様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

平成　３０　年　　６　月　１１　日現在

機関番号：　８２４０１
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研究課題名（和文）Dopaminergic regulation of fear extinction learning

研究課題名（英文）Dopaminergic regulation of fear extinction learning

研究代表者
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交付決定額（研究期間全体）：（直接経費）　　13,900,000円

研究成果の概要（和文）：We examined the contribution of the ventral tegmental area (VTA) dopamine system to fear extinction learning. We found that activity in VTA-dopamine cells is necessary for normal fear extinction learning and biochemical signaling in extinction learning circuits.

研究成果の概要（英文）：We examined the contribution of the ventral tegmental area (VTA) dopamine system to fear extinction learning. During fear conditioning, animals learn that an auditory tone stimulus predicts the occurrence of an aversive event (shock) and animals exhibit fear behaviors to the tone following learning. If the tone is presented repeatedly in the absence of the aversive event fear responses are reduced through extinction. We found that optogenetic inhibition of VTA-dopamine neurons during the shock omission period of extinction blocked extinction learning as well as biochemical signatures of neural plasticity in the extinction learning system. Furthermore, we discovered that a specific population of dopamine neurons projecting to the nucleus accumbens were responsible for this effect. These results reveal an unappreciated role for the dopamine reward system in extinguishing fear memories and suggest novel treatment avenues for fear related psychiatric disorders.

研究分野：　Neuroscience

キーワード：　Dopamine　Extinction　Fear

１．研究開始当初の背景

Emotional fear memories are adaptive but need to be controlled in many circumstances for optimal behavior. In the laboratory fear conditioning in which animals learn that a sensory cue predicts the occurrence of an aversive outcome (ex. shock). Following learning, presentation of the cue elicits emotional responses, but if presented repeatedly in the absence of shock emotional responses are extinguished. Thus the omission of the aversive event triggers a switch from fear responding to extinction. Neural plasticity in brain areas like the amygdala and medial prefrontal cortex (mPFC) are important in extinction learning, but the neural mechanisms which detect when an expected aversive event is omitted to initiate extinction are not known. Previous work has demonstrated the importance of the ventral tegmental area (VTA) dopamine system to reward learning and motivation. Specifically VTA-dopamine neurons detect when a better than expected outcome occurs. For example, VTA-dopamine cells are activated robustly by unexpected rewards and there is some evidence that these cells respond to the omission of an expected aversive outcome. This suggests that the VTA-dopamine system may function as the detector of aversive shock omission to engage fear extinction learning.

２．研究の目的

In the studies funded by this grant we set out to determine whether the VTA-dopamine system was necessary to detect when an aversive outcome was omitted to initiate extinction learning as well as the circuit mechanisms through which the dopamine system mediated these effects.

３．研究の方法

For these studies we used optogenetic brain manipulation techniques combined with behavioral assays as well as biochemical and voltammetric approaches.

４．研究成果

We found that when an expected aversive outcome does not occur, activity in midbrain dopamine neurons is necessary to extinguish behavioral fear responses and engage molecular signalling events in extinction learning circuits. Furthermore, a specific dopamine projection to the nucleus accumbens medial shell is partially responsible for this effect. By contrast, a separate dopamine projection to the medial prefrontal cortex opposes extinction learning. This demonstrates a novel function for the canonical VTA-dopamine reward system and reveals opposing behavioural roles for different dopamine neuron projections in fear extinction learning.

５．主な発表論文等

（研究代表者、研究分担者及び連携研究者には下線）

〔雑誌論文〕（計 5 件）

1) Luo, R., Uematsu, A., Weitemier, A., Aquili, L., Koivumaa, J., McHugh, T.J. and Johansen, J.P. A dopaminergic switch for fear to safety transitions. *Nature Communications*. 2018, *In press. Refereed*

2) Ozawa, T. & Johansen, J.P. Learning rules for aversive associative memory formation. *Current Opinion in Neurobiology*. 2018, 49: 148-157. *Refereed*

3) Yeh, L.-F., Watanabe, M., Sulkes-Cuevas, J. Johansen, J.P. Dysregulation of aversive signaling pathways: a novel circuit endophenotype for pain and anxiety disorders. *Current Opinion in Neurobiology* 2017, 48: 37-44. *Refereed*

4) Uematsu, A., Tan, B.Z., Ycu, E.A., Sulkes, J., Koivumaa, J., Junyent, F., Kremer, E.J., Witten, I.B., Deisseroth, K. and Johansen, J.P. Modular Organization of the Brainstem Noradrenaline System Coordinates Opposing Learning States. *Nature Neuroscience*. 2017, 20(11) 1602-1611. *Refereed*

