Discussion

Brain Mechanisms of Social Anxiety Disorder

Dr. Ballenger: What is known about dorsal raphe serotonergic control of striatal dopamine neurons?

Professor Nutt: The conventional idea is that the 5-HT input is inhibitory, for several reasons. One is that if you increase 5-HT with selective serotonin reuptake inhibitors (SSRIs), you can get symptoms that are similar to what you get with dopamine blockade, so akathisia and dystonias, as reported with some SSRIs, are effects similar to those found when blocking dopamine D_2 receptors with neuroleptics.

The second is that if you give drugs like ritanserin, you can release some of the parkinsonian-type motor effects of neuroleptics, so there is almost certainly a negative 5-HT_2 input to the striatum. It is more complicated, however, because there is almost certainly a 5-HT_{1A} input as well. That input is facilitatory because we know that with animals, if you get catalepsy with neuroleptics, you can release it with 5-HT_{1A} agonists like 8-OH-DPAT. It is a complicated pharmacology. The fact is that there is enough interaction to allow you to envisage a dopamine theory and bring in 5-HT.

Dr. Davidson: I might just mention some of the magnetic resonance studies of the Duke group. Potts and colleagues[1] showed an interesting decline of putamen volume with age that occurs to a greater extent in social phobia and that certainly directs us to dopamine and also strengthens this link with social phobia. You mentioned parkinsonism. It is almost as if we are dealing with a dopaminergic-deficient disorder that expresses itself in different ways at different ages. In another set of studies,[2] we showed an increase in choline, relative to NAA. I wondered if this could mean that when you have a reduced NAA, you have neuronal degeneration. Social phobia is a disorder with longstanding deficits that do not seem to improve with benzodiazepine treatment, because we repeated the tests after treatment.

Professor Nutt: There was an increase in the choline and NAA ratios?

Dr. Davidson: Yes. As choline is a marker of both dopamine production and serotonin production, it would be consistent with what you mentioned, but, as far as I know, those are the only studies that were replicated in the biology of social phobia.

Professor Nutt: Again, this focuses attention on a potential dopaminergic dysfunction, and these are chronic patients. Do you know if these were cross-sectional trials?

Dr. Davidson: Yes, and in the second trial we repeated MRS after treatment with clonazepam, and we found that the increases in choline were still there.

Dr. Westenberg: How sure can we be that Parkinson's disease and social phobia have a common biology rather than that social phobia is secondary to Parkinson's disease, because patients feel embarrassed by their symptoms?

Dr. Ballenger: As I understand it, there are some cases in which social anxiety disorder occurs in adulthood, with a later onset than usual, followed later by overt parkinsonism, which is a bit stronger implication of a linked pathophysiology.

Professor Nutt: So late-onset social phobia can precede parkinsonism?

Dr. Davidson: Is it necessarily late onset? Are these people who had social phobia for a long time and then as they got older developed parkinsonism?

Dr. Beidel: Coming from a different background, I have some basic questions with respect to the challenge tests. I am not familiar with all the agents that are used, but do they specifically elicit the symptomatology in social phobia?

Professor Nutt: Unlike for panic, we do not have an agent that specifically triggers social phobia. For instance, we have not found a drug challenge that causes blushing. I have looked at the literature on the neurobiology of blushing, and there is little information other than that one part of the parietal area of the brain may be involved.

Nicotinamide is a potent blush-producing agent, and we would expect patients with social phobia to be particularly sensitive to it.

Dr. Beidel: That is an important issue. We may not have the right challenges to elicit the difference in symptoms between social phobics and normals and show whether or not there is a biological basis.

We know panic patients are afraid of the symptoms and spend all their time scanning their body: "Is my heart starting to beat faster; Am I starting to get dizzy?" Social phobics are not afraid of their symptoms but are afraid that people are going to see those symptoms. I am wondering whether a pure biological drug challenge is ever going to get what we want. It is the PET study that you did or the study putting people in a task and then measuring physiology that is the challenge paradigm that is needed for social phobics, because they are not afraid of the symptoms.

Professor Nutt: We have thought about filming people in their real life and showing them a video of themselves. That may be the most fruitful way.

