_{(27)} = 2.1$, $P = 0.046$; Table 2). Vehicle-treated rats did not differ from each other, regardless of the drug injected prior to re-extinction ($P = 0.16$). CS-elicited freezing at test is shown in Figure 1D. An ANOVA yielded a significant effect of extinction drug ($F_{(1,54)} = 4.5$, $P = 0.039$), no effect of re-extinction drug ($P = 0.1$), and a significant extinction drug by re-extinction drug interaction ($F_{(1,54)} = 5.65$, $P = 0.021$). This interaction was due to FGF2-treated rats that received MK801 prior to re-extinction exhibiting significantly higher CS-elicited freezing than FGF2-treated rats that received saline prior to re-extinction ($t_{(27)} = 3.02$, $P = 0.006$). Vehicle-treated rats did not differ from each other, regardless of the drug injected prior to re-extinction ($P_s \geq 0.65$). Therefore, the results of Experiment 1 demonstrated that FGF2 administration after initial extinction causes subsequent re-extinction to remain NMDAR-dependent.

In order to ensure that the results obtained in Experiment 1 were due to the effects of FGF2 on extinction, rather than due to the effects of prior exposure to FGF2 and MK801 per se, in Experiment 2 rats received FGF2 immediately or 4 h after extinction. All rats were then retrained to fear the CS, and all were given MK801 prior to re-extinction training. We have previously demonstrated that FGF2 does not enhance extinction when administered 4 h post-extinction training (Graham and Richardson 2009b) and so if the results of the first experiment were due to the effect of FGF2 on extinction, rather than due to some nonspecific effect of FGF2 and MK801 exposure, MK801 should impair re-extinction retention for the FGF2-immediate group but not for the FGF2-4 h group.

An independent-samples *t*-test revealed no significant effect of group on pre-CS freezing levels prior to extinction training ($P = 0.41$; Table 2). A group by extinction block mixed-design ANOVA revealed a significant effect of block ($F_{(8,144)} = 13.57$, $P < 0.0001$), but no effect of group and no interaction of group-by-block ($P_s \geq 0.41$) on CS-elicited freezing throughout extinction training, indicating that both groups exhibited similar levels of conditioned fear and similar rates of extinction (Fig. 2A). Furthermore, both groups exhibited similar levels of extinction retention as there were no group differences in pre-CS or CS-elicited freezing during reacquisition ($P_s \geq 0.16$; Table 2; Fig. 2B). In addition, both groups exhibited similar rates of re-extinction as there was no effect of group on pre-CS

Table 1. Experimental designs for Experiments 1, 2, and 3

	Day 1	Day 2	Day 3	Day 4	Day 5
Experiment 1	Conditioning	Extinction	Reacquisition	Re-extinction	Test
Vehicle/Saline	CS+	CS→Vehicle	CS+	Saline→CS-	CS-
Vehicle/MK801	CS+	CS→Vehicle	CS+	MK801→CS-	CS-
FGF2/Saline	CS+	CS→FGF2	CS+	Saline→CS-	CS-
FGF2/MK801	CS+	CS→FGF2	CS+	MK801→CS-	CS-
Experiment 2	Conditioning	Extinction	Reacquisition	Re-extinction	Test
FGF2-Imm	CS+	CS→FGF2	CS+	MK801→CS-	CS-
FGF2-4 hrs	CS+	CS-4 hrs→FGF2	CS+	MK801→CS-	CS-
Experiment 3	Conditioning	Extinction	Reacquisition	Test	
Vehicle/Saline	CS+	CS→Vehicle	Saline→CS+	CS-	–
Vehicle/MK801	CS+	CS→Vehicle	MK801→CS+	CS-	–
FGF2/Saline	CS+	CS→FGF2	Saline→CS+	CS-	–
FGF2/MK801	CS+	CS→FGF2	MK801→CS+	CS-	–

($P = 0.54$) or CS-elicited freezing ($P = 0.3$) during re-extinction training (Table 2; Fig. 2C). There was a significant effect of re-extinction block ($F_{(8,144)} = 11.25$, $P < 0.0001$), indicating that freezing decreased across re-extinction trials for all rats; however, it should be noted that overall freezing levels were low because both groups had received MK801 prior to re-extinction training. At test, there were no group differences in pre-CS freezing ($P = 0.56$; Table 2), but there was a significant difference in CS-elicited freezing ($t_{(18)} = 2.21$, $P = 0.041$; Fig. 2D), indicating that rats that received FGF2 immediately after extinction training exhibited impaired re-extinction retention relative to rats that received FGF2 4 h after extinction training. It should be noted that this latter group exhibited comparable levels of re-extinction retention to vehicle-treated rats that received MK801 in Experiment 1, suggesting that the results of Experiment 1 were due to the effects of FGF2 on extinction, rather than nonspecific effects of previous exposure to both FGF2 and MK801.