5) Ozawa, T., Ycu, E.A., Kumar, A., Yeh. L-F., Ahmed, T., Koivumaa, J., and Johansen, J.P. A feedback neural circuit for calibrating aversive memory strength. *Nature Neuroscience* 2017, 20(1): 90-97. *Refereed*

〔学会発表〕（計 21 件）

1) Albert Einstein Medical School Invited Talk (New York, USA) “Brain circuits for triggering and reversing emotional memories” Joshua Johansen *January, 2018*

2) Winter Conference on Brain Research Symposium (Chair, Whistler, Canada) Instructive signals for aversive learning

and memory: "Feedforward and feedback circuits for instructing and calibrating fear learning" Joshua Johansen *January, 2018*

3) Society for Neuroscience Symposium (Chair, Washington D.C.,USA): From salient experience to learning and memory: instructive signals for aversion and reward "Feedback circuits for calibrating aversive learning signals" Joshua Johansen *November, 2017*

4) Massachusetts Institute of Technology (Boston, USA) "Brain circuits for triggering and reversing emotional memories" Joshua Johansen *September, 2017*

5) New York University (New York, USA) "Brain circuits for triggering and reversing emotional memories" Joshua Johansen *September, 2017*

6) Tokyo Metropolitan Institute of Medical Science (Tokyo, Japan) "Brain circuits for triggering and reversing emotional memories" Joshua Johansen *September, 2017*

7) European Brain, Behaviour Society Meeting (Bilbao, Spain) "Distinct Noradrenaline Cell Populations Coordinate Emotional and Flexible Learning States" Joshua Johansen *September, 2017*

8) Hokkaido University Summer School "Teaching the Brain to Fear" and "Brain Circuits for Fear and Safety Learning" Joshua Johansen *August, 2017*

9) Gordon Conference: Amygdala in health and disease (Boston, USA) "Distinct Noradrenaline Cell Populations Coordinate Emotional and Flexible Learning States" Joshua Johansen *August, 2017*

10) Keynote Lecture at Japanese Association for Study of Pain meeting (Kobe Japan) "A painmodulatory feedback circuit for calibrating emotional memory strength" Joshua Johansen *June, 2017*

11) Spring Hippocampal Research Conference Symposium (Chaired, Taormina, Italy): Connecting ensemble activity in the hippocampus to behavior "Hippocampal encoding during aversivedecision making" Joshua Johansen *June, 2017*

12) Asian College of Neuropsychopharmacology (Bali, Indonesia) "Distinct noradrenaline cell populations coordinate the balance between fear and extinction learning" Joshua Johansen *April, 2017*

13) University of California, San Francisco Invited Talk (San Francisco, USA) "Brain circuits for triggering and reversing emotional memories" Joshua Johansen *February, 2017*

14) Boston University Invited Talk (Boston, USA) "Brain Circuits for triggering and reversing emotional memories" Joshua Johansen *January, 2017*

15) Arrowhead 10 years on: What have we learned and what is there still to learn about the neuralbases of decision-making? (Sydney, Australia) "Meta-organization in the locus coeruleus noradrenaline system coordinates emotional and flexible learning states" Joshua Johansen *December, 2016*

16) Nature Conference on Neural Circuitry of Emotion (Shenzhen, China) "Multiplexed signaling across distinct noradrenaline cell populations coordinates opposing emotional learning functions" Joshua Johansen *November, 2016*

17) Tsukuba Global Science Week Meeting (Tsukuba, Japan)"Meta-organization in the brainstem noradrenaline system coordinates adaptive learning" Joshua Johansen *August, 2016*

18) Japan Neuroscience Society Meeting (Chaired, Yokohama, Japan): Long range circuit interactions controlling learned behaviors "Functional specificity based on efferent connectivity in the locus coeruleus noradrenaline system" Joshua Johansen *July, 2016*

19) FENS Symposium (Chaired, Copenhagen, Denmark): Fear extinction: from engrams to circuits "Regulation of fear & extinction learning through distinct neuromodulatory circuits" Joshua Johansen *July, 2016*

20) Pain Mechanisms and Therapeutics (Taormina, Italy) "Neural circuit mechanisms for triggering and controlling the strength of aversive memories" Joshua Johansen *June, 2016*

21) European Molecular Biology Laboratory (Monterotondo,Italy)"Neural circuit mechanisms for the initiation and adaptive control of aversive associative learning" Joshua Johansen *June, 2016*

〔図書〕（計　　件）

〔産業財産権〕

○出願状況（計　　件）

名称：
発明者：
権利者：
種類：
番号：
出願年月日：
国内外の別：

○取得状況（計　　件）

名称：
発明者：
権利者：
種類：
番号：
取得年月日：
国内外の別：

〔その他〕
ホームページ等

６．研究組織
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