Dr. Ballenger: If you go a step further, there is a partial way you can do that. If you put people in a social, evalua-

tive context and then cause some of these symptoms, for instance, blushing or hand shaking, I do not know if that really makes much sense, but it would be like the real thing.

Dr. Beidel: We do something with children as part of our exposure procedures that we call the "game of silly stuff." We make the child get up in front of a small audience and do stupid things, such as act like a elephant or sing "I'm a little teapot," that are going to elicit some degree of performance anxiety in front of the group. Something like that might be the kind of task that is needed paired with a panel of people evaluating them.

Dr. Ballenger: Can we bring the amygdala into the discussion?

Professor Nutt: The amygdala changes in anxiety with either deactivation or activation, in social phobia, in conditioned anxiety, and in PTSD, so it is almost certainly important.

Dr. Davidson: As I remember it, there are 2 components of the amygdala, which do not always behave in the same way.

Professor Lecrubier: You did not mention any animal model of social behavior that could be modified by different agents. Is there no model for social interactions?

Professor Nutt: There is a classic social interactive model in the rat that has been extensively developed by Sondra File[3] and is well validated. It is used solely and very effectively as a primary screen for anxiolytics. In this model, social interaction is increased by benzodiazepines and buspirone and decreased by anxiogenic drugs like benzodiazepine inverse agonists.

Dr. Davidson: Ondansetron was effective in that model, but turned out to be rather ineffective in social phobia.

Dr. Westenberg: It is the same with buspirone, which is also ineffective in social phobia.

Professor Nutt: This is a model of normal social interaction rather than pathological social interaction in a rat, and it raises the question whether normal social anxiety that we all have when we first meet people is part of a continuum with social phobia.

Professor Lecrubier: And the model uses an intruder?

Professor Nutt: Intruder anxiety. Fear models rely on a serious threat to life. It may not be possible to model social phobia because the concept of embarrassment may not be applicable in animals. However, dopamine-deficient mice show impaired social interaction rectified by dopaminergic agonists. Also, my drug addiction colleagues tell me that a major reason why children drink or take amphetamine is because it reduces social anxiety and allows them to interact socially. Again, this fits with the idea that dopamine release somehow facilitated social function.

Dr. Ballenger: Has anybody gone back to the model of the bashful or homophobic dog, which preceded by about 15 years our interest in social phobia? It was brought up earlier as an animal model for panic disorder, but in this context it might be worth thinking about it again.

Dr. Westenberg: There are specific strains of mice that are prone to anxiety-provoking situations. Our group is working with 5-HT_{ID} knock-out mice. These mutant animals appear to be more aggressive and impulsive than the wild types. Their physiologic responses when disturbed by, for example, the investigator are also completely different. As the 5-HT_{1D} receptor is abundant in the striatum, it may fit in with your idea about the role of dopamine in the striatum.

Professor Nutt: You think that the 1D knock-out mouse may have less anxiety and increased aggression. This is quite opposite to social phobia.

Dr. Westenberg: I have a question about your imaging data. You compared social phobia with anticipatory anxiety. Was this generalized anxiety disorder (GAD)?

Professor Nutt: No. This is a conditioned anxiety, anticipation of an electric shock. The subject never gets the shock while being scanned, but gets it afterward. If you can think of a good way of provoking GAD in the scanner, we can talk about it.

Dr. Westenberg: I mean measuring baseline levels in social phobics as compared to OCD.

Professor Nutt: No, let me explain. This is conceptually important. The power of our technique is not to do 1 baseline scan but 12 randomized scans on our social phobics (anxious and nonanxious). The anxiety goes up when they get the social phobic script and down when they get the neutral script and because each time there is a scan, you get powerful statistics. If you do just 1 baseline, you do not know what you are measuring because you do not know whether the levels of anxiety vary. How can you interpret baseline measures of anxiety? You do not know whether the GAD person is lying there anxious or not, so baseline data are very hard to interpret, which is why we use these challenge tests.

REFERENCES

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3. File SE, Lister RG, Nutt DJ. The anxiogenic action of benzodiazepine antagonists. Neuropharmacology 1982;10:1033–1037