One possible reason that FGF2-treated rats exhibit NMDAR-dependent re-extinction is that during reacquisition FGF2-treated rats may form a new CS–US association that is extinguished for the first time during re-extinction (and thus is dependent on the molecular properties of initial extinction). In contrast, vehicle-treated rats may merely retrieve the original CS–US association and the original CS–no US association during reacquisition and re-extinction, respectively. Previous research has demonstrated that initial acquisition of fear conditioning is NMDAR-dependent in rats this age (Langton et al. 2007), but to our knowledge no one has examined whether reacquisition of fear conditioning following fear extinction is, like re-extinction, NMDAR-independent. Therefore, Experiment 3 asked two

Table 2. Mean ($\pm$ SEM) pre-CS percent freezing prior to extinction, test, reacquisition, and re-extinction (where relevant) for all experiments

Experiment	Group			
Experiment 1	Vehicle/MK801	Vehicle/Saline	FGF2/MK801	FGF2/Saline
Extinction	34.6 (5.62)	26.9 (6.34)	35 (5.5)	24.9 (6.5)
Reacquisition	13.7 (4.19)	8.9 (3.69)	8.6 (3.56)	6.8 (2.48)
Re-extinction	18.6 (3.86)	33.4 (6.6)	24.1 (3.41)	38.1 (5.6)
Test	8.6 (3.97)	20.3 (6.91)	27.4 (8.11)	9.7 (3.07)
Experiment 2	FGF2-Imm	FGF2-4 hrs		
Extinction	52.5 (12.54)	39.1 (10.0)		
Reacquisition	9.8 (4.15)	3.1 (1.88)		
Re-extinction	25.2 (7.98)	18.5 (7.14)		
Test	18 (9.72)	10.5 (7.83)		
Experiment 3	Vehicle/MK801	Vehicle/Saline	FGF2/MK801	FGF2/Saline
Extinction	25 (9.17)	49.9 (9.34)	38.7 (8.89)	38.5 (10.72)
Reacquisition	0.5 (0.37)	2.6 (1.32)	2.3 (0.87)	4.5 (2.15)
Test	37.7 (10.56)	49.1 (7.59)	17.1 (4.28)	45.9 (8.84)

Figure 1. (A) Mean ($\pm$ SEM) CS-elicited freezing during extinction training in Experiment 1. Each block consists of five extinction trials. Rats were in one of four groups: Vehicle/MK801 ($n=14$), Vehicle/Saline ($n=15$), FGF2/MK801 ($n=14$), and FGF2/Saline ($n=15$). (B) Mean ($\pm$ SEM) CS-elicited freezing during reacquisition in Experiment 1. (C) Mean ($\pm$ SEM) CS-elicited freezing during re-extinction training in Experiment 1. Each block consists of five extinction trials. (D) Mean ($\pm$ SEM) CS-elicited freezing during test in Experiment 1.

questions: Is reacquisition of cued fear following extinction NMDAR-independent, and if so, does FGF2 prevent the switch from NMDAR-dependent to NMDAR-independent reacquisition? Rats received fear conditioning on day 1 and fear extinction on day 2 (followed by FGF2 or vehicle) as in Experiment 1. On day 3 rats received MK801 or saline, and 10 min later they received reacquisition training. All rats were tested for reacquisition retention on day 4 (where greater levels of freezing indicate greater retention).

An extinction drug by reacquisition drug ANOVA revealed no group differences in pre-CS freezing during the adaptation period prior to extinction (i.e., no significant main effects or interaction; $P_s \geq 0.2$; Table 2). An extinction drug by reacquisition drug by extinction block mixed-design ANOVA revealed a significant effect of block ($F_{(8,328)} = 69.16$, $P < 0.0001$), with no effect of group or interaction ($P_s \geq 0.1$), meaning that all groups exhibited similar levels of conditioned fear and similar rates of extinction (Fig. 3A). Furthermore, there were no differences between groups in levels of pre-CS or CS-elicited freezing during reacquisition training ($P_s \geq 0.11$; Table 2; Fig. 3B). At test following reacquisition, there was a significant main effect of reacquisition drug on levels of pre-CS freezing ($F_{(1,41)} = 6.28$, $P = 0.016$; Table 2). This was due to FGF2-treated rats that received MK801 prior to reacquisition exhibiting significantly less freezing than FGF2-treated rats that received saline prior to reacquisition ($t_{(21)} = 3.02$, $P = 0.007$).

Vehicle-treated rats did not differ regardless of the drug received prior to reacquisition ($P = 0.39$). An ANOVA revealed significant main effects of extinction drug ($F_{(1,41)} = 7.39$, $P = 0.010$) and reacquisition drug ($F_{(1,41)} = 5.57$, $P = 0.023$), and a significant extinction drug by reacquisition drug interaction ($F_{(1,41)} = 4.32$, $P = 0.044$) on CS-elicited freezing during test. The interaction was due to FGF2-treated rats that received MK801 prior to reacquisition exhibiting significantly less freezing than FGF2-treated rats that received saline prior to reacquisition ($t_{(21)} = 2.84$, $P = 0.01$). Vehicle-treated rats did not differ from each other regardless of the drug received prior to reacquisition ($P = 0.82$). Therefore, Experiment 3 indicated that reacquisition following extinction of conditioned fear is NMDAR-independent, and further, when extinction is combined with FGF2 it causes subsequent reacquisition to remain NMDAR-dependent.

The main findings of this study are that when FGF2 is administered following extinction this prevents the switch from NMDAR-dependent to NMDAR-independent reacquisition and re-extinction of fear. Specifically, MK801

Figure 2. (A) Mean ($\pm$ SEM) CS-elicited freezing during extinction training in Experiment 2. Each block consists of five extinction trials. Rats were in one of two groups: FGF2-imm, and FGF2-4 h ($ns = 10$). (B) Mean ($\pm$ SEM) CS-elicited freezing during reacquisition in Experiment 2. (C) Mean ($\pm$ SEM) CS-elicited freezing during re-extinction training in Experiment 2. Each block consists of five extinction trials. (D) Mean ($\pm$ SEM) CS-elicited freezing during test in Experiment 2.

Figure 3. (A) Mean ($\pm$ SEM) CS-elicited freezing during extinction training in Experiment 3. Each block consists of five extinction trials. Rats were in one of four groups: Vehicle/MK801 ($n = 11$), Vehicle/Saline ($n = 11$), FGF2/MK801 ($n = 12$), and FGF2/Saline ($n = 11$). (B) Mean ($\pm$ SEM) CS-elicited freezing during reacquisition in Experiment 3. (C) Mean ($\pm$ SEM) CS-elicited freezing during test in Experiment 3.

Further, these results cannot be due to FGF2 impairing re-extinction or reacquisition because FGF2-treated rats that received saline exhibited comparable re-extinction and reacquisition retention to vehicle-treated rats. Finally, these results cannot be due to nonspecific effects of combined FGF2 and MK801 exposure because FGF2 only prevented the switch to NMDAR-independent re-extinction when it was administered immediately and not 4 h after extinction training.

It should be noted that the variability in pre-CS levels of freezing across the three experiments reported here is likely due to the fact that all procedures took place in the same context and so during conditioning rats would have acquired fear of the CS and the context. Although somewhat more variable than the findings regarding CS-elicited freezing, the findings regarding pre-CS levels of freezing are generally consistent with the interpretation that extinction combined with FGF2 prevents the switch from NMDAR-dependent to NMDAR-independent reacquisition and re-extinction. For example, in Experiment 1 FGF2-treated rats that received MK801 prior to re-extinction exhibited higher pre-CS as well as CS-elicited freezing, suggesting that MK801 impaired re-extinction to both the context and the CS. Likewise, in Experiment 3 FGF2-treated rats that received MK801 prior to reacquisition exhibited lower pre-CS as well as CS-elicited freezing at test, suggesting that MK801 impaired reacquisition to both the context and the CS. In Experiment 2, however, no differences in pre-CS freezing at test were found. The effect of MK801 on contextual learning in FGF2-treated rats may be less robust due to the CS being a better predictor of the US than the context.

One explanation of the present findings is that during reacquisition training FGF2-treated rats form a new excitatory representation of the CS–US association (a process that is impaired by MK801), such that when they are re-extinguished they are actually extinguishing this association for the first time (a process

that is impaired by MK801). The suggestion that forming a new CS–US association during reacquisition would lead to NMDAR-dependent re-extinction is supported by previous findings that when rats are conditioned and extinguished with CS1, and then reconditioned and re-extinguished with CS2 (i.e., a novel CS), re-extinction is NMDAR-dependent (Langton and Richardson 2008). Therefore, FGF2-treated rats show the same response to MK801 during re-extinction as do rats that were retrained and re-extinguished with a novel CS. One explanation for this finding is that when FGF2 is combined with extinction it may weaken the original fear memory trace. If so, it might be expected that vehicle-treated rats should show a savings effect (i.e., faster reacquisition) in comparison to FGF2-treated rats. The present experiments did not detect such an effect, most likely because one CS–US pairing is sufficient to induce ceiling levels of freezing in this age group. Future research will need to assess this possibility, as well as to elucidate the exact molecular mechanisms by which FGF2 enhances extinction. For example, FGF2 might enhance depotentiation, the hypothesized molecular mechanism behind the erasure component of extinction (Lin et al. 2003a). Depotentiation is

associated with an increase in neurotrophic factors (Yuzaki et al. 1994). Furthermore, FGF2 exerts control over calcineurin activation (Boxer et al. 1999), which is one of the molecular signals involved in depotentiation (Lin et al. 2003b). Regardless of the mechanism, the present findings illustrate a novel way to assess the impact of a drug on the quality of extinction. Moreover, together with our previous findings that FGF2 reduces relapse, these experiments provide additional support for the idea that FGF2 may be a potentially useful pharmacological enhancer of exposure therapy in anxiety disorders, as they suggest that FGF2 may partially erase the original fear memory.

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